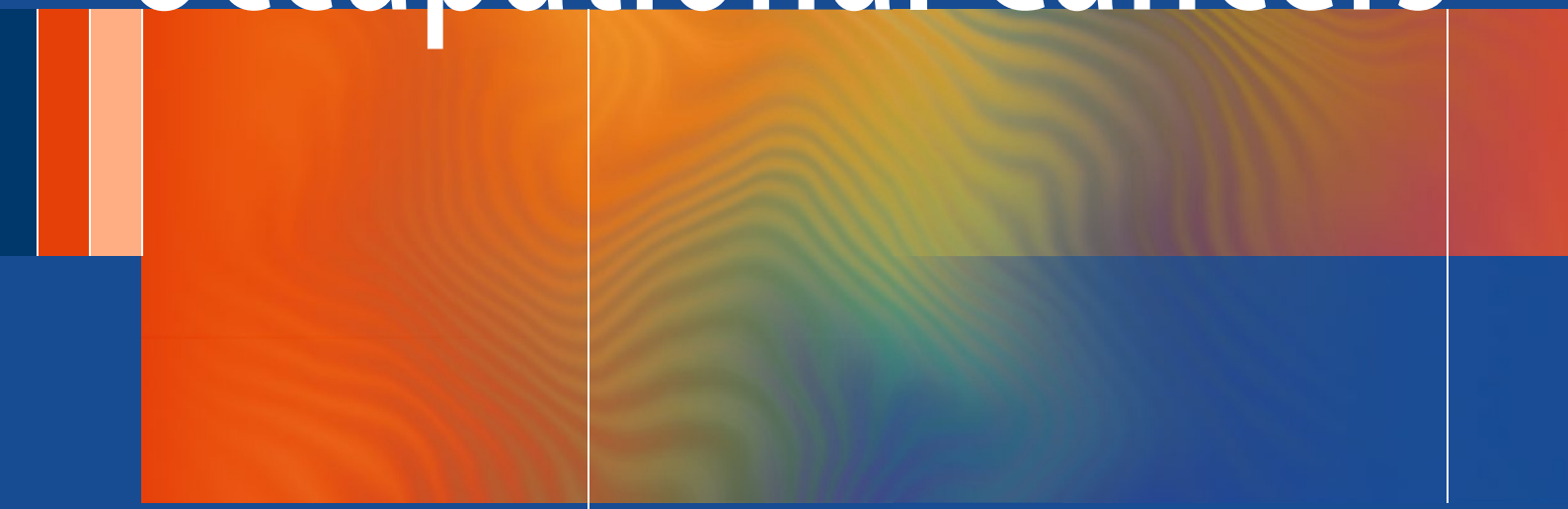
Sisko Anttila
Paolo Boffetta
Editors

Occupational Cancers



Springer

Occupational Cancers

Sisko Anttila • Paolo Boffetta
Editors

Occupational Cancers

Springer

Editors
Sisko Anttila, MD, PhD
Helsinki University Central Hospital and
Finnish Institute of Occupational Health
Helsinki
Finland

Paolo Boffetta, MD, MPH
Icahn School of Medicine at Mount Sinai
New York, NY
USA

ISBN 978-1-4471-2824-3 ISBN 978-1-4471-2825-0 (eBook)
DOI 10.1007/978-1-4471-2825-0
Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2014943112

Foreword

Combating Cancer: Past, Present and Future

Although much of cancer is preventable, it continues to exact a huge human burden, on a global scale. Early interventions by health authorities were hampered by inadequate knowledge, but greater understanding of the areas requiring focus slowly grew in the late twentieth century. This book shows the latest developments in the preventive science of occupational cancer control.

The twentieth century saw a revolution in public health and preventive medicine, which accelerated with scientific and medical advances during a time of unprecedented material growth as the century drew to a close. Industrial carcinogens opened the era of cancer prevention, and developments in the medical sciences, in toxicology in particular, have been fundamental to the progress in occupational cancer prevention [1]. However, it was the application of the new field of chronic disease epidemiology that fostered many of the most important advances in understanding and tackling occupational cancers [2]. Occupational cancer rose to prominence, as epidemiologists and toxicologists identified increasing numbers of suspect human carcinogens, and public anxiety was spurred by revelations of the toxicity of asbestos, and by the disastrous global legacy of the asbestos industry [3, 4]. The inertia of some industries, not least of the tobacco industry, to accept the obtained scientific results and to adopt costly controls to protect workers or consumers (in the case of tobacco) was not new [5]. The uncertainties inherent in epidemiological and toxicological studies were too often cited as justification for delaying or concealing, rather than incorporating the lessons of research, as the asbestos saga, or the global tobacco epidemic, have sadly shown.

Worldwide, there are some 100,000–140,000 asbestos-related deaths every year, and in high-income countries, the compensation for asbestos-related diseases is likely to reach several hundred billion euros over the coming years [6]. All forms of asbestos are now recognized as carcinogenic, and to date, more than 50 countries, including all the Member States of the European Union, have banned or restricted the use of asbestos. However, chrysotile asbestos continues to be mined and exported to developing countries by e.g., China, Canada and Russia, and India is the largest importer. Brazil also has mines. The World Health Organization and the International Labour Office have now both called for an international ban of use of all asbestos.

Even though the health hazards of old scourges, such as asbestos and silica dusts, are now well understood, they remain significant causes of occupational cancer. By the 1970s, the traditional industries were already in decline in the western world, while the chemical industry had been expanding rapidly since the Second World War. One chemical in particular, vinyl chloride monomer (VCM), used in many countries in plastics production, was assumed to be safe. However, evidence from laboratory animals revealed in 1973 that it could cause angiosarcoma of the liver, a rare tumour, in humans. Soon it was revealed that VCM workers in many countries had developed this type of tumour [7]. This then resulted in rapid actions to reduce exposure to VCM in chemical plants.

During the latter part of the twentieth century, it became clear that carcinogenesis was a multistep process. The milestones in the complexities of the neoplastic disease include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, including angiogenesis, and activating invasion and metastasis [8].

Biomarkers now play a significant role in the identification of the key events in this process. In recent decades, one of the most studied genes in epidemiology has been the TP53 tumour suppressor gene. Its role in causing liver and skin tumours is the focus of much research activity. Intermediate biomarkers, such as chromosomal damage and altered DNA repair, point toward evidence of early, non-clonal and potentially non-persistent effects, which if halted or reversed may decrease the risk of full-blown malignancy. The role of so-called 'molecular epidemiology' in the study of cancer aetiology and prevention is also on the rise.

There are currently many international initiatives addressing occupational, environmental and consumer issues in relation to the control of toxic and potentially carcinogenic substances. Improved control technologies and the adoption of risk assessment and risk management legislation have radically altered attitudes and led to far better control of exposure to chemicals, mixtures of chemicals, and physical agents, such as ionizing and non-ionizing radiation [9, 10].

However, newer concerns over cancer have arisen with the rapid introduction of technologies such as mobile phones, the use of which became widespread before studies of their potential health hazards were embarked upon [1, 11]. Today's wide interest in developing engineered nanomaterial-based products has also been cautioned by the previous lessons learnt from asbestos fibers [12, 13].

Regardless of these dangers however, the challenges facing the modern world cannot be met without the creation of new technologies. Some of these technologies will inevitably have adverse health consequences, a small proportion of which may be unforeseen under current regulatory approaches, but the fact remains that many of these new technologies have the potential to enormously improve lives.

To conclude, despite the huge advances in cancer prevention in industrialized countries in recent decades, specialist advice and expertise have not kept pace with the rapid changes in either the work or general environment, nor have they kept up with consumer products [4, 14]. Unless this shortfall is adequately dealt with, cancer prevention will continue to be of high priority in occupational health-related research, with a significant focus on diminishing the unnecessary burden of cancers worldwide.

Helsinki, Finland

Harri Vainio
Finnish Institute of Occupational Health

References

1. IARC monographs on the evaluation of carcinogenic risks to humans. http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php
2. Checkoway H, Pearce N, Kriebel D. Research methods in occupational epidemiology. 2nd ed. New York: Oxford University Press; 2004.
3. Tossavainen A. Global use of asbestos and incidence of mesothelioma. Int J Occup Environ Health. 2004;10:22–5.
4. Straif K. The burden of occupational cancer. Occup Environ Med. 2008;65:787–8.
5. Peto R, Chen ZM, Boreham J. Tobacco-the growing epidemic. Nat Med. 1999;5:15–7.
6. Ramazzini C. Asbestos is still with us: repeat call for a universal ban. Eur J Oncol. 2010;15:69–75.
7. Creech JL, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med. 1974;16:150–1.
8. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.
9. Swerdlow AJ. Effectiveness of primary prevention of occupational exposures on cancer risk. In: Hakama M, Beral V, Cullen JW, et al., editors. IARC scientific publication: evaluating effectiveness of primary prevention of cancer. Lyon: International Agency for Research on Cancer; 1990:23–56.
10. Barnes FS, Greenebaum B. Handbook of biological effects of electromagnetic fields. Biological and medical aspects of electromagnetic fields. 3rd ed. Boca Raton: CRC Press; 2008.
11. Interphone Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol. 2010;39:675–94.
12. Kane AB, Hurt RH. Nanotoxicology: the asbestos analogy revisited. Nat Nanotechnol. 2008;3:378–9.
13. Schulte P, Geraci C, Zumwalde R, Hoover M, Castranova V, Kuempel E, Murashov V, Vainio H, Savolainen K. Sharpening the focus on occupational safety and health in nanotechnology. Scand J Work Environ Health. 2008;34:471–8.
14. President's Cancer Panel. 2008–2009 annual report: reducing environmental cancer risk: what we can do now. Washington, DC: U.S. Department of Health and Human Services; 2010.

Preface

Writing of the book on occupational cancer is motivated first of all by the fact that a great proportion of occupational cancers are not recognized even in post-industrial countries. In fact, only some rare tumor types with a very strong association with certain exogenous factors, such as pleural malignant mesothelioma with asbestos exposure, liver angiosarcoma with vinyl chloride exposure, and intestinal type sinonasal adenocarcinoma with hardwood exposure, are considered as occupational diseases on a regular basis. These tumors are accepted as work-related because they rarely exist in the non-exposed, while occupational etiology of common cancers is more difficult to recognize. The best example is asbestos-related lung cancer: On the basis of epidemiology the numbers can be estimated, but much fewer cases than expected are identified and reported, although there are some differences between countries. For most common cancer types the fraction attributable to occupational factors is small and risk ratios low, but together with life-style and genetic factors, they may significantly increase an individual's personal cancer risk. Awareness of occupational and other risk factors offers an opportunity for preventive actions, such as encouragement for the cessation of smoking in order to reduce lung cancer risk and caution with hormone replacement therapy to lessen a person's breast cancer risk. The most important consequence of the identification of occupational causes of cancer, however, remains with the opportunity to eliminate the relevant exposures – or at least reduce them to a level entailing no risk.

The aim is to provide a handbook which occupational health physicians, oncologists and other medical specialists who diagnose and treat cancer patients, and those who are involved in the health care of individuals with cancer risk due to occupational exposures, could consult on occupational risk factors that may be relevant for their patients. To our knowledge, this is the first present-day book where all information about occupational risk factors of cancer can be easily found, organized by cancer sites, in order to help health professional to judge whether the question of increased cancer risk or occupational etiology of cancer is relevant in the case of a specific patient. During the years we have been involved in the research and diagnosis of occupational cancer, we have sometimes been asked by occupational health care specialists if we can recommend such a book. This book is intended also to people who are involved in worker insurance, compensation, and registries of occupational diseases, as well as to graduate and postgraduate students in occupational health and oncology.

The main part of the book consists of organ-specific chapters which provide epidemiological data on risk of the cancer in question with various occupations and with exposure to specific carcinogens, and touch other environmental and life-style risk factors. Exposure assessment, clinical and pathological findings, molecular mechanisms, biomarkers, and susceptibility factors are handled if relevant literature for the occupational cancer of the organ in question is available. As regards malignant mesothelioma and lung cancer, which represent in most populations the two most important occupation-related cancers, separate chapters are dedicated for epidemiology, clinical findings, exposure-assessment, molecular mechanisms, molecular markers, and genetic susceptibility. A few specific topics, such as occupational cancer in the past, occupational cancer burden, prevention strategies, screening for occupational cancer, occupationally derived cancer in children, and use of registries in cancer research, are handled in their own chapters. We appreciate that so many researchers felt the book on

occupational cancer so important that they were willing to dedicate their time in contributing to it, and can say that every chapter is written by well-known scientists in the field.

There is increasing amount of scientific literature about molecular mechanisms and biomarkers of cancer associated with specific carcinogenic agents. It is sometimes challenging to a person whose own field is other than molecular research, to become acquainted with the newest results. Chapters 2 and 3 introduce the basic carcinogenic mechanisms and the research on gene-environment interactions to expert and non-expert readers. Although our understanding of the molecular mechanisms of occupation-related cancer is continuously increasing, it is still premature in most instances to use this information to assess the likelihood of causation at the level of the individual patient.

The authors of each chapter were advised to review the scientific literature, and not to include jurisdiction or compensation policy, as there are remarkable differences between countries in legal systems and agreements regarding worker compensation for occupational diseases.

It is known that the scientific community is divided concerning some issues where study designs are difficult to set or results are discrepant, for example the carcinogenic potency of crystalline silica and chrysotile (white) asbestos, are disputable questions. We encouraged the authors of each chapter to present a balanced view, but did not try to influence their conclusions. In this respect, the responsibility of the contents of individual chapters remains with their authors. It is possible however that the authors' personal opinion affected which literature they cited. We tried to solve this issue by addressing some of the controversial issues in more than one chapter; for a balanced view the readers are advised to consult other chapters on the same carcinogen, and especially the epidemiology chapters, which list all relevant studies on the carcinogen in question.

We sincerely hope that this book serves well and earns its place in the hands and on the screen of all those who diagnose and treat cancer patients, are involved in occupational health care, or for any other reason are interested in occupational factors of cancer.

Helsinki, Finland — Sisko Anttila
New York, NY, USA — Paolo Boffetta

Acknowledgements

Several people and institutions have helped us in this book project. When the first outline for the contents of the book was done, Dr. Antti Tossavainen reviewed the proposal, gave valuable information, and suggested co-editors. Dr. Kurt Straif's enthusiasm towards this project has been invaluable. He worked with us during most part of the project, pointed out and invited authors, and reviewed many of the chapters. He has remarkably influenced the contents of this book. Dr. Aija Knuuttila and Dr. Agnes Kane offered their expertise in reviewing selected chapters. We are deeply indebted to all authors for putting beside their other works and using their time and expert knowledge in writing different chapters. We thank the Finnish Institute for Occupational Health (FIOH) for offering a net site for the project, Mrs. Alice Lehtinen at FIOH checked the English language for Chaps. 10, 12, and 16, and finally, FIOH and Dr. Panu Oksa provided the questionnaire for asbestos exposure assessment included in the Appendix. Our writing and editorial work was financially supported by the research funds of the Helsinki and Uusimaa Hospital District, Helsinki, Finland (SA) and by Ichan School of Medicine at Mount Sinai, New York, NY, USA (PB). Finally, we thank the developmental editor Joni Fraser, who patiently and knowledgeably worked with us through the many years of this project, and the Springer editors Manika Power, Teresa Dudley, and Joanna Bolesworth.

Contents

Contributors

Behnoush Abedi-Ardekani, MD Molecular Carcinogenesis Group, International Agency for Research on Cancer, Lyon, France

Naveed Z. Alam, MD, FRCSC, FRACS Division of Cardiothoracic Surgery, St. Vincent's Hospital, Melbourne, Melbourne, VIC, Australia

Sisko Anttila, MD, PhD Jorvi Hospital Laboratory of Pathology, Helsinki University Central Hospital, Hospital District of Helsinki and Uusimaa, Laboratory Services, HUSLAB, Helsinki, Finland

Health and Work ability, Finnish Institute of Occupational Health, Helsinki, Finland

Richard L. Attanoos, BSc, MBBS Department of Cellular Pathology, University Hospital Llandough, Cardiff, UK

Anssi Auvinen, MD, PhD Department of Epidemiology, University of Tampere, Tampere, Finland

Parveen Bhatti, BS, MS, PhD Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Paolo Boffetta, MD, MPH Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Jette Bornholdt, PhD Department of Biology, The Bioinformatics Centre, University of Copenhagen, Copenhagen, Denmark

Matthieu Carton, MD UMS 011, Population-based Epidemiologic Cohorts Unit, Inserm – Versailles St-Quentin University, Villejuif, France

Yingtai Chen, MD, PhD Department of Abdominal Tumours Surgery, Center of Pancreatic Tumours, Tumour Hospital, Chinese Academy of Medical Sciences, Beijing, China

Emanuela Ciliberto, DVM, PhD Unit of Cancer Epidemiology – Department of Medical Sciences, University of Turin, Turin, Italy

Anneclaire J. De Roos, PhD, MPH Department of Occupational and Environmental Health, School of Public Health, Drexel University, Philadelphia, PA, USA

Raja M. Flores, MD Department of Thoracic Surgery, Mount Sinai Medical Center, New York, NY, USA

Montserrat Garcia-Closas, MD, DrPH Division of Genetics and Epidemiology, Institute of Cancer Research, Sutton, UK

Mark S. Goldberg, MSc, PhD Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, QC, Canada

Doriane A. Gouas, MS Molecular Carcinogenesis Group, International Agency for Research on Cancer, Lyon, France

Tom K. Grimsrud, MD, PhD Department of Research, Cancer Registry of Norway, Oslo, Norway

Per Gustavsson, MD, PhD Unit of Occupational Medicine, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Pierre Hainaut, PhD Molecular Carcinogenesis Group, International Agency for Research on Cancer, Lyon, France

Johnni Hansen, PhD Research Center, Danish Cancer Society, Copenhagen, Denmark

Ari P. Hirvonen, PhD Finnish Institute of Occupational Health, Helsinki, Finland

Reetta Holmila, PhD Section of Molecular Carcinogenesis, International Agency for Research on Cancer, Lyon, France

Kirsti Husgafvel-Pursiainen, PhD Health and Work Ability, Systems Toxicology, Finnish Institute of Occupational Health, Helsinki, Finland

Sally J. Hutchings, BSc Epidemiology and Biostatistics, Imperial College London, London, UK

Peter D. Inskip, ScD Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Marie-Claude Jaurand, DrSc, PhD UMR-S674, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France

Didier Jean, PhD INSERM UMR-S 674, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France

Agnes B. Kane, MD, PhD Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, USA

Sara Karami, MPH, PhD Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA

Karl T. Kelsey, MD, MOH Department of Epidemiology, Department of Pathology and Laboratory Medicine, Center for Environmental Health and Technology, Brown University, Providence, RI, USA

Eeva Kettunen, PhD Health and Work Ability, Finnish Institute of Occupational Health, Helsinki, Finland

Sakari Knuutila, PhD Department of Pathology and Genetics, HUSLAB, Helsinki University Central Hospital, Helsinki, Finland

Manolis Kogevinas, MD, PhD Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

France Labrèche, MSc, PhD Research and Expertise Division, Institut de recherche Robert-Sauvé en santé et en sécurité du travail, Montreal, QC, Canada

Département de Santé environnementale et santé au travail, École de santé publique, Université de Montréal, Montreal, QC, Canada

Philip J. Landrigan, MD, MSc Department of Preventive Medicine, Mount Sinai School of Medicine, New York, NY, USA

Scott M. Langevin, PhD Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Danièle Luce, PhD Inserm UMR 1085 – Irset, Inserm (French National Institute of Health and Medical Research), Pointe-à-Pitre, Guadeloupe, French West Indies

Mana Mann, MD, MPH Department of Preventive Medicine, Mount Sinai School of Medicine, New York, NY, USA

Franco Merletti, MD Unit of Cancer Epidemiology – Department of Medical Sciences, University of Turin, Turin, Italy

Dario Mirabelli, MD Unit of Cancer Epidemiology – Department of Medical Sciences, University of Turin, Turin, Italy

Lee E. Moore, PhD, MPH Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA

Rosemary L. Nixon, BSc, MBBS, MPH, FACD, FAFOEM Occupational Dermatology Education and Research Centre, Skin and Cancer Foundation, Inc, Melbourne, Australia

André Nogueira da Costa, PhD Molecular Carcinogenesis Group, International Agency for Research on Cancer, Lyon, France

Penny E. H. Nymark, PhD New Technologies and Risks, Finnish Institute of Occupational Health, Helsinki, Finland

Elizabeth N. Pavlisko, MD Department of Pathology, Duke University Medical Center, Durham, NC, USA

Lorenzo Richiardi, MD, PhD Cancer Epidemiology Unit, CPO-Piemonte and University of Turin, Torino, Italy

Victor L. Roggli, MD Department of Pathology, Duke University Medical Center, Durham, NC, USA

Lesley Rushton, PhD, MSc, BA Epidemiology and Biostatistics, Imperial College London, London, UK

Vivi Schlünssen, MD, PhD Department of Public Health, Section for Environmental and Occupational Medicine, Aarhus University, Aarhus, Denmark

Paul A. Schulte, PhD Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Jack Siemiatycki, PhD Social and Preventive Medicine, University of Montreal, Montreal, Canada

Malcolm R. Sim, BMedSc, MBBS, MSc, PhD, FAFOEM Centre for Occupational & Environmental Health, Monash University, Melbourne, Australia

Patricia A. Stewart, PhD Stewart Exposure Assessments, LLC, Arlington, VA, USA

Kurt Straif, MD, PhD IARC Monographs Section, International Agency for Research on Cancer, Lyon, France

Stephanie S. H. Tan, MBBS Occupational Dermatology Education and Research Centre, Skin and Cancer Foundation, Inc, Melbourne, VIC, Australia

Simone L. Tramma, MD, MS Surveillance Branch, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, WV, USA

Douglas B. Trout, MD, MHS Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Chenfeng Wang, MD Department of Abdominal Tumours Surgery, Center of Pancreatic Tumours, Tumour Hospital, Chinese Academy of Medical Sciences, Beijing, China

Elisabete Weiderpass, MD, MSc, PhD Cancer Registry of Norway, Oslo, Norway

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway

Department of Genetic Epidemiology, Folkhälsan Research Center, Helsinki, Finland

C. Henrik J. Wolff, MD Health and Work Ability, Systems Toxicology/Pathology, Finnish Institute of Occupational Health, Helsinki, Finland

Victor Wünsch Filho, MD, PhD Department of Epidemiology, University of São Paulo School of Public Health, São Paulo, Brazil

Yawei Zhang, MD, PhD, MPH Department of Epidemiology and Public Health, Yale University, New Haven, CT, USA

Luisa Zuccolo, MSc, PhD School of Social and Community Medicine, University of Bristol, Bristol, UK

Historical Overview of Occupational Cancer Research

1

Jack Siemiatycki

Keywords
Occupational cancer • Occupational carcinogens • History • Listing carcinogens • Discovering carcinogens

Occupational carcinogens occupy a special place among the different classes of modifiable risk factors for cancer. The occupational environment has been a most fruitful one for investigating the pathogenesis of human cancer. Indeed, nearly half of all recognized human carcinogens are occupational carcinogens. Although it is important to discover occupational carcinogens for the sake of preventing occupational cancer, the potential benefit of such discoveries goes beyond the factory walls since most occupational exposures find their way into the general environment, sometimes at higher concentrations than in the workplace and, for some agents, with more people exposed in the general environment than in the workplace.

Early Discoveries

In 1775, Sir Percivall Pott, one of the leading British surgeons of the day, described some cases of cancer of the scrotum among English chimney sweeps. He ascribed this condition, which was known in the trade as "soot wart," to the chimney sweeps' pitifully dirty working conditions and to the "lodgment of soot in the rugae of scrotum" [1]. In the ensuing century, the syndrome became widely known, but it remained the only recognized occupationally caused cancer until the latter part of the nineteenth century. In 1875, Volkmann described a syndrome identical to "chimney sweeps cancer" of the scrotum among a group of coal tar and paraffin workers [2]. Apparent clusters of scrotal cancer were thereafter reported among shale oil workers [3] and mule spinners in the cotton textile industry [4, 5]. By 1907 the belief in the carcinogenicity of "pitch, tar, and tarry substances" was widespread enough that skin cancers among exposed workers were officially recognized as compensable in the UK. Other types of cancer were also implicated as occupationally induced. In the late nineteenth century, following several centuries of informal observations of unusually high incidence of lung tumors in residents of Joachimsthal, Czechoslovakia, and Schneeberg, Germany, it was shown that these risks were related to work in local metal mines [6–8]. At about the same time, Rehn [9] reported a striking cluster of bladder cancer cases among workers from a German plant which produced dyestuffs from coal tar.

Following the accumulation of several of these clinical case reports of high-risk occupations, the scientific investigation of cancer etiology began in earnest at the beginning of the twentieth century with experimental animal research. A major breakthrough came with the experiments of Yamagiwa and Ichikawa [10], in which they succeeded in inducing skin tumors in rabbit ears by applying coal tar. Several important experimental discoveries were made in the next 20 years, particularly by an English group led by Kennaway. In a series of experiments, they managed to isolate dibenz(a,h)anthracene and benzo(a)pyrene, both polycyclic aromatic hydrocarbons (PAHs) and active ingredients in coal tar [11–13]. These compounds may have been responsible for many of the excess risks of scrotal cancer in various groups exposed to soot and oils [14]. Several other PAHs were subsequently shown to be carcinogenic to laboratory animals, but so were substances of many other chemical families. For instance, 2-naphthylamine was shown to cause

J. Siemiatycki, PhD
Social and Preventive Medicine, University of Montreal,
850 St.-Denis St., Montreal, QC H2X OA9, Canada
e-mail: j.siemiatycki@umontreal.ca

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_1, © Springer-Verlag London 2014

bladder tumors in dogs, and this was thought to explain the bladder cancers seen earlier among dyestuffs workers.

During the first half of the twentieth century, there were additional reports of high-risk occupation groups. Respiratory cancer risks were reported in such diverse occupational settings as nickel refineries [15], coal carbonization processes [16], chromate manufacture [17], manufacture of sheep-dip containing inorganic arsenicals [18], and asbestos products manufacture [19]. This occurred before the smoking-induced epidemic of lung cancer was at its peak, when the background risks of lung cancer were low.

The era of modern cancer epidemiology began around 1950 with several studies of smoking and lung cancer. In the field of occupational cancer epidemiology, this era saw the conduct of some important studies of gas workers [20], asbestos workers [21], and workers producing dyestuffs in the chemical industry [22]. The findings of these early studies were important in highlighting significant workplace hazards, and the methods that these pioneering investigators developed for studying occupational cohorts have strongly influenced the conduct of occupational cancer research.

Subsequently, and especially with the flowering of "environmentalism" in the 1960s as a component of social consciousness, there was a sharp increase in the amount of research aimed at investigating links between the environment and cancer. Particular attention was paid to the occupational environment for several reasons. Most of the historic observations of environmental cancer risks were discovered in occupationally exposed populations. As difficult as it is to characterize and study groups of workers, it is much harder to study groups of people who share other characteristics, such as diet or general environmental pollution. Not only are working populations easier to delineate but, often, company personnel and industrial hygiene records permit some, albeit crude, form of quantification of individual workers' exposure to workplace substances. Also, the pressure of organized labor was an important force in attracting attention to the workplace. Finally, the workplace is a setting where people have been exposed to high levels of many substances which could potentially be harmful. Nonetheless, since many occupational exposures can also occur in the general environment, the cancer risks borne by workers have implications well beyond the workplace.

The burst of epidemiologic research on cancer and environment was accompanied by extensive experimental work aimed at testing the carcinogenic potential of different substances. Whereas this was carried out in an uncoordinated fashion in the early years, national bodies, most notably the National Toxicology Program in the USA, have implemented systematic strategies to test large numbers of substances with standardized state-of-the-art long-term animal studies [23].

How Evidence Has Been Accumulated on Selected Associations

Table 1.1 shows the evolution of evidence regarding ten recognized occupational risk factors [56]. For each association, the table indicates when the first suspicions were published and some of the significant pieces of evidence that came into play subsequently. The tables also give some synthetic information about the nature of the epidemiologic findings. Typically, the association was first suspected on the basis of a clinical observation, which was followed up by suggestive but inconclusive cohort studies and then by more rigorous and more persuasive cohort studies.

For most recognized carcinogens, the interval between the first clinical report and the general acceptance of the association was measured in decades. The length of the interval was great in the early period, in part because of the lack of expertise in epidemiologic research and resources to conduct such studies. For three more recent "discoveries," those relating asbestos to mesothelioma, vinyl chloride to angiosarcoma of the liver, and chloroethers to lung cancer, the interval between the first publication of a suspicious cluster and the general acceptance of a causal association was only a matter of a few years. As a rule, early reports tended to manifest higher relative risk estimates than more recent reports. This is likely due to several reasons, including the greater likelihood that outlier results will get noticed and reported and real improvements in the industrial hygiene conditions that have indeed had the effect of decreasing risks of cancer.

While it is instructive to study the history of the evolution of knowledge for recognized carcinogens, it is just as useful to understand that the trajectories of suspicion and recognition are not necessarily monotonic. That is, there are also examples of associations that have been considered possible or likely in the past that are now considered as unlikely. One such example concerns the risk of prostate cancer following exposure to cadmium. Early studies hinted at an association [57–60], but more recent and stronger studies have tended to refute the hypothesis [61–63]. For the possible association between man-made mineral fibers (MMMF) and lung cancer, the impetus and suspicion came from the similarity in physical characteristics between MMMF and asbestos. But large American and European cohort studies have failed to demonstrate an excess risk [64–66]. Still, the absolute exposure levels to MMMF have been so much lower than they have been to asbestos, that it may justly be asked whether the differential evidence of lung carcinogenicity between asbestos and MMMF is likely due to exposure levels rather than to inherent carcinogenic properties of the two classes of fibers. A third example is that of ethylene oxide and leukemia. There were reports

Table 1.1 Selected milestone publications illustrating the development of information in humans on selected well-established occupational cancers

Material/cancer	Reference	Location	Study population	Study type	Evidence of effect
Radon/lung	Härting and Hesse [6]	Germany	Miners	Case series	Moderate
	Peller [8]	Czechoslovakia	Miners	Cohort	Moderate
	Archer et al. [24]	USA	Uranium miners	Cohort	Strong
	Archer et al. [25]	USA	Uranium miners	Cohort	Strong
	Howe et al. [26]	Canada	Uranium miners	Cohort	Strong
Benzidine/bladder	Rehn [9]	Germany	Dye workers	Case series	Weak
	Scott [27]	England	Dye workers	Case series	Moderate
	Case et al. [22]	Great Britain	Dye workers	PMR	Strong
	Meigs et al. [28]	Connecticut	Benzidine makers	Cohort	Strong
Nickel and nickel					
Compounds/nasal	Annual Report [29]	Wales	Nickel refineries	Case series	Moderate
	Doll [30]	Wales	Nickel refineries	PMR	Strong
	Kaldor et al. [31]	Wales	Nickel refineries	Cohort	Strong
Arsenic/ respiratory	Henry [32]	England	Sheep-dip makers	Case series	Weak
	Hill and Faning [18]	England	Arsenical packers	PMR	Moderate
	Lee and Fraumeni [33]	Montana	Smelter workers	Cohort	Strong
	Lee-Feldstein [34]	Montana	Smelter workers	Cohort	Strong
	Pinto et al. [35]	Washington	Smelter workers (urine index)	Cohort	Strong
	Enterline et al. [36]	Washington	Smelter workers (air index)	Cohort	Strong
Asbestos/lung	Lynch and Smith [37]	South Carolina	Asbestos textile workers	Single case	Weak
	Doll [21]	England	Asbestos workers	Cohort	Weak
	Selikoff et al. [38]	USA	Insulation workers	Cohort	Moderate
	McDonald et al. [39]	Canada	Chrysotile miners	Cohort	Strong
	Dement et al. [40]	USA	Asbestos textile workers	Cohort	Strong
	Seidman et al. [41]	USA	Amosite workers	Cohort	Strong
Benzene/leukemia	Mallory et al. [42]	UK	Various occupations	Case series	Weak
	Vigliani and Saita [43]	Italy	Various occupations	Case series	Weak
	Ishimaru et al. [44]	Japan	Various occupations	Case series	Moderate
	Aksoy et al. [45]	Turkey	Shoemakers	Case series	Moderate
	Infante et al. [46]	Ohio	Pliofilm makers	Cohort	Moderate
	Rinsky et al. [47]	Ohio	Pliofilm makers	Cohort	Strong
	Yin et al. [48]	China	Benzene producers	Cohort	Strong
Chloroethers/lung	Figueroa et al. [49]	Philadelphia	Chemical workers	Case series	Moderate
	DeFonso and Kelton [50]	Philadelphia	Chemical workers	Cohort	Moderate
	McCallum et al. [51]	UK	Chloroether makers	Cohort	Strong
Vinyl chloride/ liver angiosarcoma	Creech and Johnson [52]	Kentucky	PVC makers	Case series	Weak
	Monson et al. [53]	Kentucky	PVC makers	PMR	Strong
	Waxweiler et al. [54]	USA	PVC makers	Cohort	Strong
	Fox and Collier [55]	Great Britain	PVC makers	Cohort	Moderate

From Siemiatycki et al. [56]. By permission of Oxford University Press, USA

from Sweden among producers and some users of ethylene oxide that hinted at excess risks of leukemia [67, 68]. But larger American studies have subsequently shown no such risk [69, 70]. A fourth example is that concerning acrylonitrile and lung cancer. Some American and British studies published in the early 1980s indicated possible excess risks [71–73]. But a series of large studies from Europe and the USA subsequently failed to demonstrate any risk of lung cancer. Finally, suspicions have been voiced for a long time about the possible association between formaldehyde and lung cancer. But a series of large studies have failed to demonstrate such an effect [74–78].

It is certainly clear that reports of case clusters or suspicions based on experimental findings or individual epidemiologic studies are not sufficient to predict the ultimate judgment regarding an association. Since random chance and error, supplemented by publication bias, will inevitably lead to the publication of some false-positive results, it is important to seek replication of findings.

Sources of Evidence on Risk to Humans Due to Chemicals

Direct evidence concerning carcinogenicity of a substance can come from epidemiologic studies among humans or from experimental studies of animals (usually rodents). Additional evidence comes from the results of studies of chemical structure-activity analysis, pharmacokinetics, mutagenicity, cytotoxicology, and other aspects of toxicology.

Epidemiology

Epidemiologic research provides the most relevant data for identifying occupational carcinogens and characterizing their effects in humans. It can also contribute to the understanding of the mechanism of action of occupational carcinogens. Such research requires the juxtaposition of information on illness or death due to cancer among workers and information on their past occupations, industries, and/or occupational conditions. A third, optional data set which would improve the validity of inferences drawn from that juxtaposition is the set of concomitant risk factors which may confound the association between occupation and disease.

Because of long induction periods for most cancers, current epidemiologic studies would not provide direct evidence on carcinogenic risk that might be caused by recently introduced industrial agents. Even for substances which have been with us for a long time, there are obstacles. Each human experiences, over his or her lifetime, an idiosyncratic and bewildering pattern of exposures. Not only is it impossible to completely and accurately characterize the lifetime exposure profile of an individual, but even if we could, it is a daunting statistical task to tease out the effects of a myriad of specific substances. The ascertainment of valid cancer diagnoses is also problematic since subjects are often traced via routine record sources (notably, death certificates), which may be error prone or in which cancers with long survival are poorly represented. Confounding by factors other than the one under investigation is of course an issue in occupational cancer epidemiology, as it is in other areas of epidemiology. But the problem is sometimes particularly acute in occupational epidemiology because of some highly correlated co-exposures in the occupational environment. The number of subjects available for epidemiologic study is often limited, and this compromises the statistical power to detect hazards. Despite these challenges, epidemiology has made significant contributions to our knowledge of occupational carcinogens.

Animal Experimentation

Partly in consequence of the difficulty of generating adequate data among humans and partly because of the benefits of the experimental approach, great efforts have been devoted to studying the effects of substances in controlled animal experiments. Results generated by animal studies do bear on carcinogenicity among humans. Certain fundamental genetic and cellular characteristics are similar among all mammalian species. Most recognized human carcinogens have been reported to be carcinogenic in one or more animal species; and there is some correlation between species in the target organs affected and in the carcinogenic potency [79–87].

Still, there are several reasons for caution in extrapolating from animal evidence to humans. The animal experiment is designed not to emulate the human experience but rather to maximize the sensitivity of the test to detect animal carcinogens. Doses administered are usually orders of magnitude higher than levels to which humans are exposed. The route of exposure is sometimes unrealistic (e.g., injection or implantation), and the controlled and limited pattern of co-exposures is unlike the human situation. The "lifestyle" of the experimental animal is not only different from that of humans, but it is unlike that of its species in the wild. Animals used are typically from pure genetic strains and susceptibility to carcinogens may be higher in such populations than in genetically heterogeneous human populations. Metabolism, immunology, DNA repair systems, life spans, and other physiologic characteristics differ between species. Tumors seen in animals often occur at sites that do not have a counterpart among humans (e.g., forestomach or Zymbal's glands) or that are much more rarely affected among humans (e.g., pituitary gland). The behavior of many tumors generated in experimental animals does not mimic that of malignant neoplasms in humans, and the malignant phenotype is sometimes unclear. Quantitative extrapolation of effects from rodents to humans depends on unverifiable mathematical assumptions concerning dose equivalents, dose-response curves, safety factors, etc. Different reasonable assumptions can lead to wildly divergent estimates. Some experimental carcinogens operate via mechanisms which may not be relevant to humans. A case in point is that of kidney tumors in male rats following exposure to various organic chemicals and mixtures including gasoline; these tumors are apparently caused by precipitation of α_2-microglobulin, a gender- and species-specific protein [88]. Gold et al. [89] have shown that even between two species as close on the phylogenetic scale as mice and rats, the predictive value of carcinogenicity is only in the range of 75 %.

Despite efforts to investigate the scientific basis for interspecies extrapolation and despite resources that have been

devoted to testing chemicals in animal systems, there remain serious disagreements about the predictive value of animal experimentation [23, 87, 90–97].

Short-Term Tests and Structure-Activity Relationships

To mitigate the lengthy and costly process of animal carcinogenesis testing, a number of rapid, inexpensive, and ingenious tests have been developed, to detect presumed correlates of or predictors of carcinogenicity [82, 98–101]. However, neither alone nor in combination have these approaches proven to be consistently predictive of animal carcinogenicity, much less human carcinogenicity [99, 102–104]. Their role is in screening chemicals for animal testing and in complementing the results of animal experiments.

Listing Occupational Carcinogens

Although it seems like a simple enough task, it is very difficult to draw up an unambiguous list of occupational carcinogens. The first source of ambiguity concerns the definition of an *occupational* carcinogen. Most occupational exposures are also found in the general environment and/or in consumer products; most general environmental exposures and consumer products, including medications, foods, and others, are found in some occupational environments. The distinctions can be quite arbitrary. For instance, while tobacco smoke, sunlight, and immunosuppressive medications are not primarily considered to be occupational exposures, there certainly are workers whose occupations bring them into contact with these agents. Also, while asbestos, benzene, and radon gas are considered to be occupational carcinogens, they are also found widely among the general population, and indeed it is likely that many more people are exposed to these substances outside than inside the occupational environment. There is no simple rule to earmark "occupational" carcinogens as opposed to "nonoccupational" ones. Further, some carcinogens are chemicals that are used for research purposes and to which few people would ever be exposed, whether occupationally or nonoccupationally.

A second source of ambiguity derives from the rather idiosyncratic nature of the evidence. In some instances, we know that an occupational or industrial group is at excess risk of cancer, and we have a good idea of the causative agent (e.g., scrotal cancer among chimney sweeps and PAHs in soot [14]; lung cancer among asbestos miners and asbestos fibers [63]). In some instances, we know that a group experienced excess risk, but the causative agent is unknown or at least unproven (e.g., lung cancer among painters [105]; bladder cancer among workers in the aluminum industry [105]). The strength of the evidence for an association can vary. For some associations, the evidence of excess risk seems incontrovertible (e.g., liver angiosarcoma and vinyl chloride monomer [105]; bladder cancer and benzidine [105]). For some associations, the evidence is suggestive (e.g., breast cancer and shift work [106]; bladder cancer and employment as a painter [105]). Among the many substances in the industrial environment for which there are no human data concerning carcinogenicity, there are hundreds that have been shown to be carcinogenic in some animal species and thousands that have been shown to have some effect in assays of mutagenicity or genotoxicity. These considerations complicate the attempt to devise a list of occupational carcinogens.

IARC Monographs

One of the key sources of information for listing occupational carcinogens is the Monograph Programme of the International Agency for Research on Cancer (IARC) – Evaluation of the Carcinogenic Risk of Chemicals to Humans. The objective of the IARC Programme, which has been operating since 1971, is to publish critical reviews of epidemiological and experimental data on carcinogenicity for chemicals, groups of chemicals, industrial processes, other complex mixtures, physical agents, and biological agents to which humans are known to be exposed and to evaluate the data in terms of human risk.

IARC evaluations are carried out during specially convened meetings that typically last a week. The meetings may evaluate only one agent, such as silica, they may address a set of related agents, or they may even address exposure circumstances such as an occupation or an industry. For each such meeting, and there have typically been three per year, IARC convenes an international working group, usually involving from 15 to 30 experts on the topic(s) being evaluated from four perspectives: (1) exposure and occurrence of the substances being evaluated, (2) human evidence of cancer risk (i.e., epidemiology), (3) animal carcinogenesis, and (4) other data relevant to the evaluation of carcinogenicity and its mechanisms. The working group is asked to review all of the literature relevant to an assessment of carcinogenicity. In the first part of the meeting, four subgroups (based on the four perspectives mentioned above) review and revise drafts prepared by members of the subgroup, and each subgroup develops a joint review and evaluation of the evidence on which they have focused. Subsequently, the entire working group convenes in plenary and proceeds to derive a joint text. They determine whether the epidemiological evidence

Table 1.2 Classifications used in the IARC monographs to characterize evidence of carcinogenicity

Category of evidence	In humans	In animals
Sufficient evidence of carcinogenicity	A causal relationship has been established between exposure to the agent, mixture, or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias, and confounding could be ruled out with reasonable confidence	A causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols
Limited evidence of carcinogenicity	A positive association has been observed between exposure to the agent, mixture, or exposure circumstance and cancer for which a causal interpretation is considered to be credible, but chance, bias, or confounding could not be ruled out with reasonable confidence	The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g., (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct, or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential or of certain neoplasms which may occur spontaneously in high incidences in certain strains
Inadequate evidence of carcinogenicity	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available	The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available
Evidence suggesting lack of carcinogenicity	There are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture, or exposure circumstance and any studied cancer at any observed level of exposure	Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent or mixture is not carcinogenic

From Siemiatycki et al. [56]. By permission of Oxford University Press, USA

supports the hypothesis that the substance causes cancer and, separately, whether the animal evidence supports the hypothesis that the substance causes cancer. The judgments are not simply dichotomous (yes/no), but rather they allow the working group to express a range of opinions on each of the dimensions evaluated. Table 1.2 shows the categories into which the working groups are asked to classify each substance, when examining only the epidemiological evidence and when examining only the animal experimental evidence [56]. The operational criteria for making these decisions leave room for interpretation, and the scientific evidence itself is open to interpretation. It is not surprising then that the evaluations are sometimes difficult and contentious.

The overall evaluation of human carcinogenicity is based on the epidemiological and animal evidence of carcinogenicity, plus any other relevant evidence on genotoxicity, mutagenicity, metabolism, mechanisms, or others. Epidemiological evidence, where it exists, is given greatest weight. Direct animal evidence of carcinogenicity is next in importance, with increasing attention paid to mechanistic evidence that can inform the relevance of the animal evidence for human risk assessment.

Table 1.3 shows the categories for the overall evaluation and how they are derived from human, animal, and other evidence [56]. Each substance is classified into one of the following classes (which IARC refers to as "groups": carcinogenic (Group 1), probably carcinogenic (Group 2A), possibly carcinogenic (Group 2B), not classifiable (Group 3), and probably not carcinogenic (Group 4). However, the algorithm implied by Table 1.3 is only indicative, and the working group may derive an overall evaluation that departs from the strict interpretation of the algorithm. For example, neutrons have been classified as human carcinogens (Group 1) despite the absence of epidemiological data, because of overwhelming experimental evidence and mechanistic considerations [108]. The IARC process relies on consensus, and this is usually achieved, but sometimes, differing opinions among experts lead to split decisions. In the end, the published evaluations reflect the views of at least a majority of participating experts. The results of IARC evaluations are published in readily available and user-friendly volumes, and summaries are published on a website [109].

There are some limitations to bear in mind. First, IARC does not provide any explicit indication as to whether the substance evaluated should be considered as an "occupational" exposure. Second, the evaluations are anchored in the time that the working group met and reviewed the evidence; it is possible that evidence that appeared after the IARC review could change the evaluation. Siemiatycki et al. [110] provided a consolidation of occupational carcinogens

Table 1.3 Classifications and guidelines used by IARC working groups in evaluating human carcinogenicity based on the synthesis of epidemiological, animal, and other evidence

Combinations which fit in this class				
Group	Description of group	Epidemiological evidence	Animal evidence	Other evidence
1	The agent, mixture, or exposure circumstance is carcinogenic to humans	Sufficient	Any	Any
		Less than sufficient	Sufficient	Strongly positive
2A	The agent, mixture, or exposure circumstance is probably carcinogenic to humans	Limited	Sufficient	Less than strongly positive
		Inadequate or not available	Sufficient	Strongly positive
2B	The agent, mixture, or exposure circumstance is possibly carcinogenic to humans	Limited	Less than sufficient	Any
		Inadequate or not available	Sufficient	Less than strongly positive
		Inadequate or not available	Limited	Strongly positive
3	The agent, mixture, or exposure circumstance is not classifiable as to its carcinogenicity to humans	Inadequate or not available	Limited	Less than strongly positive
		Not elsewhere classified		
4	The agent, mixture, or exposure circumstance is probably not carcinogenic to humans	Suggesting lack of carcinogenicity	Suggesting lack of carcinogenicity	Any
		Inadequate or not available	Suggesting lack of carcinogenicity	Strongly negative

This table shows our interpretation of the IARC guidelines used by the working groups to derive the overall evaluation from the combined epidemiological, animal, and other evidence. However, the working group can, under exceptional circumstances, depart from these guidelines in deriving the overall evaluation. For example, the overall evaluation can be downgraded if there is less than sufficient evidence in humans and strong evidence that the mechanism operating in animals is not relevant to humans. For details of the guidelines, refer to the Preamble of the IARC Monographs [107] From Siemiatycki et al. [56]. By permission of Oxford University Press, USA

identified by the IARC Monographs up to 2003, including identification of target organs. We use their operational definition of occupational agents. In 2008 and 2009, a series of IARC Monograph meetings were held to reevaluate evidence regarding agents that had previously been considered to be Group 1 carcinogens. The evidence of carcinogenicity was reevaluated, and where appropriate the target organs were identified.

Definite and Probable Occupational Risk Factors for Cancer

Table 1.4 shows a list of 32 agents which have been classified as Group 1 (i.e., definite) causes of cancer and which we consider to be occupational exposures. It shows the target organs at risk, and it shows the main occupations or industries in which the agents are found. The table also shows 11 occupations and industries which have been found to be at risk, but for which the responsible agent has not been identified.

Some of these carcinogens are naturally occurring substances or agents (e.g., asbestos, wood dust, solar radiation), while some are man-made (e.g., mineral oils, TCDD, vinyl chloride). Some are well-defined chemical compounds (e.g., benzene, trichloroethylene), while others are families of compounds which may include some carcinogens and some noncarcinogens (e.g., nickel compounds, acid mists, wood dust), while yet others are mixtures of varying chemical composition (e.g., diesel engine emissions, mineral oils).

Among the 11 high-risk occupations and industries shown in Table 1.3, most are industries in which the number of workers is quite small, in developed countries at least. But one occupation group, painters, stands out as an occupation group which is quite prevalent on a population basis, and for which the agent responsible for the excess risk has not been clearly identified. It may be reasonably speculated that aromatic amines such as benzidine and 2-nathphalymine may be responsible for some of the excess bladder cancer risk, but it is not obvious what the cause of lung cancer might be [111].

Table 1.5 shows a list of 27 occupational agents which have been classified as Group 2A (i.e., probable) causes of cancer. The table also shows 5 occupations and industries which have been found to be probably at risk, but for which a cause has not been identified, and another type of occupational circumstance – shift work. Some of these are agents for which there is a body of epidemiologic evidence, but that body of evidence does not permit a clear-cut determination of carcinogenicity (e.g., lead compounds, creosotes); but most agents in this table are definite animal carcinogens with little or no epidemiologic evidence to confirm or contradict the animal evidence. Most agents listed in Table 1.5 have fewer workers exposed than the agents in Table 1.4.

The Evolution of Knowledge

Table 1.6 shows how current occupational carcinogens were considered in two earlier times. The lists of agents in Tables 1.4 and 1.5 were compared with lists of carcinogens

Table 1.4 Occupational exposures, occupations, industries, and occupational circumstances classified as definite carcinogenic exposures (Group 1) by the *IARC Monographs*, Volumes 1–106

Agent, occupation, or industry	Target organ	Main industry or use
Chemical agents		
Acid mists, strong inorganic	Larynx	Chemical
4-Aminobiphenyl	Bladder	Rubber
Arsenic and inorganic arsenic compounds	Lung, skin, bladder	Glass, metals, pesticides
Asbestos (all forms)	Larynx, lung, mesothelium, ovary	Insulation, construction, renovation
Benzene	Leukemia	Starter and intermediate in chemical production, solvent
Benzidine	Bladder	Pigments
Benzo[*a*]pyrene	Lung, skin (suspected)	Coal liquefaction and gasification, coke production, coke ovens, coal tar distillation, roofing, paving, aluminum production
Beryllium and beryllium compounds	Lung	Aerospace, metals
Bis(chloromethyl)ether, chloromethyl methyl ether	Lung	Chemical
1,3-Butadiene	Leukemia and/or lymphoma	Plastics, rubber
Cadmium and cadmium compounds	Lung	Pigments, battery
Chromium (VI) compounds	Lung	Metal plating, pigments
Coal tar pitch	Lung, skin	Construction, electrodes
Engine exhaust, diesel	Lung	Transport, mining
Ethylene oxide	–	Chemical, sterilizing agent
Formaldehyde	Nasopharynx, leukemia	Plastic, textile
Ionizing radiation (including radon-222 progeny)	Thyroid leukemia, salivary gland, lung, bone, esophagus, stomach, colon, rectum, skin, breast, kidney, bladder, brain	Radiology, nuclear industry, underground mining
Leather dust	Nasal cavity	Shoe manufacture and repair
4,4′-Methylenebis(2-chloroaniline) (MOCA)	–	Rubber
Mineral oils, untreated or mildly treated	Skin	Lubricant
2-Naphthylamine	Bladder	Pigment
Nickel compounds	Nasal cavity, lung	Metal alloy
Shale oils	Skin	Lubricant, fuel
Silica dust, crystalline, in the form of quartz or cristobalite	Lung	Construction, mining
Solar radiation	Skin	Outdoor work
Soot	Lung, skin	Chimney sweeps, masons, firefighters
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD)	–	Chemical
Tobacco smoke, secondhand	Lung	Bars, restaurants, offices
ortho-Toluidine	Bladder	Pigments
Trichloroethylene	Kidney	Solvent, dry cleaning
Vinyl chloride	Liver	Plastics
Wood dust	Nasal cavity	Furniture
Occupation or industry without specification of the responsible agent		
Aluminum production	Lung, bladder	–
Auramine production	Bladder	–
Coal gasification	Lung	–
Coal tar distillation	Skin	–
Coke production	Lung	–
Hematite mining (underground)	Lung	–
Iron and steel founding	Lung	–
Isopropyl alcohol manufacture using strong acids	Nasal cavity	–
Magenta production	Bladder	–
Painter	Bladder, lung, mesothelium	–
Rubber manufacture	Stomach, lung, bladder, leukemia	–

Table 1.5 Occupational exposures, occupations, industries, and occupational circumstances classified as probable carcinogenic exposures (Group 2A) by the *IARC Monographs*, Volumes 1–106

Agent, occupation, or industry	Suspect target organ	Main industry or use
Chemical agents		
Acrylamide	–	Plastics
Bitumens (combustion products during roofing)	Lung	Roofing
Captafol	–	Pesticide
alpha-Chlorinated toluenes (benzal chloride, benzotrichloride, benzyl chloride) and benzoyl chloride (combined exposures)	–	Pigments, chemicals
4-Chloro-*ortho*-toluidine	Bladder	Pigments, textiles
Cobalt metal with tungsten carbide	Lung	Hard metal production
Creosotes	Skin	Wood
Diethyl sulfate	–	Chemical
Dimethylcarbamoyl chloride	–	Chemical
1,2-Dimethylhydrazine	–	Research
Dimethyl sulfate	–	Chemical
Epichlorohydrin	–	Plastics
Ethylene dibromide	–	Fumigant
Glycidol	–	Pharmaceutical industry
Indium phosphide	–	Semiconductors
Lead compounds, inorganic	Lung, stomach	Metals, pigments
Methyl methanesulfonate	–	Chemical
2-Nitrotoluene	–	Production of dyes
Non-arsenical insecticides	–	Agriculture
PAHs (several apart from BaP)	Lung, skin	Coal liquefaction and gasification, coke production, coke ovens, coal tar distillation, roofing, paving, aluminum production
Polychlorinated biphenyls	–	Electrical components
Styrene-7,8-oxide	–	Plastics
Tetrachloroethylene (perchloroethylene)	–	Solvent
1,2,3-Trichloropropane	–	Solvent
Tris(2,3-dibromopropyl) phosphate	–	Plastics, textiles
Vinyl bromide	–	Plastics, textiles
Vinyl fluoride	–	Chemical
Occupation or industry without specification of the responsible agent		
Art glass, glass containers, and pressed ware (manufacture of)	Lung, stomach	–
Carbon electrode manufacture	Lung	–
Food frying at high temperature	–	–
Hairdressers or barbers	Bladder, lung	–
Petroleum refining	–	–
Occupation circumstance without specification of the responsible agent		
Shift work involving circadian disruption	Breast	Nursing, several others

noted by a WHO expert panel in 1964 [112] and also with the list accrued by the IARC Monograph Programme in 1987 [113]. One third of today's Group 1 definite occupational carcinogens were already recognized as such by 1964. Two-thirds were considered to be definite or probable as of 1987. In contrast, none of today's Group 2A probable occupational carcinogens had even been mentioned as of 1964, and about one-third were mentioned as of 1987. While it is possible for the classification of agents to change over time in either direction, in practice there have been rather few instances of agents being "downgraded" between successive periods. Notable counterexamples are:

- 3,3 Dichlorobenzene, which was considered a definite carcinogen in 1964 and was only considered as possible as of 1987 and as of 2002
- Acrylonitrile and propylene oxide, which were considered probable carcinogens in 1987 and only as possible in 2002

The number of occupational agents rated by IARC as Group 1 carcinogens has tapered off since 1987, while the proportion of Group 2B evaluations increased. This reflects the fact that, when the Monograph Programme began, there was a "backlog" of agents for which strong evidence of carcinogenicity had accumulated, and, naturally, these were the

Table 1.6 How current IARC Group 1 ($n=32$) and Group 2A ($n=27$) occupational carcinogens (agents, not occupations or industries) were rated in 1964 and 1987

Past rating	Current Group 1	Current Group 2A
1964 WHO rating		
Well-documented carcinogen	9	0
Suspected carcinogen	1	0
Not mentioned	22	27
Total	32	27
1987 IARC rating		
Group 1	14	0
Group 2A	6	8
Group 2B	3	5
Group 3	1	0
Not rated	8	15
Total	32	27

agents that IARC initially selected for review. Once the agents with strong evidence had been dealt with, IARC started dealing with others.

Many of the recognized definite occupational carcinogens were already suspected or established by the 1960s. It may be that there were only a limited number of strong occupation-cancer associations, and these were sufficiently obvious that they could produce observable clusters of cases for astute clinicians to notice. It may be that levels of exposure to occupational chemicals were so high before the 1960s as to produce high cancer risks and cancer clusters, but that improvements in industrial hygiene in industrialized countries have indeed decreased risks to levels that are difficult to detect.

While the evaluation of the hypothesis of an agent causing human cancer depends critically on epidemiological and experimental evidence, the initial suspicion can be provoked by epidemiological surveillance, by experimental evidence, or by clinical cluster observations. Indeed, most definite occupational carcinogens were first suspected on the basis of case reports by clinicians or pathologists [114]. These discoveries were usually coincidental [115]. It is thus reasonable to suspect that there may be some, perhaps many, as yet undiscovered occupational carcinogens.

Interpreting the Lists

The determination that a substance or circumstance is carcinogenic depends on the strength of evidence at a given point in time. The evidence is sometimes clear-cut, but more often it is not. The balance of evidence can change in either direction as new data emerge.

The characterization of an occupation or industry group as a "high-risk group" is strongly rooted in time and place. For instance, the fact that some groups of nickel refinery workers experienced excess risks of nasal cancer does not imply that all workers in all nickel refineries will be subject to such risks. The particular circumstances of the industrial process, raw materials, impurities, and control measures may produce risk in one nickel refinery but not in another or in one historic era but not in another. The same can be said of rubber production facilities, aluminum refineries, and other industries and occupations. Labeling a chemical substance as a carcinogen in humans is a more timeless statement than labeling an occupation or industry as a high-risk group. However, even such a statement requires qualification. Different carcinogens produce different levels of risk, and for a given carcinogen, there may be vast differences in the risks incurred by different people exposed under different circumstances. Indeed there may also be interactions with other factors, environmental or genetic, that produce no risk for some exposed workers and high risk for others.

This raises the issue of quantitative risk assessment, which is an important tool in prevention of occupational cancer. While it would be valuable to have such information, for many agents, the information base on dose-response to support such quantification is fragmentary.

Illustrative Examples and Controversies

In this section, we present a few examples to illustrate some of the difficulties inherent in research to evaluate occupational carcinogens.

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs comprise a large family of chemical compounds which are produced during incomplete combustion of organic material and in particular fossil fuels. PAHs are found in many occupations and industries, and they are found in such non-occupational settings as vehicle roadways, homes heated by burning fuel, barbequed foods, cigarette smoke, and many more.

As described above, the earliest known occupational carcinogens were coal-derived soots, oils, and fumes that caused skin cancers. Animal experiments showed that several of the chemicals found in these complex mixtures were carcinogenic. These chemicals were in the family of polycyclic aromatic hydrocarbons. When epidemiologic evidence accumulated on lung cancer risks among workers exposed to complex mixtures derived from coal, petroleum, and wood, it was widely felt that the responsible agents were likely to be PAHs. Several of the complex mixtures (coal tars and pitch, mineral oils, shale oils, soots) which are classified as IARC Group 1 carcinogens include PAHs, and several of the

industries in which cancer risks have been identified (coal gasification, coke production, aluminum production, iron and steel founding) are industries in which PAHs are prevalent. Paradoxically, however, there is only one specific PAH on the Group 1 list – benzo(a)pyrene. Some others are classed in Group 2A. This is because it is virtually impossible to epidemiologically isolate the effect of one versus another of the components of these carcinogenic mixtures. Because of the non-feasibility of measuring all PAHs when they are measured for industrial hygiene purposes, benzo(a) pyrene has typically been considered a representative marker of PAHs. While this marker may be available for epidemiologic purposes, it cannot be assumed that this is the only PAH present or how its presence is correlated with those of other PAHs. Similar considerations apply to urinary 1-OH-pyrene, the most widely used biomarker of internal PAH dose, whose excretion depends on the composition of the mixture of PAH and on metabolic pathways under the control of polymorphic genes. It is possible that biomarker and genetic studies will provide the additional information that would permit the determination that specific PAHs are definite human carcinogens.

Diesel and Gasoline Engine Emissions

Engine emissions are common in many workplaces and are ubiquitous environmental pollutants. Based in part on experimental evidence and in part on epidemiologic evidence, there has long been suspicion that emissions from diesel-powered engines may be lung carcinogens; but, until recently, the epidemiologic evidence was considered inconclusive [116–118]. The difficulty of drawing inferences regarding the effect of diesel exhaust was in part due to some methodological limitations and in part due to the indirect nature of the evidence. Namely, most of the studies had used certain job titles (most often, truck driver) as proxies for occupational exposure to diesel exhaust. Few studies were able to control for the potential confounding effect of cigarette smoking and of other occupational exposures. Many of the studies had low statistical power and/or insufficient follow-up time. Finally, the relative risk estimates in most studies ranged from 1.0 to 1.5, making it difficult to exclude the possibility of chance or bias. The number of diesel-powered vehicles is increasing in many countries. Because of the significant scientific and public policy implications [119, 120], it is important to derive more definitive inferences regarding the potential human carcinogenicity of diesel emissions. Recently some studies of diesel-exposed mine workers and railroad workers have provided more definitive evidence that the associations previously observed are probably true [121–124], and IARC classified diesel engine emissions as a human carcinogen [125].

There is less evidence, both experimental and epidemiologic, for a carcinogenic effect of exposure to gasoline engine emission than to diesel emission.

Engine emission provides an example of a common dilemma in occupational and environmental cancer risk assessment. A chemical analysis of both gasoline and diesel exhaust shows the presence of many substances which are considered carcinogenic, notably some nitro-PAHs which are classed by IARC as 2A and 2B. Should the presence of a carcinogen within a complex mixture automatically trigger a labeling of the mixture as carcinogenic, irrespective of the epidemiologic evidence on the mixture? There is no wide consensus on this issue, but it has important consequences. For instance, it would have meant that both diesel and gasoline engine emissions would have been classified long ago as probable or definite human carcinogens.

Asbestos

Few health issues have sparked as much public concern, controversy, and expense as has asbestos-related cancer risk. Asbestos is a term describing a family of naturally occurring fibrous silicates which have varied chemical and physical compositions and which have been widely used in industrial and consumer products for over a century. The main fiber types are called chrysotile and amphibole. Exposure to asbestos fibers has occurred in many occupations, including mining and milling, manufacture of asbestos-containing products, and the use of these products. Currently, in developed countries, construction and maintenance workers constitute the largest group of asbestos-exposed workers, resulting from application and removal of asbestos products and building demolition. Asbestos was one of the most ubiquitous workplace exposures in the twentieth century.

Case reports linking asbestos with lung cancer started to appear in the 1930s and 1940s [37], but the first formal investigations were published in the 1950s and 1960s [21, 126]. In the early 1960s, reports appeared linking asbestos exposure to a hitherto unrecognized tumor of the pleura and peritoneum called mesothelioma [127]. By the mid-1960s, it was clear that the very high and virtually uncontrolled exposure conditions prevalent up to then could induce lung cancer and mesothelioma.

While asbestos production and use have declined dramatically in most industrialized countries since 1975, public concern and controversy have not [128–134]. Asbestos fibers are highly persistent and widespread in the environment, partly because of its widespread industrial use in the past and partly because it is a natural geological component of outcroppings in many areas of the world. Measurements carried out in all kinds of nonoccupational settings have detected asbestos fibers, and it has become clear that asbestos is a

widespread environmental pollutant, albeit at much lower levels than in some workplaces. Also, because of long latency periods, we are still seeing the cancer impact of high occupational exposure levels experienced 30–50 years ago, and we will for some time to come. Since exposure levels are much lower than they used to be, it is of interest to determine the risk due to low levels of asbestos exposure. Risk assessment models have been developed to extrapolate from high to low exposure levels, but these models have not been validated [135].

Many countries have banned use of asbestos, while some others have instituted regulatory limits orders of magnitude below levels that had been known to produce harmful effects. The availability of alternative non-asbestos substitution products makes such strategies feasible. Perhaps because they are not carcinogenic or perhaps because exposure levels to the substitution products are much lower than that experienced by asbestos-exposed workers in the past, there has been no demonstrated cancer risk related to the substitution products.

While asbestos use has declined in developed countries, its use has been increasing in some developing countries.

Cadmium and Cadmium Compounds

Cadmium has been produced and used in alloys and various compounds for several end products including batteries, pigments, electroplating, and some plastics [63]. Exposure varies widely between industries in both types of cadmium compounds and level of exposure. Following reports in a few small cohorts of excess cases of prostate cancer among workers in battery plants, an early IARC working group concluded that there was moderately persuasive evidence of an excess risk of prostate cancer as a result of cadmium exposure [136, 137]. They noted in passing that one of the cohorts also reported an excess of lung cancer. In the following decade, a number of additional cohort studies were undertaken in cadmium-exposed workers [138]. There was no additional evidence of an increase in prostate cancer risk. But the evidence on lung cancer, which was unremarkable in the first few studies, became much more pronounced as additional data were accumulated. By 1993, another IARC working group pronounced cadmium a Group 1 carcinogen but solely on the basis of its association with lung cancer. Still, the assessment of carcinogenicity of cadmium highlighted several methodological problems. The number of long-term, highly exposed workers was small, the historical data on exposure to cadmium was limited, and the ability to define and examine a gradient of exposure was limited to one study. Confounding by cigarette smoking in relation to lung cancer was difficult to address. Control of the confounding effect of co-exposure to other metals, particularly arsenic and nickel, was limited and remains somewhat problematic.

Styrene

Styrene is one of the most important industrial chemicals. The major uses are in plastics, latex paints and coatings, synthetic rubbers, polyesters, and styrene-alkyd coatings [139]. These products are used in construction, packaging, boats, automotive (tires and body parts), and household goods (e.g., carpet backing). Nearly 18 million tons were used worldwide in 1998. It has been estimated that as many as one million workers in the USA may be exposed to styrene, and the numbers worldwide would be much greater. In addition, there is widespread low-level environmental exposure.

The first evidence of a possible cancer risk came from case reports of leukemia and lymphoma among workers in various styrene-related industries [140–142]. A number of cohort studies have been carried out since then in Europe and the USA in various industries [143–147]. The interpretation of these studies has been bedeviled by four main problems: the different types of industries in which these studies were carried out make it difficult to compare results across studies; within most industries, styrene is only one of several chemical exposures, and these tend to be highly correlated with styrene exposure; the pattern of results has been unpersuasive, though there are a couple of hints of excess risk of leukemia in some subgroups of some cohorts; and finally, the classification of hematopoietic malignancies is complicated [148].

The substantial body of epidemiologic evidence can reasonably be interpreted as showing no cancer risk, or it can be interpreted as showing suggestions of risk of leukemia in some subgroups of some cohorts. The IARC working group leaned in the latter direction as they categorized the human evidence as “limited” rather than “inadequate.” The studies already conducted have been large, and there have been several of them. It is not clear that another study would resolve the issue [149].

Nor does the experimental evidence provide clear guidance. The animal experimental evidence is equivocal, and human biomarker studies show some signs of DNA adduct formation.

1,3-Butadiene

Concern about the possible carcinogenicity of 1,3-butadiene in humans derives from the results of animal experiments, which showed an increased incidence of leukemia in mice and, to a lesser extent, rats [150]. Data on the carcinogenicity of butadiene in humans derive essentially from studies conducted among workers employed in the production of the monomer and in the production of styrene-butadiene rubber (SBR), where high exposure levels occurred in the past.

A series of analyses examined the mortality of approximately 17,000 male workers from eight SBR-manufacturing facilities in the USA and Canada. Although mortality from leukemia was only slightly elevated in the most recent updates [151–153], large excesses of mortality from leukemia were seen in workers in the most highly exposed areas of the plants and among hourly paid workers, especially those who had been hired in the early years and had been employed for more than 10 years. These excesses were seen for both chronic lymphocytic and chronic myelogenous leukemia, with significant exposure-response relationships. The analyses showed that the exposure-response for butadiene and leukemia was independent of exposures to benzene, styrene, and dimethyldithiocarbamate [152, 153]. The inferences from these analyses are limited because of the difficulty of diagnosing and classifying lymphatic and hematopoietic malignancies. There was some evidence of an association between exposure to butadiene and non-Hodgkin lymphoma in studies in the butadiene monomer industries [154–156].

Overall, the epidemiological evidence from the styrene-butadiene and the butadiene monomer industries indicates an increased risk for hematolymphatic malignancies. Studies from the styrene-butadiene industry show an excess of leukemia and a dose-response relationship with cumulative exposure to butadiene, while studies from the monomer industry show an excess of hematolymphatic malignancies in general attributable both to leukemia and malignant lymphoma. It will be difficult to find exposed populations in which to try to replicate these findings.

Vinyl Chloride

Vinyl chloride (VC) is a large volume industrial chemical with many practical applications. In the early 1970s, clinicians observed a cluster of cases of angiosarcoma of the liver among a group of workers in a plant using VC [52]. The tumor is so rare that they were struck by the cluster. Within a very short time, other similar clusters were reported, and the association was quickly accepted as causal [157, 158]. The discovery was facilitated by the rarity of the tumor, the strength of the association, and the fact that there are no other known risk factors for this tumor and thus little danger of confounding. Early cohort studies confirmed the strong effect of vinyl chloride on risk of angiosarcoma of the liver and also raised questions about a possible association with lung cancer. In fact the data were suggestive enough in the 1980s that an effect on lung cancer was considered likely [113, 159]. However, subsequent studies have failed to demonstrate such an effect, and it is likely that the early reports were distorted by confounding or chance [160]. While there is growing evidence that lung cancer is not a target organ, it is becoming more plausible, as a result of recent meta-analyses [160], that exposure to VC may cause hepatocellular carcinoma as well as liver angiosarcoma. Detecting an association of moderate strength with a fairly rare tumor which has a long latency is difficult, and it will take more data to confirm it. A further complication is whether some of the hepatocellular carcinomas are in fact misdiagnosed angiosarcomas. An additional source of potential bias and confusion derives from the observation, in the two multicenter cohort studies [161, 162], that diagnostic misclassification may occur between liver angiosarcoma and soft tissue sarcomas, and, given the rarity of soft tissue sarcomas, this could artificially create the appearance of an association with soft tissue sarcomas. Because of the drastic decrease in exposure levels that took place in the vinyl chloride industry after the discovery of its carcinogenic activity, it is unlikely that there will be new cohorts of highly exposed workers to investigate. It is conceivable that new data can be generated from further follow-up of existing cohorts; however, the maximum latent period for most cancers is likely to be approaching, and additional cancers are increasingly likely to reflect background and risk factors other than vinyl chloride. Molecular epidemiology provides another avenue for exploring the carcinogenic effects of VC, notably studies of mutation in the p53 gene [163–165].

Radium and Radon

Radium and radon provide an interesting contrast from the point of view of prevention strategies. Both radium and radon gas induce tumors in exposed workers through ionizing radiation. Radium was used by dial painters and caused osteosarcomas. Radon gas caused lung cancer in miners. The risk due to radium was easily eliminated by, in effect, eliminating the occupation of radium dial painting. Mining cannot be eliminated, and radon gas is an inevitable exposure in mines. The best strategy here is to find a cost-effective way to reduce exposures by engineering methods, while also improving the epidemiologic database on dose-response relationships. Radon also provides one of the most successful examples of the use of high-dose occupational data for the purpose of extrapolation to lower-dose environmental exposure levels [166].

Some Methodological Considerations

The main stages in occupational cancer epidemiology are detection/discovery of hazards, which can be broken down into hypothesis generation and hypothesis testing, and characterization of risks. This categorization is simplistic. In reality, a given piece of research may serve two or three of these stages, and the operational distinctions among them are ambiguous. But it is a useful conceptual framework.

Before the 1950s, the generation of hypotheses relied primarily on astute clinicians to notice clusters of cancer among groups of workers, and the investigation of hypotheses was carried out by means of industry-based historical cohort studies. Thereafter, new approaches were introduced, including attempts to generate hypotheses from analyses of routine record sources (such as death certificates) and from case-control studies. For testing hypotheses and characterization of hazards, there was increasing use of case-control methods. The various approaches that are used in occupational cancer epidemiology can be divided in two major families: community-based studies and industry-based studies. The following sections describe some of the salient features of these designs and their advantages and disadvantages in this area.

Industry-Based Studies

In an industry-based study, the population under investigation is defined on the basis of belonging to a union or working for a company or some other work-related institution. Because of the long latency of cancer, the study design typically used is a historical cohort design [167]. A given workforce is generally exposed to a relatively narrow range of occupational substances, and for this reason the prime role of cohort studies has been and remains to investigate specific associations (or to "test hypotheses" or characterize relationships), rather than to generate hypotheses. But this is an oversimplification; a typical cohort study produces results on possible associations between one or more exposures and many types of cancer. Since it is often difficult or costly in practice to constitute an appropriate group of unexposed subjects with whom to compare the exposed and since the cohort usually constitutes a very small fraction of the entire population, it is expedient and often acceptable to take the disease or death rates in the entire population (national or regional) as a close approximation of those in the unexposed. The latter are easily available from published statistics or databases. When the disease experience of the exposed cohort is compared with that of the entire population, it is possible to take into account such basic demographic variables as age, sex, and race. The most common statistical approach is indirect standardization, and the resulting parameter is called a standardized mortality ratio (SMR) or standardized incidence ratio (SIR).

There are two significant advantages of the cohort approach, both relating to exposures of workers. The first is the opportunity it affords to focus on a group of workers with relatively high exposure levels, thereby improving the chances of detecting a risk. Secondly, by focusing on a single industry or company, it is sometimes possible to derive detailed and valid data on the exposure histories of study subjects. It is common for companies to maintain job history records for each worker, and these are often maintained for decades. Depending on the nature of the industry, the company, and the relationship established between the investigator and the company, it may be possible to obtain detailed historic exposure measurements, and these might be linkable to the job histories of individual workers. It may also be possible to consult company hygienists or engineers or other workers who can inform the investigator about past conditions and exposure circumstances. The cooperation of employers is usually a sine qua non to conduct such studies.

It is sometimes possible to obtain quite high-quality historic exposure information and to use this in assessing and characterizing hazards [167–169]. Notable examples include studies on formaldehyde [75, 170], asphalt workers [171], acrylonitrile [172, 173], and nickel compounds [174]. In some historic examples, such as in certain cohorts of asbestos workers, there were no available quantitative data on exposure levels, but the industrial process was thought to be so "simple" that only one substance was thought to be worth considering as an explanation for the excess risk of the entire cohort [175]. Such reasoning may be acceptable in a few industries, such as the extractive industries; but most industrial processes entail diverse mixtures of exposures. The success at characterizing past exposures will depend on the skill and resources of the investigating team and the availability of adequate industrial hygiene data. Ingenious methods have been brought to bear by industrial hygienists working with epidemiologists to evaluate historic exposures to specific substances in various cohorts [176].

Community-Based Case-Control Studies

In a community-based study, the population is typically defined on the basis of living in a given geographic area or falling in the catchment area of a set of health-care providers. Questionnaire-based case-control studies provide the opportunity to collect information on lifetime occupation histories and on other relevant cofactors directly from cancer patients or close relatives and appropriate controls. From this, it is possible to estimate cancer risks in relation to various occupational circumstances.

Case-control studies provide the opportunity to conduct analyses based on job titles. Analyses using job titles are useful. Several associations with cancer have been discovered by means of analyses on job titles. Such analyses are most valid and valuable when the workers have a relatively homogeneous exposure profile. Examples might include miners, motor vehicle drivers, butchers, and cabinetmakers. Whatever attempts are made to derive specific exposures in community-based studies, it is nevertheless worthwhile to also conduct the statistical analyses to evaluate risks by job titles. However,

job titles are limited as descriptors of occupational exposures [115]. On the one hand, many job titles cover workers with very diverse exposure profiles. On the other hand, many exposures are found to occur across many occupation categories. In such circumstances, epidemiologic analyses by job title may entail too much noise to allow for a signal to be detected. Several approaches have been used to ascertain exposures in community-based studies, including self-reported checklist of exposures, job-exposure matrix (JEM), and expert assessment [177].

Some Trends in Epidemiologic Research on Occupational Cancer

Since the revolution in genetic research methods, there has been a shift in research resources on occupational cancer from an attempt to assess the main effects of occupations and occupational exposures to an attempt to assess so-called gene-environment interactions. While this is an interesting and worthwhile pursuit, it has not yet led to a proportionate increase in knowledge of new carcinogens. It remains the case that almost all the knowledge that has accrued about occupational risk factors has been gained without recourse to genetic interactions. It is important to avoid the temptation to shift all the "research eggs" into the basket of gene-environment interaction studies and to keep some of the resources in research approaches that have proven their worth.

In the past, the main focus of attention was on occupational exposures associated with "dirty" industrial environments. But over the past few decades, as "dirty" environments have been cleaned up or eliminated, there has been increasing attention to nonchemical agents in the work environment. Physical agents such as radon gas and electromagnetic fields have been investigated, but behavioral and ergonomic characteristics such as physical activity (or sedentarism) and shift work have come into view as potential cancer risk factors.

Industries and occupations are in constant evolution. Even if we knew all there was to know about the cancer risks in today's occupational environments, which we do not, it is important to continue to monitor cancer risks in the occupational environment because it is always changing and introducing new exposures and circumstances (e.g., nanoparticles, radiofrequency fields).

While the lists of occupational risk factors in Tables 1.4 and 1.5 are lengthy, they are not complete. There are likely many more occupational carcinogens that have not been discovered or properly documented. For many if not most occupational circumstances, there is no epidemiological evidence one way or the other concerning carcinogenicity. One of the foremost problems in occupational epidemiology is how to uncover the hidden part of the iceberg of occupational carcinogens.

Continued Importance of Research on Occupational Cancer

In the 1960s and 1970s, the field of occupational cancer research was one of the most thriving areas of epidemiological research. This was fed by the social trends which raised the profile of environmentalism and workers' health and by important discoveries of occupational carcinogens such as asbestos. There was a perception that research on environmental causes of cancer was important and that it would be feasible to make breakthroughs. Workers' organizations were active and vocal in calling for improved working conditions and for the research that would support such action. Many young investigators, influenced by the *zeitgeist* of the 1960s, were ideologically drawn to a research area which would dovetail with their political and social interests. In contrast, today we perceive a waning of interest and enthusiasm. What has happened?

The reasons are complex, but may well include the following. The political/social climate that supported work on occupational health has greatly changed. In western countries, the economies and workforces have shifted, and there are fewer blue-collar industrial workers than there were 30 years ago. Union membership, especially in blue-collar unions, has declined, and the unions have become less militant. These trends have been fostered by technology (e.g., computerization and robotization) and by globalization. To a certain extent, "dirty jobs" have been eliminated or exported from western to developing countries. The bottom line is that a smaller fraction of the western workforce is involved in traditional "dirty jobs." Another factor is that, as mentioned above, most large workplaces have become much cleaner, at least in some industrialized countries.

Another reason for the deflation of interest in this area is that the expectations of some for quick and dramatic discoveries of "smoking guns" like asbestos did not pan out. The expectations were unrealistic, but that was not clear at the time. There was a widespread belief that there were many cancer-causing hazards in the workplace and it would only be a matter of shining some light in the right places to find them. There was much more epidemiological research in the 1970s, 1980s, and 1990s than there had been in the preceding decades. While this research produced a large number of important findings, these were incremental in the overall scheme of things and, for some, did not seem proportional to the effort.

In the face of these social and economic changes and the ostensible diminishing returns from research in occupational cancer, is this an area of investigation that should be fostered? Our answer is an unambiguous "Yes!" for the following reasons and with the following caveats:

(a) In industrialized countries, a large fraction of the workforce still works in circumstances which bring workers into contact with chemical agents. Even if the fraction is

less than it was a century ago, it is still sizeable and will remain so for the foreseeable future. While industrial design and hygiene have succeeded in lowering exposures in many industries, there remain pockets where exposure levels remain high.

(b) The story of occupational hygiene conditions in developing countries is less rosy. Enormous numbers of people are now working in insalubrious conditions. As life expectancy in these populations rises with increasing affluence and improved living conditions and medical care, the numbers of cancer cases and most likely the numbers of occupationally related cancers are steadily increasing. There is a tremendous opportunity for epidemiologists to investigate occupation-cancer relationships in developing countries.

(c) There are many thousands of chemicals in workplaces. Many of them are obscure and involve relatively few workers; but many involve exposure for thousands of workers. Of these, only a small fraction have been adequately investigated with epidemiological data.

(d) The industrial environment is constantly evolving with the introduction of new and untested chemicals. We need to maintain a monitoring capacity to detect "new" occupational carcinogens. A recent example of a suspected carcinogen is indium phosphide in the semiconductor industry [178].

(e) The occupational environment is one that lends itself to preventive intervention.

(f) Many chemicals in the workplace find their way into the general environment, either via industrial effluent or via their use in consumer products. Hazards identified in the workplace often have an importance that goes beyond the factory walls.

(g) The discovery of occupational carcinogens is important to understanding the principles of carcinogenesis: workers represent a "natural experiment" of high exposure to a potentially carcinogenic agent.

(h) The ability to detect hazards is increasing with improvement of methods for exposure assessment and outcome assessment, as well as the tendency to use larger study sizes.

References

1. Pott P. Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures and the mortification of the toes and feet. London: T. J. Carnegy; 1775.
2. Volkmann R. Paraffin und Russkrebs (Schornsteinfegerkrebs). Beitrage zur Chirurgie. Leipzig: Druck und Verlag von Breitkopf und Hartel; 1875. p. 370–81.
3. Bell J. Paraffin epithelioma of the scrotum. Edinb Med J. 1876;22:135–7.
4. Morley J. The lymphatics of the scrotum in relation to the radical operation for scrotal epithelioma. Lancet. 1911;2:1545–7.
5. Southam AH, Wilson SR. Cancer of the scrotum: the aetiology, clinical features, and treatment of the disease. Br Med J. 1922;2:971–3.
6. Härting FH, Hesse W. Der Lungenkrebs, die Bergkrankheit in den Schneeberger Gruben. Vrtljhrssch Gerichtl Med. 1879;30:296–309.
7. Pirchan A, Sikl H. Cancer of the lung in the miners of Jachymov (Joachimstal). Report of cases observed in 1929-1930. Am J Cancer. 1932;16(4):681–722.
8. Peller S. Lung cancer among mine workers in Joachimsthal. Hum Biol. 1939;11(1):130–43.
9. Rehn L. Blasengeschwulste bei Fuchsin-Arbeitern. Arch Klin Chir. 1895;50:588–600.
10. Yamagiwa K, Ichikawa K. Experimental study of the pathogenesis of carcinoma. J Cancer Res. 1918;3:1–29.
11. Kennaway EL, Hieger I. Carcinogenic substances and their fluorescence spectra. Br Med J. 1930;1:1044–6.
12. Cook JW, Hieger I, Kennaway EL, Mayneord WV. The production of cancer by pure hydrocarbons. Proc R Soc Lond B Biol Sci. 1932;111:455–84.
13. Hieger I. The isolation of a cancer-producing hydrocarbon from coal tar. J Chem Soc. 1933:395.
14. Waldron A. A brief history of scrotal cancer. Br J Ind Med. 1983;40:390–401.
15. Bridge JC. Annual report of the chief inspector for the year 1932. London: HMSO; 1933.
16. Kuroda S, Kawahata K. Uber die gewerbliche Entstehung des Lungenkrebses bei Generatorgasarbeitern. Z Krebsforsch. 1936; 45:36–9.
17. Machle W, Gregorius F. Cancer of the respiratory system in the United States chromate-producing industry. Public Health Rep. 1948;63:1114–27.
18. Hill AB, Faning EL. Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. I. Mortality experience in the factory. Br J Ind Med. 1948;5:1–6.
19. Merewether ERA. Asbestosis and carcinoma of the lung. Annual report of the chief inspector of factories for the year 1947. London: HMSO; 1949. p. 79–81.
20. Doll R. The causes of death among gas-workers with special reference to cancer of the lung. Br J Ind Med. 1952;9:180.
21. Doll R. Mortality from lung cancer in asbestos workers. Br J Ind Med. 1955;12:81.
22. Case RAM, Hosker ME, McDonald DB, Pearson JT. Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. Part I. The role of aniline, benzidine, alpha-naphthylamine and beta-naphthylamine. Br J Ind Med. 1954;11:75.
23. Bucher JR. The National Toxicology Program rodent bioassay: designs, interpretations, and scientific contributions. Ann N Y Acad Sci. 2002;982:198–207.
24. Archer VE, Magnuson JH, Holaday DA, et al. Hazards to health in uranium mining and milling. J Occup Med. 1962;4:55–60.
25. Archer VE, Gillam JD, Wagoner JK. Respiratory disease mortality among uranium miners. Ann N Y Acad Sci. 1976;271:280–93.
26. Howe GR, Nair RC, Newcombe HB, Miller AB, Burch JD, Abbatt JD. Lung cancer mortality (1950-80) in relation to radon daughter exposure in a cohort of workers at the Eldorado port radium uranium mine: possible modification of risk by exposure rate. J Natl Cancer Inst. 1987;79(6):1255–60.
27. Scott TS. The incidence of tumours in a dyestuffs factory. Br J Ind Med. 1952;9:127–32.
28. Meigs JW, Marrett LD, Ulrich FU, Flannery JT. Bladder tumor incidence among workers exposed to benzidine: a thirty-year follow-up. J Natl Cancer Inst. 1986;76:1–8.
29. Chief Inspector of Factories. Annual report of the chief inspector of factories for the year 1932. London; 1933.
30. Doll R. Cancer of the lung and nose in nickel workers. Br J Ind Med. 1958;15:217–23.

31. Kaldor J, Peto J, Easton D, Doll R, Hermon C, Morgan L. Models for respiratory cancer in nickel refinery workers. J Natl Cancer Inst. 1986;77(4):841–8.
32. Henry SA. Industrial maladies. London: Legge; 1934.
33. Lee AM, Fraumeni Jr JF. Arsenic and respiratory cancer in man: an occupational study. J Natl Cancer Inst. 1969;42(6):1045–52.
34. Lee-Feldstein A. Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. J Occup Med. 1986;28(4):296–302.
35. Pinto SS, Henderson V, Enterline PE. Mortality experience of arsenic-exposed workers. Arch Environ Health. 1978;33(6):325–30.
36. Enterline PE, Henderson VL, Marsh GM. Exposure to arsenic and respiratory cancer. A reanalysis. Am J Epidemiol. 1987;125(6): 929–38.
37. Lynch KM, Smith WA. Pulmonary asbestosis III: carcinoma of lung in asbesto-silicosis. Am J Cancer. 1935;24:56–64.
38. Selikoff IF, Churg J, Hammond EC. Asbestos exposure and neoplasia. JAMA. 1964;118:22–6.
39. McDonald JC, Liddell FDK, Gibbs GW, Eyssen GE, McDonald AD. Dust exposure and mortality in chrysotile mining, 1910-75. Br J Ind Med. 1980;37:11–24.
40. Dement JM, Harris Jr RL, Symons MJ, Shy CM. Exposures and mortality among chrysotile asbestos workers. Part II: mortality. Am J Ind Med. 1983;4(3):421–33.
41. Seidman H, Selikoff IJ, Gelb SK. Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. Am J Ind Med. 1986;10(5–6):479–514.
42. Mallory TB, Gall EA, Brickley WJ. Chronic exposure to benzene (benzol). III the pathologic results. J Ind Hyg Toxicol. 1939;21:355–77.
43. Vigliani EC, Saita G. Benzene and leukemia. N Engl J Med. 1964;271:872–6.
44. Ishimaru T, Okada H, Tomiyasu T, Tsuchimoto T, Hoshino T, Ichimaru M. Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki. Am J Epidemiol. 1971;93(3):157–65.
45. Aksoy M, Erdem S, DinCol G. Leukemia in shoe-workers exposed chronically to benzene. Blood. 1974;44(6):837–41.
46. Infante PF, Rinsky RA, Wagoner JK, Young RJ. Leukaemia in benzene workers. Lancet. 1977;2(8028):76–8.
47. Rinsky RA, Smith AB, Hornung R, et al. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med. 1987;316(17): 1044–50.
48. Yin SN, Li GL, Tain FD, et al. Leukaemia in benzene workers: a retrospective cohort study. Br J Ind Med. 1987;44(2):124–8.
49. Figueroa WG, Raszkowski R, Weiss W. Lung cancer in chloromethyl methyl ether workers. N Engl J Med. 1973;288(21):1096–7.
50. DeFonso LR, Kelton Jr SC. Lung cancer following exposure to chloromethyl methyl ether. An epidemiological study. Arch Environ Health. 1976;31(3):125–30.
51. McCallum RI, Woolley V, Petrie A. Lung cancer associated with chloromethyl methyl ether manufacture: an investigation at two factories in the United Kingdom. Br J Ind Med. 1983;40(4):384–9.
52. Creech Jr JL, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med. 1974;16(3):150–1.
53. Monson RR, Peters JM, Johnson MN. Proportional mortality among vinyl-chloride workers. Lancet. 1974;2(7877):397–8.
54. Waxweiler RJ, Stringer W, Wagoner JK, Jones J, Falk H, Carter C. Neoplastic risk among workers exposed to vinyl chloride. Ann N Y Acad Sci. 1976;271:40–8.
55. Fox AJ, Collier PF. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br J Ind Med. 1977;34(1):1–10.
56. Siemiatycki J, Richardson L, Boffetta P. Occupation. In: Schottenfeld D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. 3rd ed. Oxford: Oxford University Press; 2006. p. 322–54.
57. Potts CL. Cadmium proteinuria: the health of battery workers exposed to cadmium oxide dust. Ann Occup Hyg. 1965;8:55–61.
58. Kipling MD, Waterhouse JA. Cadmium and prostatic carcinoma. Lancet. 1967;1:730–1.
59. Lemen RA, Lee JS, Wagoner JK, Blejer HP. Cancer mortality among cadmium production workers. Ann N Y Acad Sci. 1976;271:273–9.
60. Sorahan T, Waterhouse JAH. Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. Br J Ind Med. 1983;40:293–300.
61. Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. Mortality among a cohort of U.S. cadmium production workers - an update. J Natl Cancer Inst. 1985;74(2):325–33.
62. Kazantzis G, Blanks RG, Sullivan KR, Nordberg GF, Herber RFM, Alessio L. Is cadmium a human carcinogen? Cadmium in the human environment: toxicity and carcinogenicity. Lyon: IARC; 1992. p. 435–46.
63. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens, part C: arsenic, metals, fibres, and dusts, vol. 100. Lyon: IARC (International Agency for Research on Cancer); 2012.
64. Boffetta P, Saracci R, Andersen A, et al. Cancer mortality among man-made vitreous fiber production workers. Epidemiology. 1997;8(3):259–68.
65. Marsh GM, Buchanich JM, Youk AO. Historical cohort study of US man-made vitreous fiber production workers: VI. Respiratory system cancer standardized mortality ratios adjusted for the confounding effect of cigarette smoking. J Occup Environ Med. 2001;43(9):803–8.
66. Kjaerheim K, Boffetta P, Hansen J, et al. Lung cancer among rock and slag wool production workers. Epidemiology. 2002;13(4):445–53.
67. Hogstedt C, Malmqvist N, Wadman B. Leukemia in workers exposed to ethylene oxide. JAMA. 1979;241(11):1132–3.
68. Hogstedt C, Aringer L, Gustavsson A. Epidemiologic support for ethylene oxide as a cancer-causing agent. JAMA. 1986;255(12):1575–8.
69. Stayner L, Steenland K, Greife A, et al. Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. Am J Epidemiol. 1993;138(10):787–98.
70. Teta MJ, Benson LO, Vitale JN. Mortality study of ethylene oxide workers in chemical manufacturing - a ten year update. Br J Ind Med. 1993;50(8):704–9.
71. O'Berg MT. Epidemiologic study of workers exposed to acrylonitrile. J Occup Med. 1980;22(4):245–52.
72. Werner JB, Carter JT. Mortality of United Kingdom acrylonitrile polymerisation workers. Br J Ind Med. 1981;38(3):247–53.
73. Delzell E, Monson RR. Mortality among rubber workers: VI. Men with potential exposure to acrylonitrile. J Occup Med. 1982;24(10):767–9.
74. Acheson ED, Barnes HR, Gardner MJ, Osmond C, Pannett B, Taylor CP. Formaldehyde in the British chemical industry: an occupational cohort study. Lancet. 1984;1:611–6.
75. Blair A, Stewart P, O'Berg M, et al. Mortality among industrial workers exposed to formaldehyde. J Natl Cancer Inst. 1986;76(6):1071–84.
76. Bertazzi PA, Pesatori A, Guercilena S, Consonni D, Zocchetti C. Carcinogenic risk for resin producers exposed to formaldehyde: extension of follow-up. Med Lav. 1989;80(2):111–22.
77. Andjelkovich DA, Janszen DB, Brown MH, Richardson RB, Miller FJ. Mortality of iron foundry workers: 4. Analysis of a subcohort exposed to formaldehyde. J Occup Environ Med. 1995;37(7):826–37.
78. Mahboubi A, Koushik A, Siemiatycki J, Lavoue J, Rousseau MC. Assessment of the effect of occupational exposure to formaldehyde on the risk of lung cancer in two Canadian population-based case-control studies. Scand J Work Environ Health. 2013;39: 401–10.

79. Shubik P, Clark Griffin A, Shaw CR. Identification of environmental carcinogens: animal test models. In: Griffin AC, Shaw CR, editors. Carcinogens: identifications and mechanisms of action. New York: Raven; 1979. p. 37–47.
80. Berenblum I. Carcinogenicity testing for control of environmental tumor development in man. Isr J Med Sci. 1979;15(6):473–9.
81. Wilbourn J, Haroun L, Heseltine E, Kaldor J, Partensky C, Vainio H. Response of experimental animals to human carcinogens: an analysis based upon the IARC Monographs programme. Carcinogenesis. 1986;7(11):1853–63.
82. Montesano R, Bartsch H, Vainio H, Wilbourn J, Yamasaki H. Long-term and Short-term assays for carcinogens: a critical appraisal. Lyon: International Agency for Research on Cancer; 1986.
83. Rall DP, Hogan MD, Huff JE, Schwetz BA, Tennant RW. Alternatives to using human experience in assessing health risks. Annu Rev Public Health. 1987;8:355–85.
84. Allen BC, Crump KS, Shipp AM. Correlation between carcinogenic potency of chemicals in animals and humans. Risk Anal. 1988;8(4):531–50.
85. Gold LS, Slone TH, Ames BN, Gold LS, Zeiger E. Chapter 4. Overview and update of analyses of the carcinogenic potency database. In: Gold LS, Zeiger E, editors. Handbook of carcinogenic potency and genotoxicity databases. Boca Raton: CRC Press; 1997. p. 661–85.
86. Haseman JK. Using the NTP database to assess the value of rodent carcinogenicity studies for determining human cancer risk. Drug Metab Rev. 2000;32(2):169–86.
87. Tomatis L, Wilbourn J. Evaluation of carcinogenic risks to humans: the experience of IARC. In: Iversen OH, editor. New Frontiers in cancer causation. Washington, DC: Taylor and Francis; 1993. p. 371–87.
88. Swenberg JA, Lehman-McKeeman LD, Capen CC, Dybing E, Rice JM, Wilbourn JD. Alpha 2-urinary globulin associated nephropathy as a mechanism of renal tubule cell carcinogenesis in male rats. In: Capen CC, Dybing E, Rice JM, Wilbourn JD, editors. Species differences in thyroid, kidney and urinary bladder carcinogenesis. Lyon: International Agency for Research on Cancer; 1999. p. 95–118.
89. Gold LS, Slone TH, Ames BN. What do animal cancer tests tell us about human cancer risk?: overview of analyses of the carcinogenic potency database. Drug Metab Rev. 1998;30(2):359–404.
90. Purchase IFH, Bannasch P. Carcinogenic risk assessment: are animals good surrogates for man? In: Bannasch P, editor. Cancer risks: strategies for elimination. Berlin: Springer; 1986. p. 65–79.
91. Gold LS, Bernstein L, Magaw R, Slone TH. Interspecies extrapolation in carcinogenesis: prediction between rats and mice. Environ Health Perspect. 1989;81:211–9.
92. Cohen SM. Human relevance of animal carcinogenicity studies. Regul Toxicol Pharmacol. 1995;21(1):75–80; discussion 81–86.
93. Ashby J. Alternatives to the 2-species bioassay for the identification of potential human carcinogens. Hum Exp Toxicol. 1996;15(3):183–202.
94. Freedman DA, Gold LS, Lin TH. Concordance between rats and mice in bioassays for carcinogenesis. Regul Toxicol Pharmacol. 1996;23(3):225–32.
95. Tomatis L, Kaldor JM, Bartsch H, Schottenfeld D, Fraumeni Jr JF. Experimental studies in the assessment of human risk. In: Schottenfeld D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. 2nd ed. New York: Oxford University Press; 1996. p. 11–27.
96. Gottmann E, Kramer S, Pfahringer B, Helma C. Data quality in predictive toxicology: reproducibility of rodent carcinogenicity experiments. Environ Health Perspect. 2001;109(5):509–14.
97. Brent RL. Utilization of animal studies to determine the effects and human risks of environmental toxicants (drugs, chemicals, and physical agents). Pediatrics. 2004;113(3 Suppl):984–95.
98. Ashby J, Tennant RW. Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by US NCI/NTP (MYR 01277). Mutat Res. 1988;204(1):17–115.
99. Zeiger E. Identification of rodent carcinogens and noncarcinogens using genetic toxicity tests: premises, promises, and performance. Regul Toxicol Pharmacol. 1998;28(2):85–95.
100. Waters MD, Stack HF, Jackson MA, McGregor DB, Rice JM, Venitt S. Short-term tests for defining mutagenic carcinogens. In: McGregor DB, Rice JM, Venitt S, editors. The use of short- and medium-term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation. Lyon: IARC; 1999.
101. Weisburger JH. Carcinogenicity and mutagenicity testing, then and now. Mutat Res. 1999;437(2):105–12.
102. Tennant RW, Spalding J, Stasiewicz S, Ashby J. Prediction of the outcome of rodent carcinogenicity bioassays currently being conducted on 44 chemicals by the National Toxicology Program. Mutagenesis. 1990;5(1):3–14.
103. Huff J, Weisburger E, Fung VA. Multicomponent criteria for predicting carcinogenicity: dataset of 30 NTP chemicals. Environ Health Perspect. 1996;104 Suppl 5:1105–12.
104. Kim BS, Margolin BH. Prediction of rodent carcinogenicity utilizing a battery of in vitro and in vivo genotoxicity tests. Environ Mol Mutagen. 1999;34(4):297–304.
105. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens, part F: chemical agents and related occupations, vol. 100. Lyon: IARC (International Agency for Research on Cancer); 2012.
106. Hansen J, Stevens RG. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. Eur J Cancer. 2012;48(11):1722–9.
107. International Agency for Research on Cancer. Preamble to the IARC monographs. 2006. http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf. Accessed 18 June 2013.
108. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans, Ionizing radiation, part 1. X-radiation and g-radiation, and neutrons, vol. 75. Lyon: IARC (International Agency for Research on Cancer); 2000.
109. IARC. IARC monographs on the evaluation of carcinogenic risks to humans. 2013. http://monographs.iarc.fr/. Accessed 27 June 2013.
110. Siemiatycki J, Richardson L, Straif K, et al. Listing occupational carcinogens. Environ Health Perspect. 2004;112(15):1447–59; see errata: 113(2); A 89.
111. Guha N, Merletti F, Steenland NK, Altieri A, Cogliano V, Straif K. Lung cancer risk in painters: a meta-analysis. Cien Saude Colet. 2011;16(8):3613–32.
112. World Health Organization. Prevention of cancer. Report of a WHO expert committee. Geneva: World Health Organization; 1964.
113. IARC. Evaluation of the carcinogenic risk of chemicals to humans. Supplement 7: overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. Lyon: IARC (International Agency for Research on Cancer); 1987.
114. Doll R. 7th Walter Hubert Lecture: Pott and the prospects for prevention. Br J Cancer. 1975;32:263–72.
115. Siemiatycki J, Day NE, Fabry J, Cooper JA. Discovering carcinogens in the occupational environment: a novel epidemiologic approach. J Natl Cancer Inst. 1981;66(2):217–25.
116. Nauss KM, Busby WF, Cohen AJ, et al. Critical issues in assessing the carcinogenicity of diesel exhaust: a synthesis of current knowledge. Diesel exhaust: a critical analysis of emissions, exposure, and health effects. Cambridge: Health Effects Institute; 1995. p. 11–61.
117. Katsouyanni K, Pershagen G. Ambient air pollution exposure and cancer [review]. Cancer Causes Control. 1997;8(3):284–91.
118. Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons [review]. Cancer Causes Control. 1997;8(3):444–72.

119. Weeks JL. Reducing risk of lung cancer from diesel exhaust in underground mines. Am J Ind Med. 1998;34(3):203–6.
120. Silverman DT. Is diesel exhaust a human lung carcinogen? Epidemiology. 1998;9(1):4–6.
121. Attfield MD, Schleiff PL, Lubin JH, et al. The diesel exhaust in miners study: a cohort mortality study with emphasis on lung cancer. J Natl Cancer Inst. 2012;104(11):869–83.
122. Silverman DT, Samanic CM, Lubin JH, et al. The diesel exhaust in miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst. 2012;104(11):855–68.
123. Garshick E, Laden F, Hart JE, et al. Lung cancer in railroad workers exposed to diesel exhaust. Environ Health Perspect. 2004;112(15):1539–43.
124. Laden F, Hart JE, Eschenroeder A, Smith TJ, Garshick E. Historical estimation of diesel exhaust exposure in a cohort study of US railroad workers and lung cancer. Cancer Causes Control. 2006;17(7):911–9.
125. Benbrahim-Tallaa L, Baan RA, Grosse Y, et al. Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. Lancet Oncol. 2012;13(7):663–4.
126. Selikoff IJ. Historical developments and perspectives in inorganic fiber toxicity in man. Environ Health Perspect. 1990;88:269–76.
127. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in North Western Cape Province. Br J Ind Med. 1960;17:260–71.
128. Doll RPJ. Asbestos: effects on health of exposure to asbestos. London: Her Majesty's Stationery Office; 1985.
129. Nicholson WJ. Airborne asbestos health assessment update. Washington, DC: Office of Health and Environmental Assessment, U.S. Environmental Protection Agency; 1986.
130. Stone R. No meeting of the minds on asbestos. Science. 1991;254(5034):928–31.
131. Upton ABJBM, et al. Asbestos in public and commercial buildings: a literature review and synthesis of current knowledge. Report to: Health Effects Institute – Asbestos Research (HEI-AR). Cambridge: Health Effects Institute; 1991.
132. IPCS (International Programme on Chemical Safety). Chrysotile asbestos. Geneva: World Health Organization; 1998.
133. Ramazzini C. Call for an international ban on asbestos. J Occup Environ Med. 1999;41(10):830–2.
134. Siemiatycki J. Should Canadian health care professionals support the call for a worldwide ban on asbestos? Can Med Assoc J. 2001;164(4):495–7.
135. Camus M, Siemiatycki J, Meek B. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. N Engl J Med. 1998;338(22):1565–71.
136. IARC. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to man, Some inorganic and organometallic compounds, vol. 2. Lyon: IARC (International Agency for Research on Cancer); 1973.
137. IARC. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man, Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics, vol. 11. Lyon: IARC (International Agency for Research on Cancer); 1976.
138. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans, Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry, vol. 58. Lyon: IARC (International Agency for Research on Cancer); 1993.
139. Collins DE, Richey Jr FA, Kent JA. Sythetic organic chemicals. Riegel's handbook of industrial chemistry, vol. 9th. New York: Van Nostrand Reinhold; 1992. p. 800–62.
140. Block JB, Ede L. A Kentucky study: 1950-1975. In: Proceeding of NIOSH styrene-butadiene rubber briefing, Covington, Kentucky, April 30, 1976. Cincinnati: National Institute for Occupational Safety and Health; 1976. p. 28–32.
141. Lemen RA, Young R, Ede L. Investigation of health hazards in styrene-butadiene rubber facilities. In: Proceeding of NIOSH styrene-butadiene rubber briefing, Covington, Kentucky, April 30, 1976. Cincinnati: National Institute for Occupational Safety and Health; 1976. p. 3–8.
142. Nicholson WJ, Selikoff IJ, Seidman H. Mortality experience of styrene-polystyrene polymerization workers. Initial findings. Scand J Work Environ Health. 1978;4 Suppl 2:247–52.
143. Bond GG, Bodner KM, Olsen GW, Cook RR. Mortality among workers engaged in the development or manufacture of styrene-based products - an update. Scand J Work Environ Health. 1992;18(3):145–54.
144. Wong O, Trent LS, Whorton MD. An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. Occup Environ Med. 1994;51(6):386–96.
145. Kogevinas M, Ferro G, Andersen A, et al. Cancer mortality in a historical cohort study of workers exposed to styrene. Scand J Work Environ Health. 1994;20(4):251–61.
146. Kolstad HA, Juel K, Olsen J, Lynge E. Exposure to styrene and chronic health effects: mortality and incidence of solid cancers in the danish reinforced plastics industry. Occup Environ Med. 1995;52(5):320–7.
147. Delzell E, Macaluso M, Sathiakumar N, Matthews R. Leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate among workers in the synthetic rubber industry. Chem Biol Interact. 2001;135–136:515–34.
148. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans, Some traditional herbal medicines, some mycotoxins, naphthalene and styrene, vol. 82. Lyon: IARC (International Agency for Research on Cancer); 2002.
149. Boffetta P, Adami HO, Cole P, Trichopoulos D, Mandel JS. Epidemiologic studies of styrene and cancer: a review of the literature. J Occup Environ Med. 2009;51(11):1275–87.
150. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans, Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide, vol. 71. Lyon: IARC (International Agency for Research on Cancer); 1999.
151. Sathiakumar N, Graff J, Macaluso M, Maldonado G, Matthews R, Delzell E. An updated study of mortality among North American synthetic rubber industry workers. Occup Environ Med. 2005;62(12):822–9.
152. Delzell E, Sathiakumar N, Graff J, Macaluso M, Maldonado G, Matthews R. An updated study of mortality among North American synthetic rubber industry workers. Res Rep (Health Eff Inst). 2006;132:1–63; discussion 65–74.
153. Cheng H, Sathiakumar N, Graff J, Matthews R, Delzell E. 1,3-butadiene and leukemia among synthetic rubber industry workers: exposure-response relationships. Chem Biol Interact. 2007;166(1–3 Special Issue SI):15–24.
154. Ward EM, Fajen JM, Ruder AM, Rinsky RA, Halperin WE, Fesslerflesch CA. Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. Environ Health Perspect. 1995;103(6):598–603.
155. Ward EM, Fajen JM, Ruder AM, Rinsky RA, Halperin WE, Fessler-Flesch CA. Mortality study of workers imployed in 1,3-butadiene production units identified from a large chemical workers cohort. Toxicology. 1996;113:157–68.
156. Divine BJ, Hartman CM. A cohort mortality study among workers at a 1,3 butadiene facility. Chem Biol Interact. 2001;135(Special Issue SI):535–53.
157. Tabershaw IR, Gaffey WR. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J Occup Med. 1974;16(8):509–18.
158. IARC. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to man, Some anti-thyroid and related substances, nitrofurans and industrial chemicals, vol. 7. Lyon: IARC (International Agency for Research on Cancer); 1974.

159. Doll R. Effects of exposure to vinyl chloride. An assessment of the evidence. Scand J Work Environ Health. 1988;14(2):61–78.
160. Boffetta P, Matisane L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health. 2003;29(3):220–9.
161. Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bigelow C. Historical cohort study of 10 109 men in the North American vinyl chloride industry, 1942-72: update of cancer mortality to 31 December 1995. Occup Environ Med. 2000;57(11):774–81.
162. Ward E, Boffetta P, Andersen A, et al. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. Epidemiology. 2001;12(6):710–8.
163. Marion MJ, Boivin-Angele S. Vinyl chloride-specific mutations in humans and animals. In: Singer B, Bartsch H, editors. Exocyclic DNA adducts in mutagenesis and carcinogenesis. Lyon: IARC; 1999. p. 315–24.
164. Barbin A. Etheno-adduct-forming chemicals: from mutagenicity testing to tumor mutation spectra. Mutat Res. 2000;462(2–3):55–69.
165. Weihrauch M, Lehnert G, Kockerling F, Wittekind C, Tannapfel A. p53 mutation pattern in hepatocellular carcinoma in workers exposed to vinyl chloride. Cancer. 2000;88(5):1030–6.
166. NAS (National Academy of Sciences). The health effects of exposure to indoor radon (BEIR VI). Washington, DC: National Academy Press; 1999.
167. Checkoway H, Pearce N, Kriebel D. Research methods in occupational epidemiology. 2nd ed. New York: Oxford University Press; 2004.
168. Rappaport SM, Smith TJ. Exposure assessment for epidemiology and hazard control. Chelsea: Lewis Publishers; 1991.
169. Armstrong BK, White E, Saracci R. Principles of exposure measurement in epidemiology. Oxford: Oxford University Press; 1994.
170. Blair A, Stewart PA. Correlation between different measures of occupational exposure to formaldehyde. Am J Epidemiol. 1990;131(3):510–6.
171. Burstyn I, Boffetta P, Kauppinen T, et al. Estimating exposures in the asphalt industry for an international epidemiological cohort study of cancer risk. Am J Ind Med. 2003;43(1):3–17.
172. Swaen GMH, Bloemen LJN, Twisk J, et al. Mortality update of workers exposed to acrylonitrile in the Netherlands. Scand J Work Environ Health. 1998;24 Suppl 2:10–6.
173. Stewart PA, Zaebst D, Zey JN, et al. Exposure assessment for a study of workers exposed to acrylonitrile. Scand J Work Environ Health. 1998;24 Suppl 2:42–53.
174. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Exposure to different forms of nickel and risk of lung cancer. Am J Epidemiol. 2002;156(12):1123–32.
175. Selikoff IJ, Hammond EC, Seidman H, et al. Cancer risk of insulation workers in the United States. Biological effects of asbestos. Lyon: International Agency for Research on Cancer; 1973. p. 209–16.
176. Smith TJ, Hammond SK, Wong O. Health effects of gasoline exposure 1. Exposure assessment for US distribution workers. Environ Health Perspect. 1993;101 Suppl 6:13–21.
177. Siemiatycki J. Exposure assessment in community-based studies of occupational cancer. Occup Hyg. 1996;3:41–58.
178. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans, Cobalt in hard-metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide, vol. 86. Lyon: IARC (International Agency for Research on Cancer); 2006.

Genetics and Gene-Environment Interactions

2

Scott M. Langevin and Karl T. Kelsey

Keywords
Genetics • Epigenetics • Gene-environment interactions • Gene-gene interactions • Xenobiotic metabolism • Metabolic polymorphism and cancer • Genome-wide association studies

Genetics and Heritability

The field of genetics is generally considered to have originated with Charles Darwin's widely famous book *On the Origin of the Species* (1854) [1], in which he presented his novel theory of evolution. This was followed shortly thereafter by Gregor Johann Mendel's 1866 publication of his work on heritability [2]. Through his famous observations of pea plants, Mendel established the notion of heritability, observing that traits are passed on from parents to offspring in a predictable fashion. Together these publications would combine to form the underpinnings of our contemporary conception of genetics and heritability and set the stage for the modern-day genetic revolution. Nearly a century later, in 1953, Watson and Crick would uncover the double-helical structure of DNA [3], unleashing a chain of discoveries pertinent to molecular genetics, which, when combined with the Nobel prize-winning description of the DNA polymerase chain reaction (PCR) methodology [4], would allow rapid, accurate, and affordable characterization of genetic variation. This forms the basis for modern genetic and molecular epidemiology, with which came the recognition of specific genetic susceptibilities to chronic diseases, such as cancer, and their interactions with our environment.

Genetic information passes from each parent to his or her offspring in its most basic form, as *deoxyribonucleic acid* (DNA). DNA is composed of two simple polymers, each consisting of a strand of nitrogenous bases connected to a sugar-phosphate backbone. These strands are complementary to one another, forming a double-helical structure [3]. There are four possible nitrogenous bases, or nucleotides: adenine (A), thymine (T), guanine (G), and cytosine (C). Based on chemical structure, adenine and guanine are purines (double-ring bases) and pair with their respective pyrimidines (single-ring bases), thymine and cytosine [5].

To allow it to fit into the nucleus of a cell, the DNA is condensed by winding around histone proteins and organized into 23 distinct structures in humans, called *chromosomes* [5]. *Germ cells*, a term used to describe *gametes* (i.e., sperm or ova), are *haploid*, meaning that they only carry half of the genetic information of the individual, or one copy of each chromosome. By contrast, all normal *somatic cells*, which refer to all other non-gamete cells that make up the organism, are *diploid* in humans. This means that they have duplicate copies of each chromosome: one copy from the mother and one from the father. Under certain pathologic conditions, chromosome copy number can deviate from this normal, or *euploid*, chromosomal configuration. This is often the case with most forms of cancer. Deviation from the diploid configuration in somatic cells is termed *aneuploidy*. Chromosomes can be subdivided into *autosomal*, or non-gender-specific chromosomes, denoted numerically as 1–22, and *sex chromosomes*, consisting of X or Y. Normal human

S.M. Langevin, PhD (✉)
Department of Environmental Health, University of Cincinnati College of Medicine,
3223 Eden Avenue, ML0056, Cincinnati, OH 45267, USA
e-mail: scott_langevin@brown.edu

K.T. Kelsey, MD, MOH
Department of Epidemiology, Department of Pathology and Laboratory Medicine, Center for Environmental Health and Technology, Brown University,
70 Ship Street, Box G-E5, Providence, RI 02912, USA
e-mail: karl_kelsey@brown.edu

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_2,

karyotypes, or chromosomal arrangements, consist of two copies of each autosomal chromosome. In addition, somatic cells in normal women each contain two X chromosomes, whereas somatic cells in normal men have one X and one Y chromosome.

Each chromosome is made up of a collection of *genes* that provide the code for proteins, which are expressed as traits, such as the presence or absence of facial freckles. There are estimated to be between 20,000 and 25,000 genes in the human genome [6], and for each of these genes, there are two copies or *alleles* on chromosomes in somatic cells, one from each parent. Collectively, a person's genetic information is referred to as the *genome*, which was recently mapped in 2003 as a result of the Human Genome Project [7]. An individual with two of the same alleles for a given gene is said to be *homozygous* for that gene, whereas someone with two different alleles for a gene is called *heterozygous*. A *dominant* allele is one that is expressed if a person has at least one copy of the allele. A person who is either heterozygous or homozygous for a dominant allele will express the trait. Using facial freckles as an example, a person with at least one allele coding for freckles, where presence of freckles is the dominant trait, will express that trait and have facial freckles. Conversely, a *recessive* allele is one that requires both copies of the same allele to be expressed. In other words, a person would have to be homozygous for the recessive allele in order to express the trait, such as is the case with the absence of facial freckles. Additionally, some traits may not follow the dominant/recessive scheme but rather may exhibit *codominance* or *incomplete dominance*. Codominance refers to equal expression of both alleles in a heterozygote. This is the case with blood types, where there are three possible alleles: one coding for antigen A, another for antigen B, and the third coding for no antigen (O). Although either A or B antigen allele is dominant over O, A and B antigen alleles are said to be codominant because individuals homozygous for A and B antigens equally express both as AB blood type, rather than one type over another [5]. Incomplete dominance occurs when one neither allele is dominant over the other, resulting in an intermediate phenotype. This is exemplified by the genetic disorder familial hypercholesterolemia, where a person who is homozygous for the hypercholesterolemia allele has no low-density lipoprotein (LDL) receptors on his or her liver cells (resulting in very high levels of circulating cholesterol), a heterozygote has half the number of normal receptors, and a homozygote with both normal alleles has a full complement of LDL receptors [8].

Now that we have introduced the concept of genes and gene expression, let us revisit the concept of the sex chromosomes. Relative to the X chromosome, the Y chromosome has undergone drastic changes during the course of mammalian evolution. It has evolved to contain much fewer active genes than the X chromosome, with limited homology between the sex chromosomes [9]. To avoid a gender imbalance of protein expression due to copy number differences in sex chromosomes, a process called *X-chromosome inactivation* occurs in women. During X-chromosome inactivation, genes on one of the two X chromosomes are randomly silenced during embryogenesis, resulting in a mosaic pattern of X-linked gene expression, where half of the cells express paternal X-linked genes and half express maternal X-linked genes [9].

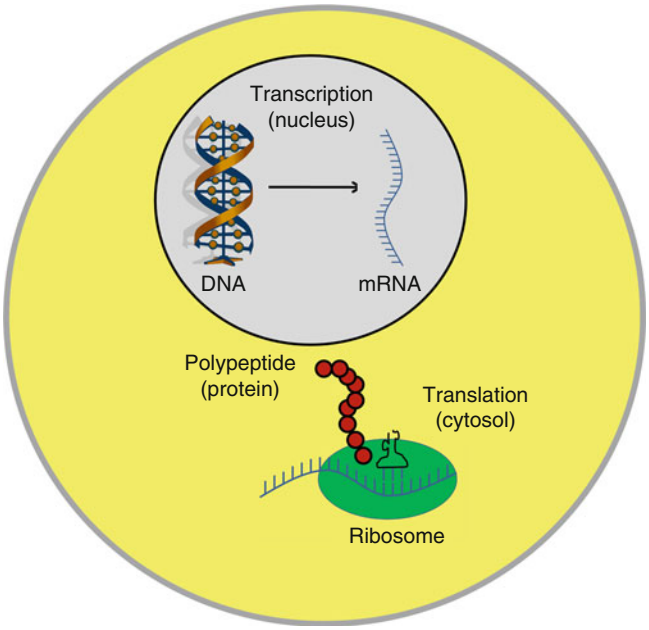


Fig. 2.1 A simplified schematic representation of gene expression. Transcription of DNA to mRNA occurs in the nucleus following binding of transcription factors to the promoter region of the gene. The mRNA is transported across the nuclear membrane to a ribosome located in the cytosol, where it is then translated into a single chain of amino acids called a polypeptide (protein), determined by the codons in the mRNA sequence

On a molecular level, gene expression is a multistep process, first involving translation of the gene, followed by transcription of the gene to protein (Fig. 2.1). A gene is first transcribed into a complementary single-stranded ribonucleic acid called *messenger RNA* (mRNA). Genetic code is read like a book, only instead of right to left, the code is read from 5′ (the upstream end) to 3′ (the downstream end). Complementary DNA strands (recall that there are two strands in the double helix) run in opposite directions (antiparallel) on each molecule so that the 5′ end of one strand is aligned with the 3′ end of the other. Genes from *eukaryotic* (multicellular) organisms are arranged into several subcomponents. These include a noncoding 5′ promoter region, a coding region consisting of *exons* and *introns*, and another noncoding region at the terminal end of the gene called the 3′ untranslated region (3′ UTR). Within the coding sequence of the gene, which describes the region that is transcribed into

messenger RNA (mRNA), exons refer to segments that code for protein, while introns are noncoding segments that are spliced out during mRNA processing prior to translation into protein. Differential splicing of introns and exons allows for expression of *isoforms* of proteins. Isoforms are alternate forms of the same protein. This occurs in the vast majority of human genes and serves to increase the diversity of proteins that can be produced from a finite number of genes in the human genome. Induction of transcription is activated by the binding of *transcription factors*, proteins that signal the start of transcription, in the regulatory sequence of the gene located upstream (5′) of the transcription start site. mRNA then migrates from the nucleus to a ribosome in the cytosol. Each consecutive three-base combination of the mRNA along the mRNA sequence, referred to as a *codon*, encodes either an *amino acid* or a *stop codon*. Amino acids constitute the basic building blocks of proteins and are sequentially linked in the ribosome to form a *polypeptide*. Polypeptide refers to a linear chain of amino acids that will eventually be formed into a protein. The stop codon tells the ribosome to end translation of the mRNA during the translation step. There are 20 different amino acids that are found in proteins, ten of which are synthesized in humans (the rest are obtained through diet). However, there are 64 different codon combinations that encode 21 possibilities (20 amino acids plus a stop codon), which means that some codon combinations have overlapping specifications. This has important ramifications for mutation effects, which will be further discussed below.

Charles Darwin's book, *On the Origin of the Species* [1], mentioned at the start of this chapter, describes the theory of natural selection and evolution. The contents provide the foundation for our present-day understanding of evolutionary pressure and the importance of genetic variation within populations. Darwin proposed that organisms that are better adapted to their environment survive and pass on their traits to their offspring. For this to occur, genetic assortment resulting in variable expression of traits must exist. Genetic variation within populations, collectively referred to as the *gene pool*, comes to be as a result of *mutations*, or alterations in the genetic code. While people are 99.9 % genetically identical to one another, it is the 0.1 % that is different is what makes us genetically diverse. Although it seems it, this is not an insignificant fraction if one considers that the human genome consists of nearly 3.2 billion bases [10]. Mutations that occur in germ cells, called *germline* mutations, can be passed along to offspring and potentially propagated throughout the population, while mutations that occur in somatic cells cannot. Some genes, due to evolutionary pressures, are highly conserved, meaning that they are the same in nearly all people, or even across species. This typically occurs in genes that code for functions that are essential to the viability of the organism, such as is the case with DNA helicases [11], which are involved in DNA replication, transcription, and repair. Conversely, other genes are much more variable among humans due to inherited mutations that have spread throughout the population over time. This is, in part, due to evolutionary pressures requiring adaptations in response to the environment, although some may also arise in subpopulations as a result of *founder effects*. A founder effect describes the phenomena where a small group or subpopulation becomes isolated and interbreeding occurs resulting in a loss of genetic variation [12]. A mutant allele that occurs at a frequency of at least 1 % in the general population is referred to as a *polymorphism*; genes exhibiting variability throughout the population are said to be *polymorphic*. The allele with the highest frequency in the general population is referred to as the *wild type*, whereas the less common allele is described as the *variant*. Of course, just as founder effects can result in quite high rates of mutation that are regionally propagated, normal polymorphisms also have different frequencies in different populations as a result of the migration of these different populations around the globe and of the timing of the origin of the genetic variant as humans migrated.

There are several different ways in which mutations can take place. Some common mutations resulting in heritable alterations in genetic code include *single-nucleotide polymorphisms* (SNP), involving the substitution of a base, and frameshift mutations, in which bases are inserted into or deleted from the sequence, throwing off the amino acid sequence of the protein [5]. SNPs are the most common source of genetic variability, occurring every 100–300 bases and accounting for 90 % of all interpersonal variability in human populations [13]. SNPs can either be *synonymous*, meaning that the base-change does not result in an altered amino acid sequence (recall that several codon combinations encode the same amino acid), or *non-synonymous*, meaning that the SNP results in the substitution of a new amino acid into the sequence, potentially changing the protein structure and function (also called a *missense mutation*). A mutation resulting in a premature insertion of a stop codon, called a *nonsense mutation*, causes truncation of the protein and generally results in loss of function [5]. Although synonymous SNPs do not alter the protein structure itself, this does not mean that they cannot have a relevant effect on gene expression. For example, a base alteration at a transcription factor binding site may result in decreased gene expression and therefore less available enzyme.

This variability in human genes nicely illustrates the concept of interpersonal susceptibility to diseases or susceptibility to environmental insult. Variability in traits involved in protecting us from disease can result in differential risk levels between individuals. Alterations in certain genes may influence the response to DNA damage or the way that environmental toxicants (or their metabolites) are processed and

excreted. The remainder of the chapter will focus, in detail, on genetic susceptibility due to variation and interaction with environmental exposures.

Phenotype Versus Genotype

An important distinction that must be made in genetics is the difference between *genotype* and *phenotype*. In the context of the material introduced earlier in the chapter, genotype describes the genetic code (DNA sequence) for a specific gene, whereas phenotype describes the traits expressed. A major caveat of genetics is that there is not always perfect concordance between genotype and phenotype. In fact, this is the case more often than not. It is important to remember that it is the phenotype that ultimately matters when it comes to physiology and disease development. There are a lot of different factors involved in this disconnect, including complex interrelationships between genes and among pathways, interpersonal variation in exposure to exogenous factors, and epigenetic modifications affecting gene expression (to be described later in this chapter). *Penetrance* describes the degree to which a gene expresses an associated trait [5], or otherwise put, it is the concordance between genotype and phenotype. In terms of cancer, genetic variants can be described as high-penetrance, moderate-penetrance, or low-penetrance risk alleles. The latter two categories are often collectively referred to as susceptibility genes.

High-penetrance alleles, in the context of cancer, are those that impart a high risk of cancer development during the lifetime of the allele carrier; they have often been termed "disease genes" as a direct result of this high penetrance. Fortunately, these alleles are relatively rare, generally with a minor allele frequency that is less than 0.1 % [14]. Although the individual risk of expressing the associated phenotype (in this case, cancer) to anyone carrying the high-penetrance allele is high, the population attributable risk of diseases from these mutations is low, since few people are carriers of the mutant allele. In fact, it is widely accepted that high-penetrance genes account for less than 5 % of all cancers [15]. There are several well-known examples of high-penetrance alleles associated with cancer development. Once such example is that of germline *BRCA1*/*BRCA2* mutations and the strongly associated risk of developing breast or ovarian cancer. Women carrying a *BRCA1* mutation have approximately 65 and 39 % chance of developing breast or ovarian cancer, respectively, by the age of 70 years [16]. The *BRCA2* mutation bears a slightly lower respective risk of 45 % and 11 % risk for developing breast or ovarian cancer, over the same time frame [16]. The overall prevalence of these mutations is estimated between 1 in 400 to 1 in 800 in the general population and about 1 in 40 among Ashkenazi Jews [17]. Note that although the risk of cancer is very high, not everyone with the mutation will develop cancer (i.e., express the phenotype). The inherited colorectal cancer susceptibility syndromes, familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), represent another set of high-penetrance alleles. These syndromes are associated with a drastically elevated lifetime risk of around 80 % for developing colorectal cancer, often with a relatively early age of onset [18]. FAP is due to a germline mutation in the *APC* gene, characterized by early development of hundreds of adenomatous polyps in the colon [18]. It occurs at a frequency of approximately 1 in 8,000 to 1 in 14,000 in the general population and accounts for less than 1 % of all colorectal cancers. HNPCC, also referred to as Lynch syndrome, occurs in approximately 1 in 1,000 to 1 in 3,000 people [19] as a result of germline mismatch repair gene mutations (*MLH1*, *MSH2*, *MSH6*, *PMS1*, or *PMS2*) [18]. In addition to its associated risk for colorectal cancer, Lynch syndrome also confers an elevated risk of developing several other malignancies, including cancer of the endometrium, ovary, stomach, small intestine, bladder, or biliary tract [18]. Other examples of high-penetrance cancer risk alleles include constitutional *CDKN2A* mutation and melanoma, familial *Rb* mutation and retinoblastoma, and constitutional *p53* mutation and Li-Fraumeni syndrome (a dominant disorder associated with drastically increased risk of various cancers with an early age of onset). It is important to note that although the risk of developing disease over a lifetime is generally very high for these alleles, the risk still does not usually reach 100 %, with rare exceptions.

Moderate-penetrance alleles, a sort of intermediate category, are still relatively rare, but generally less so than their high-penetrance counterparts. They typically have a minor allele frequency less than 2 % and are associated with, as the name implies, a moderate increase in disease risk [14]. These mutations tend to be population specific, often due to underlying founder effects [14]. There are several moderate-penetrance risk alleles associated with breast cancer, including constitutive mutations in *ATM*, *CHEK2*, *BRIP1*, or *PALB2* [14]. *APC* I1307K is another such allele, associated with a moderate increase in risk for colorectal cancer, and is present in approximately 6 % of Ashkenazi Jews [14]. Although carriers of the *APC* I1307K do not develop FAP, the mutation is still associated with a risk that is 1.5–2 times that of wild-type individuals [18].

The third of the aforementioned categories is that of low-penetrance alleles. These alleles tend to be relatively common, often with a minor allele frequency greater than or equal to 10 % [14]. However, by comparison with the previous categories, these confer a much lower individual risk for disease. Although the individual risk is low, the population attributable risk can be relatively high due to the frequent occurrence of the allele in the general population. This is in

stark contrast to high-penetrance alleles, which, recall, confer high individual risk of disease but bear a low population risk. Numerous low-penetrance alleles exist, including common polymorphisms found in genes coding for enzymes relating to the metabolism of exogenous substances, DNA repair, cell cycle, cell signaling, major histocompatibility complex genes, or any other such variants that can result in a small increase in susceptibility to disease. Several such low-risk susceptibility alleles will be presented in detail later in this chapter. Although these alleles only present a marginal risk in any given person, it is important to remember that they are more common, and thus in aggregate, these genes may combine or interact to exert a substantially elevated individual risk of disease.

Gene-Environment Interactions

Variation in genes with key roles in response to and metabolism of exogenous chemical exposures (called *xenobiotics*) by itself may not be sufficient to alter disease susceptibility. There first must be a xenobiotic exposure in order for the physiological response (or lack thereof) to have an impact. In other words, an effect modification between genotype and environmental or occupational exposures can take place, and this is known as a *gene-environment interaction* (Fig. 2.2). While we are in near constant contact with low levels of carcinogens due to both man-made and naturally occurring exposures, there are still interpersonal variations in exposure levels according to a range of factors, such as where we live or work as well as the personal lifestyle choices that we make. This concept is exemplified by the interaction of beryllium and a polymorphism in the human leukocyte antigen gene, *HLA-DPB1*, with respect to risk for chronic beryllium disease (CBD). Beryllium is a lightweight metal used in many industrial processes. Exposure to the metal usually stems from inhalation of beryllium dust, generated during a variety of industrial processes. Inhalation triggers a type IV antigen-specific immune response, which can give rise to a granulomatous pathologic process in the lung of those exposed, resulting in decreased breathing function. However, CBD only develops in an estimated 2–16 % of those exposed [20]. The reason why some people develop CBD following beryllium exposure, while others do not, can be largely explained by a polymorphism in the gene encoding human leukocyte antigen (*HLA-DPB1**E69). The *HLA-DPB1**E69 allele has been associated with increased sensitivity to beryllium and thus with development of CBD among those exposed [21–25]. Otherwise put, CBD cannot occur without a chronic beryllium exposure, but among those exposed, the risk of disease development is modulated by the presence or absence of the *HLA-DPB1**E69 allele.

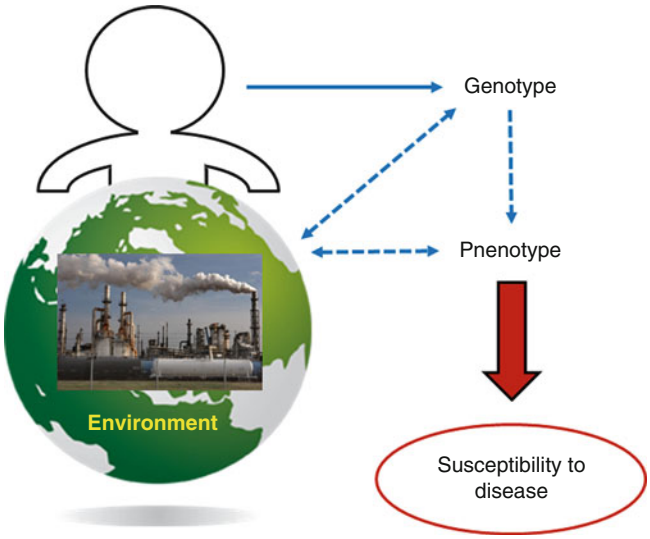


Fig. 2.2 This cartoon illustrates the interaction between genotype, phenotype, and the environment and the resultant effect on disease susceptibility. Each person has a unique collection of genes, collectively referred to as the genome. These genes may be expressed as phenotypes (traits) in varying degrees, dependent upon both host and environmental factors. Phenotypic expression, of a xenobiotic-metabolizing enzyme or DNA repair gene for example, can interact with an environmental or occupational exposure to modify an individual's susceptibility to disease

Xenobiotic Metabolism and Excretion

As previously discussed, we are constantly exposed to xenobiotic compounds, stemming from environmental and occupational exposures, as well as our own personal behaviors. Many of these exposures may confer a carcinogenic effect, either directly or through the action of their metabolites. Chemical compounds that can directly interact with DNA are called *direct carcinogens* (also referred to as proximal or ultimate carcinogens). However, the majority of carcinogens require metabolic activation in order to produce reactive intermediates capable of interacting with and damaging DNA. These are termed *procarcinogens* (also referred to as proximate carcinogens). These concepts will be discussed in further detail in Chap. 3, but for now, it is important to understand the basic concept. Interpersonal variability in susceptibility to disease may, in part, be explained by genetic differences in how we metabolize, excrete, and repair damage arising from these exposures. Genetic polymorphisms can affect the rates of key cellular functions aimed at limiting damage from both exogenous and endogenous exposures by altering or inactivating (or conceptually even enhancing) enzymatic activity or through reduced (or enhanced) gene expression.

Metabolism and excretion of xenobiotic compounds is often characterized by a two-step process: *activation* followed by *conjugation* [26]. The activation step, or *phase I*,

entails enzymatically catalyzed oxidation, reduction, hydroxylation, or other such reactions creating intermediaries for conjugation of the xenobiotic molecule. These reactive metabolites are then conjugated during *phase II*, inactivating it and allowing for its eventual excretion. Since metabolites are often more reactive and therefore potentially carcinogenic, following phase I but are deactivated in phase II, it follows that the rate of reaction in each step has important ramifications in terms of carcinogenic exposure and cancer risk. An important caveat is that these categories are not absolute, nor are they mutually exclusive. Some enzymes may catalyze a phase I reaction in some circumstances and phase II reactions in others. Additionally, a third and more recently acknowledged phase of xenobiotic metabolism (*phase III*) exists, involving active transmembrane transport of xenobiotics for excretion following inactivation [26].

Several classes of xenobiotics are able to stimulate expression of xenobiotic-metabolizing enzymes [26, 27]. Coordinate expression of gene batteries consisting of both phase I and phase II xenobiotic-metabolizing enzymes is inducible via xenobiotic receptors, which include receptors from the nuclear receptor superfamily (CAR, PXR, and PPAR) as well as the aryl hydrocarbon receptor (AHR). These receptors bind to xenobiotic response elements (XREs), also sometimes called dioxin response elements, in the 5′ promoter region of their target xenobiotic-metabolizing genes [27], thus inducing transcription. The AHR, for example, is capable of simultaneously inducing transcription of a battery of xenometabolic genes in humans, including *CYP1A1*, *CYP1A2*, *CYP1B1*, *NQO1*, *GSTA2*, *UGT1A1*, and *UGT1A6*. Therefore, these xenobiotic receptors play a crucial role in the activation of xenobiotic response to exogenous chemicals.

Phase I Polymorphisms and Cancer

The cytochrome P450 enzyme (CYP) superfamily makes up the largest group of phase I enzymes, comprising approximately 70–80 % of all phase I enzymes [28]. They are key players in the detoxification of many chemical carcinogens, including those found in cigarette smoke, along with other environmental and industrial exposures. There are currently 57 known CYP genes, divided among 18 families [29]. These enzymes may be expressed either hepatically or extrahepatically, dependent upon the gene. The most critical CYP enzymes in xenobiotic metabolism involve members of the CYP1, CYP2, and CYP3 families [30]. Several of the most commonly studied polymorphic CYPs are presented below, although this is merely intended to serve as an introduction and not meant to be an exhaustive list by far.

CYP1A1 is a polymorphic gene encoding an enzyme involved in the detoxification of a broad range of carcinogens, including but not limited to polycyclic aromatic hydrocarbons, *N*-nitrosamine, aromatic amines, 1,3-butadiene, and ethylene oxide [30, 31], all of which are all major constituents of tobacco smoke. Due to the importance of this enzyme in xenobiotic metabolism, the associations of several *CYP1A1* polymorphisms with various cancers have been widely studied, although with often mixed, and therefore inconclusive, results. To date, 12 variant *CYP1A1* alleles have been identified [32].

CYP1B1 is a polymorphic extrahepatically expressed cytochrome enzyme. It is involved in the metabolism of estrogen steroids but also plays a crucial role in the metabolism of polycyclic aromatic hydrocarbons (some of which it has very high affinity for), heterocyclic amines, arylamines, and nitroarenes [33]. More than 26 polymorphisms in the CYP1B1 gene have been identified, 19 of which are nonsynonymous [33]. As such, this enzyme has also been widely studied in relation to cancer and has been associated with several cancer types.

Another polymorphic and widely studied cytochrome enzyme is *CYP2E1*. This cytochrome, the only one identified in the CYP2E family, is hepatically expressed [33]. Several of the polymorphisms have been associated with altered levels of enzyme activity [34, 35], making them of interest to study due to interpersonal variation in phenotype associated with the polymorphisms. *CYP2E1* is of particular interest in the context of occupational and environmental exposures since its product plays a role in phase I metabolism of several industrial alkanes, alkenes, halogenated hydrocarbons, benzene, chloroform, vinyl chlorides, and a host of other chemicals relevant to industrial toxicology [36], many of which are known to be carcinogenic. It is also the inducible cytochrome metabolizer of ethanol, known as the microsomal ethanol oxidizing system [37], although it has a much lower affinity for ethanol compared to alcohol dehydrogenase, another hepatically expressed alcohol metabolizing enzyme.

Other polymorphic cytochromes have been extensively studied due to their crucial role in pharmacokinetics (drug metabolism). However, these enzymes still play a role in the metabolism of other substrates stemming from environmental or occupational exposures. *CYP3A4* and *CYP2D6* are both hepatically expressed cytochromes, considered to be two of the most important cytochrome enzymes for drug metabolism. However, they also have substrates that include organophosphate pesticides [38] and the tobacco smoke-derived procarcinogen 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK) [39], respectively. As such, although the major research focus has been on pharmacokinetic effects, both have also been investigated for their potential roles in cancer susceptibility.

Phase II Polymorphisms and Cancer

Many different enzymes are capable of carrying out phase II reactions. Here we will present some examples of commonly studied phase II enzymes in the context of cancer: the glutathione S-transferases (GST), N-acetyltransferases (NAT), and NQO1.

Glutathione S-transferases (GSTs; EC 2.5.1.18) are a superfamily of cytosolic phase II xenobiotic-metabolizing enzymes, whose function is to catalyze the detoxification of electrophilic metabolites, including benzo[α]pyrene and other polycyclic aromatic hydrocarbons (PAH) found in tobacco smoke, foods cooked at high temperatures, and combustion by-products, forming soluble, nontoxic peptide derivatives to be excreted [40]. At present, there are seven families of human cytosolic GSTs: alpha, mu, pi, sigma, omega, theta, and zeta [41]. The most commonly studied GST variants include *GSTM1* deletion, *GSTT1* deletion, and *GSTP1* Ile105Val (rs1695) polymorphism. The *GSTM1* and *GSTT1* deletions are recessive variants for which homozygous deletions result in null activity of their respective enzymes. *GSTP1* Ile105Val is a non-synonymous SNP that leads to a substitution of isoleucine by valine at amino acid position 105, resulting in alterations in the substrate binding site and enzyme activity [42]. These variants are very common; the *GSTM1* null genotype has an estimated prevalence of about 53 % for Whites and Asians and of approximately 27 % in people of African descent; the *GSTT1* null genotype has a prevalence of approximately 20 % for Whites and 47 % among Asians; and *GSTP1* Ile105Val variant G allele frequency of about 26 % among Whites [43]. Due to the high population frequency of these polymorphisms and the nature of their substrates, the GST genes have been widely studied with respect to cancer.

N-acetyltransferases (NAT; EC 2.3.1.5) are a family of phase II cytosolic enzymes that are expressed both hepatically and extrahepatically. *N*-acetylation constitutes the primary route for xenobiotic metabolism of aromatic amines and hydrazines, both of which are of interest for industrial toxicology and also stem from smoking and cooking by-products. Some aromatic amines are classified as definite human carcinogens (group 1) by the International Agency for Research on Cancer (IARC) [44]. There are two known active *N*-acetyltransferase isoenzymes found in humans: NAT1 and NAT2. These isoenzymes share 80–95 % homology and have overlapping substrates [45]. The N-acetylation phenotype associated with *NAT2* is quite variable in humans due to 30 alleles deriving from 13 SNPs [36]. Due to the high concordance with genotype, acetylator status is generally defined by phenotype, as either "slow," "intermediate," or "rapid," describing their respective capacities to inactivate reactive substrates. This distinction can be made via either genotyping [46] or phenotyping using appropriate substrates, such as caffeine [36]. Like its counterpart, *NAT1* also exhibits a high degree of variability, with 26 reported allelic variants [36], some of which also correlate with enzyme activity, particularly the *NAT1**4 and *10 alleles [36, 47].

NAD(P)H:quinone oxidoreductase (NQO1: EC 1.6.99.2) is a versatile antioxidant enzyme that functions as a phase II xenobiotic metabolizer by catalyzing detoxification of electrophilic molecules [48]. More specifically, NQO1 is involved in oxidative reduction of quinones, nitroaromatics, and azo dyes [48]. It has also been extensively studied for its role in reductive activation of important chemotherapeutic compounds [49, 50]. A common polymorphism involving a C to T transition at base pair 609, *NQO1 C609T* (rs1800566) is associated with loss of NQO1 enzyme activity [51].

Other Polymorphisms and Cancer

Xenobiotic-metabolizing genes are not the only polymorphic genes with potential implications for disease susceptibility. There is a host of other forms of genetic polymorphisms that can result in phenotypic variability and potentially alter susceptibility to cancer. Susceptibility genes can include, but are not limited to, variable genes involved in DNA repair, cell cycle, cell signaling, major histocompatibility complex genes, or those involved with induction of xenobiotic-metabolizing genes, such as the previously mentioned *AHR* gene. It is also important to recognize that not all environmental exposures are chemical in nature. For example, functional polymorphisms in genes responsible for repairing DNA damage sustained from radiation exposure, such as *XRCC1* Arg399Gln, which confers a three- to fourfold decrease in enzyme repair capacity [52], could result in increased susceptibility to disease. The former examples provided in this chapter are meant only to introduce the reader to some of the most commonly studied SNPs in relation to cancer, particularly in the context of environmental and occupation exposures, rather than to provide an exhaustive list of possible susceptibility genes. Specific genetic variants and their association with occupational cancer will be introduced later in further detail in the subsequent organ-specific chapters in this book.

Population Stratification

One of the central assumptions behind Mendelian genetics is that random mating takes place. To the contrary, we know that this is often not the case. In human populations, geographic and sociopolitical barriers have (and still do) prevented random mating across the general global population. The result is differences in allele frequencies of certain genes by race or ethnicity. This is an important concept to consider

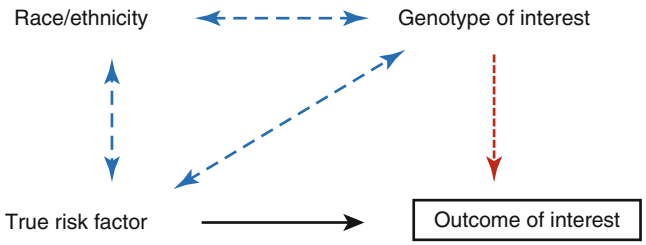


Fig. 2.3 A schematic diagram illustrating population stratification. In population stratification, a true causal risk factor for the outcome of interest, which could be genetic or environmental in nature, is associated with race/ethnicity. Therefore, any genotype that is also associated with ethnicity will be correlated with the true risk factor. Thus, the genotype will errantly appear to be associated with the outcome of interest, unless either the true risk factor or race/ethnicity is properly accounted and controlled for in the analysis. The *black solid one-way arrow* depicts a true causal relationship. The *blue bidirectional dashed arrows* represent a noncausal correlation. The *red unidirectional dashed arrow* indicates a confounded association due to population stratification (Adapted from Wacholder et al. [54], by permission of Oxford University Press)

because it can generate misleading results due to *population stratification* in genetic association studies if not properly accounted and controlled for. Population stratification refers to the nonhomogeneous genetic makeup of the source population by or within a racial or ethnic group [53, 54]. In the event that true risk factor for a disease is associated with race or ethnicity, any genotype, causal or not, will also be correlated with the true risk factor, which can create a false appearance of an association of the genotype with the disease, when in fact there is no relationship (Fig. 2.3). Consider a hypothetical example devised by Lander and Schork [55], where an admixed study population consisting of large proportions of subjects with Chinese and European heritage is assessed. In this population, it will appear that any genotype that occurs more frequently in people of Chinese ancestry compared to those of European ancestry is positively correlated with a phenotypic expression of an "ability to eat with chopsticks," unless either chopstick use or race/ethnicity is properly controlled for in the analysis.

Gene-Gene Interactions

Up to this point, the discussion has focused on how genes can interact with the environment, but it is important to mention that they can also interact with one another. In fact, in most instances, barring the most simplistic genetic scenarios, there is a woven web of complexity, made up of high-order interactions between multitudes of genes. At the most basic level, first-order gene-gene interactions can be observed (referring to an interaction between two genes); however, the reality is most likely not this simplistic. Staying with the xenobiotic metabolism and cancer susceptibility theme, this is demonstrated by interactions between phase I and phase II genes. An active phase I genotype that results in creation of reactive intermediaries at a higher rate may interact with a phase II genotype conferring and slower rate of conjugation, thus resulting in elevated cancer risk due to prolonged exposure to carcinogenic metabolites. At present, there limited reports in the literature regarding gene-gene interactions, in part due to the low degree of statistical power that most studies have to detect such an association. This is exemplified by the reported interaction observed in a pooled analysis of *CYP1A1* variants and *GSTM1*/*GSTT1* deletion polymorphisms with respect to lung cancer risk [56], where there was evidence of increased susceptibility among subjects with *CYP1A1**2A or 4 alleles and *GSTM1*/*GSTT1* deletions. Similar findings have subsequently been reported stemming from a case-control study of lung cancer, where an interactive effect between *CYP1A1**2a and *GSTM1* deletion was observed [57].

Genome-Wide Association Studies (GWAS)

Recent advances in technology, allowing for the conduct of genome-wide association studies (GWAS), capable of simultaneous assessment of up to one million SNPs, have further progressed our understanding of genetic susceptibility to cancer. However, despite early enthusiasm, this technology has not thus far identified any additional high-penetrance genes, and we are still only able to explain a fraction of familial cancer risk (8 % for breast cancer, 20 % for prostate cancer, and 6 % for colorectal cancer [58]). This is perhaps in part due to a small associated risk per gene for a large number of polymorphisms among the general population. Genes with small effect sizes are likely to be missed by GWAS due to insufficient statistical power for their detection. Nonetheless, GWAS has led to the identification of more than 100 low-penetrance cancer susceptibility loci (genes or chromosomal gene locations), most of which were previously unknown [59]. One susceptibility locus in particular, chromosomal region 8q24, has stood out as being associated with multiple cancer types, including prostate, breast, colorectal, bladder, glioma, gastric, and chronic lymphocytic leukemia (CLL) [58, 60].

Epigenetics and Environmental/ Occupational Exposure

Our genetic code is not the only biological program capable of interacting with exogenous chemicals. As an added complexity, alterations in our *epigenetic* configuration may stem from and interact with occupation and environmental exposures. In contrast with genetics, which represents our DNA code, epigenetics is a broad term used to define stable and

heritable changes that either alter or have the potential to alter gene expression without changing the actual DNA sequence [61]. These alterations include DNA methylation, histone modifications (acetylation methylation, sumoylation, or ubiquitylation), and microRNA expression and play critical roles in the regulation of gene expression, embryonic development, and genomic stability. Epigenetic modifications are signaled by the not yet understood histone code, which delineates the configuration of the DNA and therefore largely controls availability of the DNA for interaction with control proteins and for expression of genes.

DNA methylation is the most commonly studied epigenetic modification in humans due to its stability and amenability to measurement. The covalent attachment of a methyl group to cytosine at the 5-carbon of the pyrimidine ring results in 5-methylcytosine, which occurs in the context of CpG dinucleotides, where cytosine is positioned upstream and adjacent to guanine [62]. CpGs often occur in enriched regions referred to as CpG islands (CGI), which tend to be differentially located in the 5′ promoter regions of genes. Although approximately 70–90 % of all CpGs in the human genome are methylated under normal conditions [63], CGIs are generally not methylated in non-pathologic cells [62]; however, exceptions exist. While CGI methylation in gene promoters is generally associated with transcriptional repression of the gene, methylation of individual CpGs located outside of CGIs, particularly those located in DNA sequence repeat and pericentromeric regions, helps to maintain genomic stability [64, 65].

It is widely appreciated that cancer development is accompanied by epigenetic alterations, including localized promoter *hypermethylation* of tumor suppressor genes and genome-wide *hypomethylation*, particularly of repetitive elements [66, 67]. In fact, it has been recently established that the magnitude and direction of DNA methylation in response to aging and environmental exposures occurs in a CpG context-dependent manner, based upon the biology of the sequence in which it is embedded (i.e., CpG island, type of repeat sequence, transcription factor binding site, etc.) [68, 69]. Promoter hypermethylation is associated with transcriptional silencing, is at least as common as DNA mutation in the inactivation of tumor suppressor genes, and is considered to be a major event in carcinogenesis. There are approximately 100–400 hypermethylated CpG islands in the promoter regions of most tumors [66]. Conversely, hypomethylation describes a general loss of methylation, with tumor cells losing between 20–60 % of their genomic 5-methylcytosine relative to normal tissue [70].

A relatively new body of literature has begun to arise, describing the interplay between epigenetics and occupation or environment, in the context of cancer development. Epigenetic changes can occur in response to environmental or occupation exposures, bringing about alterations in gene expression and therefore eliciting phenotypic variation. Environmental exposures can alter the epigenetic regulation of the genome, although the precise mechanisms are still largely unknown. In support of this, a landmark study of monozygotic twins reported that while identical twins are epigenetically indistinguishable early in life, their epigenetic profiles become increasingly different later in life [71], which is likely attributable to differences in environmental exposures over the course of time. In experimental models, exposure to arsenic depletes S-adenosylmethionine (SAM), the primary methyl donor in DNA methylation, thus inducing global hypomethylation [72, 73], but has also been associated with promoter hypermethylation of *p53* [74] and *RASSF1A* [75]. Ultraviolet radiation exposure has been reported to induce global hypomethylation [76], while ionizing radiation has been shown to induce hypermethylation of *CDKN2A* [77]. Nickel can actuate de novo methylation of tumor suppressor genes through induction of heterochromatin conformation by suppressing H4 acetylation [78, 79]. Chromium exposure can cause gene silencing via histone acetylation through interactions with histone acetyltransferase (HAT) and histone deacetylase complex (HDAC) enzymes [80], which are the enzymes responsible for adding and removing histone acetylation marks, respectively. Other metals such as cadmium and zinc also can affect epigenetics, both of which have been shown to inhibit DNA methyltransferase (DNMT) activity (enzymes responsible for catalyzing the transfer of methyl groups to DNA) [81, 82]. Additionally, HDAC inhibitors bind through zinc at zinc-binding domains, preventing chromatin condensation [83].

People are most susceptible to epigenetic dysregulation during prenatal and neonatal development, puberty, and old age [80]. In addition to cancer research, a lot of research now centers around the importance of environmental exposures during intrauterine development and its effect on health throughout the life course [84].

References

1. Darwin C. On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life. 1st ed. London: John Murran; 1859.
2. Mendel G. Versuche über Pflanzen-Hybriden. Transactions of Verhandlungen des naturforschenden Vereines in Brünn. 1866; 4(1865):3–270.
3. Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. Nature. 1953;171(4356):737–8.
4. Mullis KB. The unusual origin of the polymerase chain reaction. Sci Am. 1990;262(4):56–61, 64–55.
5. Klug WS, Cummings MR. Genetics: a molecular perspective. Upper Saddle River: Pearson Education, Inc.; 2003.
6. Stein LD. Human genome: end of the beginning. Nature. 2004; 431(7011):915–6.
7. International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. Nature. 2004;431(7011):931–45.

8. Kumar V, Abbas A, Fausto N, Mitchell R, editors. Basic pathology. 8th ed. Philadelphia: Saunders Elsevier; 2007.
9. Morey C, Avner P. Genetics and epigenetics of the X chromosome. Ann N Y Acad Sci. 2010;1214:E18–33.
10. Human genome project information: the science behind the human genome project. US Department of Energy, Biological and Environmental Research Information System (BERIS). http://www.ornl.gov/sci/techresources/Human_Genome/project/info.shtml. Accessed 14 Aug 2011.
11. Abdelhaleem M. Helicases: an overview. Methods Mol Biol. 2010;587:1–12.
12. Ferla R, Calo V, Cascio S, et al. Founder mutations in BRCA1 and BRCA2 genes. Ann Oncol. 2007;18 Suppl 6:vi93–8.
13. Human genome project information: SNP fact sheet. US Department of Energy, Biological and Environmental Research Information System (BERIS). http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml. Accessed 12 Aug 2011.
14. Fletcher O, Houlston RS. Architecture of inherited susceptibility to common cancer. Nat Rev Cancer. 2010;10(5):353–61.
15. Vineis P. The relationship between polymorphisms of xenobiotic metabolizing enzymes and susceptibility to cancer. Toxicology. 2002;181–182:457–62.
16. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72(5):1117–30.
17. Petrucelli N, Daly MB, Feldman GL. Hereditary breast and ovarian cancer due to mutations in BRCA1 and BRCA2. Genet Med. 2010;12(5):245–59.
18. Rowley PT. Inherited susceptibility to colorectal cancer. Annu Rev Med. 2005;56:539–54.
19. Desai TK, Barkel D. Syndromic colon cancer: lynch syndrome and familial adenomatous polyposis. Gastroenterol Clin North Am. 2008;37(1):47–72, vi.
20. Fontenot AP, Maier LA. Genetic susceptibility and immune-mediated destruction in beryllium-induced disease. Trends Immunol. 2005;26(10):543–9.
21. Richeldi L, Sorrentino R, Saltini C. HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. Science. 1993;262(5131):242–4.
22. Wang Z, White PS, Petrovic M, et al. Differential susceptibilities to chronic beryllium disease contributed by different Glu69 HLA-DPB1 and -DPA1 alleles. J Immunol. 1999;163(3):1647–53.
23. Richeldi L, Kreiss K, Mroz MM, Zhen B, Tartoni P, Saltini C. Interaction of genetic and exposure factors in the prevalence of berylliosis. Am J Ind Med. 1997;32(4):337–40.
24. Saltini C, Richeldi L, Losi M, et al. Major histocompatibility locus genetic markers of beryllium sensitization and disease. Eur Respir J. 2001;18(4):677–84.
25. Rossman MD, Stubbs J, Lee CW, Argyris E, Magira E, Monos D. Human leukocyte antigen class II amino acid epitopes: susceptibility and progression markers for beryllium hypersensitivity. Am J Respir Crit Care Med. 2002;165(6):788–94.
26. Omiecinski CJ, Vanden Heuvel JP, Perdew GH, Peters JM. Xenobiotic metabolism, disposition, and regulation by receptors: from biochemical phenomenon to predictors of major toxicities. Toxicol Sci. 2011;120 Suppl 1:S49–75.
27. Kohle C, Bock KW. Coordinate regulation of Phase I and II xenobiotic metabolisms by the Ah receptor and Nrf2. Biochem Pharmacol. 2007;73(12):1853–62.
28. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science. 1999;286(5439):487–91.
29. Singh MS, Michael M. Role of xenobiotic metabolic enzymes in cancer epidemiology. Methods Mol Biol. 2009;472:243–64.
30. Autrup H. Genetic polymorphisms in human xenobiotica metabolizing enzymes as susceptibility factors in toxic response. Mutat Res. 2000;464(1):65–76.
31. Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. Chem Res Toxicol. 1998;11(6):559–603.
32. CYP1A1 Allele Nomenclature. 2009. http://www.cypalleles.ki.se/cyp1a1.htm. Accessed 15 Aug 2011.
33. Bozina N, Bradamante V, Lovric M. Genetic polymorphism of metabolic enzymes P450 (CYP) as a susceptibility factor for drug response, toxicity, and cancer risk. Arh Hig Rada Toksikol. 2009;60(2):217–42.
34. Bogaards JJ, van Ommen B, van Bladeren PJ. Interindividual differences in the in vitro conjugation of methylene chloride with glutathione by cytosolic glutathione S-transferase in 22 human liver samples. Biochem Pharmacol. 1993;45(10):2166–9.
35. Raucy JL, Kraner JC, Lasker JM. Bioactivation of halogenated hydrocarbons by cytochrome P4502E1. Crit Rev Toxicol. 1993;23(1):1–20.
36. Thier R, Bruning T, Roos PH, et al. Markers of genetic susceptibility in human environmental hygiene and toxicology: the role of selected CYP, NAT and GST genes. Int J Hyg Environ Health. 2003;206(3):149–71.
37. Bolt HM, Roos PH, Thier R. The cytochrome P-450 isoenzyme CYP2E1 in the biological processing of industrial chemicals: consequences for occupational and environmental medicine. Int Arch Occup Environ Health. 2003;76(3):174–85.
38. Eaton DL. Biotransformation enzyme polymorphism and pesticide susceptibility. Neurotoxicology. 2000;21(1–2):101–11.
39. Neafsey P, Ginsberg G, Hattis D, Sonawane B. Genetic polymorphism in cytochrome P450 2D6 (CYP2D6): population distribution of CYP2D6 activity. J Toxicol Environ Health B Crit Rev. 2009;12(5–6):334–61.
40. Frova C. Glutathione transferases in the genomics era: new insights and perspectives. Biomol Eng. 2006;23(4):149–69.
41. Parl FF. Glutathione S-transferase genotypes and cancer risk. Cancer Lett. 2005;221(2):123–9.
42. Ali-Osman F, Akande O, Antoun G, Mao JX, Buolamwini J. Molecular cloning, characterization, and expression in Escherichia coli of full-length cDNAs of three human glutathione S-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. J Biol Chem. 1997;272(15):10004–12.
43. Garte S, Gaspari L, Alexandrie AK, et al. Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev. 2001;10(12):1239–48.
44. Aromatic amines etc. IARC monographs on the evaluation of carcinogenic risks to humans. IARC Monographs, Vol. 99, IARC 2010.
45. Indulski JA, Lutz W. Metabolic genotype in relation to individual susceptibility to environmental carcinogens. Int Arch Occup Environ Health. 2000;73(2):71–85.
46. Cascorbi I, Drakoulis N, Brockmoller J, Maurer A, Sperling K, Roots I. Arylamine N-acetyltransferase (NAT2) mutations and their allelic linkage in unrelated Caucasian individuals: correlation with phenotypic activity. Am J Hum Genet. 1995;57(3):581–92.
47. Ishibe N, Kelsey KT. Genetic susceptibility to environmental and occupational cancers. Cancer Causes Control. 1997;8(3):504–13.
48. Dinkova-Kostova AT, Talalay P. NAD(P)H:quinone acceptor oxidoreductase 1 (NQO1), a multifunctional antioxidant enzyme and exceptionally versatile cytoprotector. Arch Biochem Biophys. 2010;501(1):116–23.
49. Kelsey KT, Ross D, Traver RD, et al. Ethnic variation in the prevalence of a common NAD(P)H quinone oxidoreductase polymorphism and its implications for anti-cancer chemotherapy. Br J Cancer. 1997;76(7):852–4.

50. Ross D, Kepa JK, Winski SL, Beall HD, Anwar A, Siegel D. NAD(P)H:quinone oxidoreductase 1 (NQO1): chemoprotection, bioactivation, gene regulation and genetic polymorphisms. Chem Biol Interact. 2000;129(1–2):77–97.
51. Traver RD, Horikoshi T, Danenberg KD, et al. NAD(P)H:quinone oxidoreductase gene expression in human colon carcinoma cells: characterization of a mutation which modulates DT-diaphorase activity and mitomycin sensitivity. Cancer Res. 1992;52(4):797–802.
52. Ginsberg G, Angle K, Guyton K, Sonawane B. Polymorphism in the DNA repair enzyme XRCC1: utility of current database and implications for human health risk assessment. Mutat Res. 2011;727(1–2):1–15.
53. Taioli E, Pedotti P, Garte S. Importance of allele frequency estimates in epidemiological studies. Mutat Res. 2004;567(1):63–70.
54. Wacholder S, Rothman N, Caporaso N. Population stratification in epidemiologic studies of common genetic variants and cancer: quantification of bias. J Natl Cancer Inst. 2000;92(14):1151–8.
55. Lander ES, Schork NJ. Genetic dissection of complex traits. Science. 1994;265(5181):2037–48.
56. Vineis P, Anttila S, Benhamou S, et al. Evidence of gene-gene interactions in lung carcinogenesis in a large pooled analysis. Carcinogenesis. 2007;28(9):1902–5.
57. Shah PP, Singh AP, Singh M, et al. Interaction of cytochrome P4501A1 genotypes with other risk factors and susceptibility to lung cancer. Mutat Res. 2008;639(1–2):1–10.
58. Stadler ZK, Vijai J, Thom P, et al. Genome-wide association studies of cancer predisposition. Hematol Oncol Clin North Am. 2010;24(5):973–96.
59. Varghese JS, Easton DF. Genome-wide association studies in common cancers–what have we learnt? Curr Opin Genet Dev. 2010;20(3):201–9.
60. Grisanzio C, Freedman ML. Chromosome 8q24-Associated Cancers and MYC. Genes Cancer. 2010;1(6):555–9.
61. Calvanese V, Lara E, Kahn A, Fraga MF. The role of epigenetics in aging and age-related diseases. Ageing Res Rev. 2009;8(4):268–76.
62. Tost J. DNA methylation: an introduction to the biology and the disease-associated changes of a promising biomarker. Mol Biotechnol. 2010;44(1):71–81.
63. Miranda TB, Jones PA. DNA methylation: the nuts and bolts of repression. J Cell Physiol. 2007;213(2):384–90.
64. Ehrlich M. DNA hypomethylation, cancer, the immunodeficiency, centromeric region instability, facial anomalies syndrome and chromosomal rearrangements. J Nutr. 2002;132(8 Suppl):2424S–9.
65. Hoffmann MJ, Schulz WA. Causes and consequences of DNA hypomethylation in human cancer. Biochem Cell Biol. 2005;83(3):296–321.
66. Esteller M. Epigenetics in cancer. N Engl J Med. 2008;358(11):1148–59.
67. Gronbaek K, Hother C, Jones PA. Epigenetic changes in cancer. APMIS. 2007;115(10):1039–59.
68. Langevin SM, Houseman EA, Christensen BC, et al. The influence of aging, environmental exposures and local sequence features on the variation of DNA methylation in blood. Epigenetics. 2011;6(7):908–19.
69. Christensen BC, Houseman EA, Marsit CJ, et al. Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. PLoS Genet. 2009;5(8):e1000602.
70. Lujambio A, Esteller M. How epigenetics can explain human metastasis: a new role for microRNAs. Cell Cycle. 2009;8(3):377–82.
71. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A. 2005;102(30):10604–9.
72. Chen H, Liu J, Zhao CQ, Diwan BA, Merrick BA, Waalkes MP. Association of c-myc overexpression and hyperproliferation with arsenite-induced malignant transformation. Toxicol Appl Pharmacol. 2001;175(3):260–8.
73. Zhao CQ, Young MR, Diwan BA, Coogan TP, Waalkes MP. Association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Proc Natl Acad Sci U S A. 1997;94(20):10907–12.
74. Davis CD, Uthus EO, Finley JW. Dietary selenium and arsenic affect DNA methylation in vitro in Caco-2 cells and in vivo in rat liver and colon. J Nutr. 2000;130(12):2903–9.
75. Marsit CJ, Houseman EA, Schned AR, Karagas MR, Kelsey KT. Promoter hypermethylation is associated with current smoking, age, gender and survival in bladder cancer. Carcinogenesis. 2007;28(8):1745–51.
76. Herceg Z. Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. Mutagenesis. 2007;22(2):91–103.
77. Cameron EE, Bachman KE, Myohanen S, Herman JG, Baylin SB. Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer. Nat Genet. 1999;21(1):103–7.
78. Broday L, Cai J, Costa M. Nickel enhances telomeric silencing in Saccharomyces cerevisiae. Mutat Res. 1999;440(2):121–30.
79. Davis CD, Uthus EO. DNA methylation, cancer susceptibility, and nutrient interactions. Exp Biol Med (Maywood). 2004;229(10):988–95.
80. Weidman JR, Dolinoy DC, Murphy SK, Jirtle RL. Cancer susceptibility: epigenetic manifestation of environmental exposures. Cancer J. 2007;13(1):9–16.
81. Poirier LA, Vlasova TI. The prospective role of abnormal methyl metabolism in cadmium toxicity. Environ Health Perspect. 2002;110 Suppl 5:793–5.
82. Takiguchi M, Achanzar WE, Qu W, Li G, Waalkes MP. Effects of cadmium on DNA-(Cytosine-5) methyltransferase activity and DNA methylation status during cadmium-induced cellular transformation. Exp Cell Res. 2003;286(2):355–65.
83. Furumai R, Matsuyama A, Kobashi N, et al. FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases. Cancer Res. 2002;62(17):4916–21.
84. Barker DJ. The developmental origins of adult disease. J Am Coll Nutr. 2004;23(6 Suppl):588S–95.

Mechanisms of Environmental and Occupational Carcinogenesis

3

Scott M. Langevin and Karl T. Kelsey

Keywords
Mechanisms of carcinogenesis • Chemical carcinogenesis • DNA damage • DNA repair • Genetics • Epigenetic changes

Introduction

Carcinogenesis is a multistep process, marked by an accumulation of genetic and epigenetic alterations, culminating in the development of cells that have lost the ability to control growth, potentially taking on an invasive phenotype and becoming a clinically appreciated disease. These alterations can arise as a result of exogenous physical, chemical, and biological exposures stemming from the environment, including those encountered in the occupational setting.

Hanahan and Weinberg have described six hallmark capacities necessary for cancer development [1, 2]. These pathways include sustained proliferative signaling; evasion of growth suppressors; resistance to cell death; establishment of unlimited reproductive potential (cellular immortality); induction of *angiogenesis* (growth of new blood vessels) as a source of oxygen, nutrient, and waste exchange; and activation of *invasion* (movement of cancer through the basement membrane of the tissue or into other adjacent normal tissues [3]) and *metastasis* (relocation of malignant cells from their original site to elsewhere in the body [3]). These events largely occur as a result of the activation of *oncogenes* and inactivation of *tumor suppressor genes*. An oncogene is a cancer-inducing gene [3] that is capable of helping the cell survive and proliferate. A *proto-oncogene* is a normal gene that can undergo alterations resulting in altered enzyme activity, regulation, expression, or stability, enabling it to become an oncogene. Conversely, a tumor suppressor gene is a gene that protects the cell from cancer [3], such as through inhibition of proliferation or induction of apoptosis.

Oncogenes are generally described as acting in a dominant fashion, while tumor suppressor genes are considered, in general, to follow a recessive model. Increased activity or expression of a single allele is sufficient for the activation of an oncogene, as it acts to produce increased signaling providing for a growth or survival advantage. Historically, Knudson's two-hit hypothesis has dictated that the inactivation of a tumor suppressor gene typically requires a loss of function of both alleles [4, 5]. This can occur, for example, by deletion of one allele (often termed *loss of heterozygosity* (LOH)) with mutation of a second allele. This is because the inactivation of one allele is generally insufficient, since the enzyme can still be produced as long as there is still one normal allele. There is, however, mounting evidence that this may be an oversimplification and that even partial inactivation of tumor suppressor genes can lead to *haploinsufficiency*, which arises when one wild-type allele is insufficient to provide the full functionality of two wild-type alleles and can play a role in the carcinogenic process [6]. Genetic and epigenetic changes can occur as a result of environmental or occupational exposures, contributing to carcinogenesis through facilitation of these hallmark events.

S.M. Langevin, PhD
Department of Environmental Health,
University of Cincinnati College of Medicine,
3223 Eden Avenue, ML0056, Cincinnati, OH 45267, USA
e-mail: scott_langevin@brown.edu

K.T. Kelsey, MD, MOH (✉)
Department of Epidemiology, Department of Pathology and Laboratory Medicine, Center for Environmental Health and Technology, Brown University,
70 Ship Street, Box G-E5, Providence, RI 02912, USA
e-mail: karl_kelsey@brown.edu

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_3,

Field Cancerization and Expanding Fields

Our tissues regularly encounter a variety of exogenously and endogenously derived exposures that are capable of inducing genetic and epigenetic alterations, which will be described in detail later in this chapter. This is particularly true of the epithelial layers which are chronically exposed to a host of environmental and occupational *carcinogens*. The term carcinogen describes any agent that contributes to the formation of malignant cells [3]. In 1953, Slaughter and colleagues [7] proposed the "field cancerization" model, in which they suggested that in people with multiple cancers at a single site or organ, the tumors develop from distinct clones arising due to accumulation of independent mutations associated with chronic exposure of the epithelium to environmental carcinogens. It has since been demonstrated that second primary tumors arising distant from the site of the original primary can be clonally related [8]. This theory has since been revised as the "expanding fields" model, which proposes that a single stem cell in the basal layer of the epithelium undergoes a transformation that confers a growth or survival advantage. This cell then clonally expands and gradually replaces the normal epithelium. As cells within the expanding field acquire new advantageous alterations, various subclones develop within the field, which, as aforementioned hallmarks are satisfied, can eventually propagate into distinct but related tumors.

Environmental and Occupational Sources of DNA Damage

DNA damage can take many different forms, which are categorized in Table 3.1. There is a wide variety of damage that can occur, including adduct formation, cross-linkage, oxidation, deamination of bases, and breaks in the DNA sugar-phosphate backbone [9, 10]. The short-term consequences vary, although ultimately unrepaired DNA damage that does not trigger apoptosis (programmed cell death) can result in incorporation of mutations into the cellular genome that can be passed on to subsequent generations of cells.

DNA damage can arise as a result of both exogenous and endogenous exposures. Damage causing exposures that are encountered via the environment or in an occupational setting are considered to be exogenous, although certain exogenous exposures can trigger internal reactions that generate endogenous carcinogens. Potential environmental or occupational sources of DNA damage include both physical and chemical agents. Physical carcinogens may include forms of *ionizing radiation* [11] (radiation with sufficient energy to break atomic bonds), such as x-rays or emissions from radioactive elements, while chemical agents can derive from a wide variety of sources, including combustion or heat generation, pollution sources, food additives, and occupational exposures, and are further described in the subsequent section.

Mechanisms of Carcinogenesis

Physical Carcinogenesis

As previously discussed, one source of physical DNA damage is ionizing radiation. This includes high-frequency (short wavelength) forms of radiation with sufficient energy to break covalent bonds, including x-ray or products of radioactive decay such as gamma radiation [11]. Ionizing radiation can induce DNA damage in a variety of ways. These higher frequency forms of ionizing radiation include x-rays, cosmic gamma rays from space, or radioactive decay (including gamma rays and alpha and beta radiation particles) of unstable elements like uranium-238 or radon gas. They exert their primary mutagenic effect through induction of single- and double-stranded breaks, chromosomal breaks, and oxidative lesions through the formation of free radicals, although they are also capable of generating interstrand cross-link lesions [12]. Despite the fact that double-stranded breaks occur much less frequently than single-stranded breaks or base lesions, they are considered to be the most toxic form of damage resulting from ionizing radiation, due to their great potential for inducing deletions and loss of heterozygosity.

Ultraviolet light, which is only marginally ionizing, is also capable of inducing DNA damage. It exerts the bulk of its carcinogenic action through covalent cross-linkage of pyrimidines (C or T bases), connecting bases on opposing strands of the double helix preventing separation of the strands during transcription, inhibiting the process. It can also generate UV signature mutations involving C to T *transitions* (a transition is an interchange between either two purines or two pyrimidines), primarily at dipyrimidinic or 5-methylcytosine sites, and stimulation of oxidative damage, caused by the production of reactive oxygen species (ROS) through the activation of small molecules, including riboflavin, tryptophan, and porphyrin [13–16].

Another form of physical agent that has been increasingly studied in recent years is electromagnetic field (EMF) nonionizing radiation. As opposed to ionizing radiation, nonionizing radiation does not have sufficient energy to break atomic bonds [11]. The effect of this kind of low-frequency radiation on human health is controversial. The primary issue is that there is no consensus on whether or not nonionizing radiation has any biological/physiological effect in human cells, much less if it plays a role in human pathologic processes. Although some studies have found associations with damage or disease, the literature surrounding their biological implication is extremely conflicting and contradictory and therefore inconclusive [17].

Table 3.1 Major types of DNA damage

Damage type	Description	Consequence
Small adduct (alkylation)	Covalent attachment of an alkyl group to the DNA molecule	Destabilize the DNA and create abasic sites
Bulky adduct	Covalent attachment of a large molecule to the DNA molecule	Blocks transcriptional machinery and distorts DNA, inducing chromosomal breaks and deletions
Cross-linkage	Covalent linkage of the DNA strands	Strands cannot separate, inhibiting DNA replication or transcription
Oxidation	Oxidative damage caused by the reaction of free radicals with DNA	Induction of base mispairings and DNA strand breaks
Deamination	Hydrolytic reaction resulting in the loss of a base	Loss of base and corresponding coding information
DNA strand breaks	Double- or single-stranded break in DNA phosphate backbone	Chromosomal breaks, deletion, and genomic instability

Chemical Carcinogenesis

A chemical carcinogen is a substance with a distinct chemical composition that has a carcinogenic capacity. The husband and wife tandem of James and Elizabeth Miller established the notion that most chemical carcinogens do not directly interact with DNA but rather must be metabolized in order to exert their carcinogenic effect [18]. Direct carcinogens, which are also referred to as proximal or ultimate carcinogens, are compounds that can react with DNA in their natural unmetabolized state. Examples of direct carcinogens include ethylene oxide, formaldehyde, and a number of chemotherapeutic alkylating agents [19], all of which are directly DNA reactive with no need for further metabolic conversion. Conversely, procarcinogens (sometimes called proximate carcinogens) must be metabolized to produce reactive intermediates capable of interacting with and damaging DNA. It is estimated that around one-quarter of chemical carcinogens are direct acting, while the remaining three-quarters fall into the latter category, requiring activation [20]. They primarily act by damaging DNA through the formation of covalent lesions such as adducts or cross-linkage, through oxidative damage stemming from free-radical production, or through induction of epigenetic alterations [20]. In contrast to endogenous carcinogens, which are already internalized, chemical carcinogens or their reactive metabolites must be capable of entering the cell to generate DNA damage, meaning that they must either possess lipophilic properties allowing for passive transport or be actively transported across the cellular membrane [20].

A major way in which chemical carcinogens exert effect is through covalent bonding to DNA nucleotides, forming *DNA adducts*. DNA adducts can be considered in two broad categories: (1) small (low molecular weight) adducts and (2) bulky (macromolecular) adducts. It is important to note that most DNA adducts do not give rise to mutations. Some adducts may have little effect on the integrity of the DNA, while others are much more mutagenic. Most adducts forming chemical carcinogens are hard electrophiles (nonpolar molecules with a positively charged electrophilic center) that irreversibly and stably adduct to hard nucleophilic sites (non- or low-polarized site with a strong electronegative charge) on DNA, whereas other reactive chemicals, such as aldehydes and ketones, are soft electrophiles (polarized molecules with a partial positive charge) and reversibly react with soft nucleophilic sites (polarizable sites with low electronegativity) on DNA [20, 21]. This is an important chemical distinction since the ability of a chemical to form stable adducts is associated with increased mutagenicity [22, 23]. The binding position of the adduct on a nucleotide also matters with respect to carcinogenic potential, so chemical agents with an affinity for binding at certain sites may be more potent carcinogens.

Small, low molecular weight DNA adducts are commonly formed through *alkylation*. These alkylation lesions involve the covalent attachment of a functional alkyl group to the DNA molecule. Alkyl groups are organic chemical groups consisting only of carbon and hydrogen atoms, with the general chemical formula C_nH_{2n+1} [24]. Methyl groups ($-CH_3$) are the most common alkyl group adducted to DNA [25]. Generally speaking, alkylation lesions occurring on a base-ring nitrogen tend to be less mutagenic relative to those occurring on ring oxygen [26]. These adducts can destabilize DNA leading to *apurinic* (degradation of a purine base) or *apyrimidinic* (degradation of a pyrimidine base) sites, collectively referred to as *abasic* sites, and can also potentially result in misincorporation of bases if the alkylation occurs at base-pairing sites [27]. For example, O^6-methylguanine is errantly recognized as adenine and O^4-methylthymidine is read as cytosine. Additionally, some alkylating agents are capable of inducing DNA interstrand cross-link lesions, which prevent the DNA strand from separating, inhibiting transcription or replication [28], and may generate double-stranded breaks during the repair process [29, 30].

In contrast, bulky adducts, which are much larger, chiefly exert their effect by blocking DNA transcription or replication machinery or through induction of chromosomal breaks and large deletions that can lead to loss of heterozygosity [20]. Both experimental and epidemiological evidence suggest a strong association between DNA adduct formation and cancer development [22, 23, 31–36]. As with

small adducts formed by alkylation damage, the location of adduct formation on the DNA molecule matters with respect to mutagenicity [20]. For example, benzo[α]pyrene is a polycyclic aromatic hydrocarbon found in cigarette smoke, well-cooked foods, and combustion products and exhaust fumes [19]. It generates an often-studied bulky adduct, benzo[α]pyrene-7,8-diol-9,10-epoxide, which binds to the N2 amino group of guanine bases in the minor groove of the DNA helix, distorting its structure and inducing mutations [9, 20]. Similarly, aromatic amine adducts, although more complex, can produce reactive intermediates that can form stable adducts at the C8-, N2-, or O6-position of guanine, although the major form of aromatic amine adducts are C8-deoxyguanosine lesions that occupy the major groove of the helix, which produce conformational changes to the DNA and inducing sequence alterations [9, 20].

Additionally, some exogenous chemicals or their metabolic intermediaries are also capable of inducing oxidative DNA damage, frequently as a result of by-products produced during their metabolism. In fact, oxidative damage accounts for a large portion of DNA mutations [37]. This occurs primarily through production of *free radicals* (reactive molecules or ions with unpaired electrons), such as reactive oxygen species (ROS) [38]. Generation of ROS can occur as a direct result of exogenous chemicals or, as will be discussed in a subsequent section, indirectly through induction of inflammation. Oxidative damage can produce a variety of molecular anomalies including strand breaks and covalent base lesions [38]. However, the predominant lesions induced are 8-hydroxydeoxyguanosine lesions and thymine glycol, which can result in base mispairings, potentially leading to base-misincorporation mutations [39]. Dioxins and dioxin-like polychlorinated biphenyls (PCBs) are prime examples of such carcinogens for which the carcinogenic properties derive from free-radical production [40].

Up to this point, the majority of carcinogens that have been discussed involve organic chemicals, meaning that the molecules contain carbon atoms. However, several toxic metals or metalloids (inorganic compounds) are considered by the International Agency for Cancer Research (IARC) to be definite or probable carcinogens [41–43], including nickel, cobalt, lead, vanadium, beryllium, arsenic, and chromium. People can be exposed to such metals environmentally, such as through diet, pollution, and occupation. They are of interest due to their long-standing biopersistence, since they do not degrade [44], although the carcinogenic mechanisms for most are not as well elucidated as they are for organic chemical carcinogens. Despite that metals and metalloids are often not potent mutagens and do not typically produce adducts, many metals are able to exert an effect through other chemical means. The carcinogenicity of different metals operates through various pathways, some of which include, but are not necessarily limited to, induction of genetic and epigenetic alterations, deregulation of cellular proliferation and metabolism, aberrant activation of signal transduction pathways, generation of reactive oxygen species, and induction of hypoxia pathways [45], or by competitive binding with enzyme-associated metals, such as may be the case with the inhibition of zinc-finger DNA repair proteins by arsenic, cadmium, nickel, cobalt, or lead [46].

Endogenous Mechanisms Activated by Exogenous Exposures

Environmental or occupational exposures may also act indirectly by stimulating endogenous mechanisms that create carcinogenic effects. Spontaneous DNA damage may arise as a result of internal processes, leading to hydrolysis, adduct formation, and generation of free radicals, including reactive oxygen species, reactive nitrogen species, and lipid peroxidation [38]. Hydrolysis can create abasic sites or result in deamination [27, 47, 48]. Adducts derived from endogenous reactions, such as production of aldehydes [49] or estrogen metabolites [50], which, as with exogenously derived adducts, are capable of inducing mutations. Reactive oxygen species can produce oxidative lesions, single-stranded breaks, or phosphoglycolates (a lesion produced at the sites of radiation-induced DNA strand breaks [51]) [38, 52]. Reactive nitrogen species, such as nitric oxide or peroxynitrite, can also create oxidative lesions and/or covalent adducts [53]. Lipid peroxidation is a process by which ROS oxidize polyunsaturated fatty acids producing lipid hydroperoxides and lipid peroxyl radicals and generate covalent adducts, including DNA cross-links [38, 54]. Many of these internally generated DNA damaging processes can occur in response to exogenous exposures, for example from an inflammatory response, particularly in the presence of chronic exposures, such as regular inhalation of cigarette smoke or particulate matter or of biopersistent particles that do not easily degrade and remain in tissues, as is the case with asbestos fibers and many metals or metalloids.

DNA Repair

Our DNA is the repository for all of our genetic information, providing the blueprint for our cellular functions. Therefore, protection of DNA integrity is of paramount importance in maintaining healthy cells. To this end, organisms have evolved complex mechanisms to repair damaged DNA. To illustrate the importance, consider that an estimated 20,000 DNA damaging events occur per cell per day [55]. Unrepaired

DNA damage can either result in cellular death or incorporation of mutations into the genetic code that can be passed on to subsequent generations of cells. In humans, there is wide interindividual variation in DNA repair rates [9], which, in part, could help to account for differences in cancer susceptibility between people. Broadly speaking, there are seven classes of DNA repair: direct reversal, base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), interstrand cross-link repair, double-stranded DNA break repair, and DNA damage tolerance, which are explained in further detail below. The loss of any of these functions can result in an elevated rate of mutations compromising genomic integrity.

Direct Reversal Repair

Some DNA damage can be repaired solely through a chemical process, referred to as direct reversal repair. One such mechanism involves removal of alkylation damage from nucleotides. In this process, the alkyl lesion is directly transferred from the alkylated base to a DNA alkyltransferase [9]. Each alkyltransferase molecule is only capable of carrying out this reaction once, after which it is rendered inactive. The DNA repair enzyme O-6-methylguanine-DNA methyltransferase (MGMT) is capable of carrying out such a reaction with the common O^6-alkyguanine and O^4-alkylthymine lesions. The loss of MGMT expression in tumors is associated with genomic instability and generally poorer prognosis. A notable exception is when the patient is treated with an alkylating chemotherapeutic agent, such as temozolomide, as is observed with glioblastoma patients [56]. In this case, loss of expression has a positive influence on outcome, since these drugs exert their main effect by stimulating apoptosis through accumulation of unrepaired alkyl damage in actively replicating tumor cells, which occurs less effectively when the lesions are actively repaired. In addition to correction of alkyl lesions, other examples of direct chemical repair include reparation of ultraviolet light-induced pyrimidine dimers by DNA photolyase [57] or of small single-stranded DNA breaks by DNA ligase [58].

Base Excision Repair

Base excision repair (BER) is specific for correction of damaged bases, in particular apurinic or apyrimidinic bases [59, 60]. A key function of this mechanism is the removal of small, non-helix-distorting DNA lesions, such as those caused by alkylating agents [9]; thus, this mechanism has some functional overlap with direct DNA repair. BER is initiated through the action of DNA glycosylases (e.g., hOgg1 or MYH) that remove the damaged base, creating an apurinic site. This area on the damaged strand is then cleaved by an apurinic endonuclease (AP endonuclease), followed by DNA synthesis by a DNA polymerase (pol β, pol γ, pol δ, pol ε, or pol λ) and ligation (ligase I, II, IIIα, IIIβ, or IV) using the non-damaged strand as a template [59, 60]. The relevance of BER to cancer is exemplified by heritable germline mutations in the aforementioned *MYH* glycosylase, which is involved in the removal of the damaged base. This results in *MYH*-associated polyposis (MAP), predisposing individuals to development of multiple adenomatous polyps between the age of 40 and 60 years old, with an elevated risk of colorectal cancer [61].

Nucleotide Excision Repair

Nucleotide excision repair (NER) is another mechanism that serves to remove adducts. However, in contrast with BER which tends to repair small adducts, NER is specific for recognition and removal of bulky DNA adducts [62, 63]. As previously discussed, bulky adducts can distort the helical structure and obstruct transcription and replication. Broadly speaking, NER consists of three basic steps: (1) recognition of the lesion, (2) unwinding of the DNA surrounding the lesion, and (3) incision and removal of the lesion [62]. Dependent upon how the damage is detected, NER can be further subdivided into transcription-coupled (TC-NER) or global genome (GG-NER) mechanisms. In TC-NER, RNA polymerase (RNA pol II) detects the lesion during transcription, as suggested by the name, when it encounters the stalled replication fork. Alternatively, in GG-NER, bulky lesions are recognized independent of transcription by damage-sensing proteins, such as the DDB1/DDB2 and XPC-hHR23B heterodimers. In either case, the damage-sensing step is followed by the binding of a pre-incision complex comprised of XPA, replication protein A (RPA), and the multi-subunit transcription factor IIH (TFIIH), which includes XPB and XPD helicase subunits. The DNA surrounding the lesion is then unwound, after which ERCC1-XPF and XPG endonucleases make incisions 24–32 base pairs around the 5′ and 3′ end of the damage, respectively [62, 63]. The damaged segment of DNA is then removed and the resultant gap is filled in by DNA polymerase and ligase. The critical importance of NER is demonstrated by several severe syndromes involving photosensitivity that arise in individuals with inherited recessive XP helicase defects. These syndromes include the non-cancer-associated Cockayne syndrome and trichothiodystrophy, as well as xeroderma pigmentosum [63, 64], which is associated with greater than 1,000-fold increased risk for UV-induced skin and ocular cancer [64].

Mismatch Repair

Recall that normally in DNA, adenine from one strand must pair with a guanine on the complementary strand, while cytosine must pair with thymine. However, the pairing of noncomplementary bases can occur due to DNA replication errors leading to errant base insertion or as a result of damage induced by base lesions, such as deamination [65]. Mismatch repair is a post-replication mechanism that is specific for base mispairings [65]. Mismatches are recognized by the MutHLS system, consisting of a MutS heterodimer (Msh2/Msh3 or Msh2/Msh6) and MutL heterodimer (composed of Mlh1 paired with Pms1, Pms2, or Mlh3), and MutH endonuclease [65, 66]. When damage is sensed, MutS and MutL activate the MutH endonuclease, which makes an incision on the unmethylated daughter strand. DNA helicase II (UvrD) is recruited to the incision site, unwinding the DNA strands. The MutHLS complex then slides along the daughter strand in the direction of the mismatch, accompanied by an exonuclease that excises the lesion. The resultant single-stranded gap is then filled in by DNA polymerase III and DNA ligase [65]. Lynch syndrome is an inherited cancer syndrome due to germline mutations in one of several mismatch repair genes, including *MLH1*, *MSH2*, *MSH6*, and/or *PMS2* [67, 68], resulting in accumulation of genetic damage and genomic instability. Lynch syndrome, also referred to as hereditary non-polyposis colorectal cancer (HNPCC), is estimated to account for 3 % of colorectal cancer cases and is additionally associated with elevated incidence of cancers of the endometrium, ovary, bladder, stomach, small intestine, pancreas, gall bladder, bile duct, brain, and skin [67, 68].

Interstrand Cross-Link Repair

This DNA repair mechanism is specific for cross-links between opposing strands of the DNA double helix. There are several mechanisms involved in human interstrand cross-link repair, most of which utilize NER pathways in conjunction with machinery from homologous recombination, mismatch repair, Fanconi anemia, and/or translesion synthesis pathways [69]. There are three basic contexts in which interstrand cross-link repair can occur: (1) DNA replication-coupled repair, (2) transcription-coupled repair, and (3) a global pathway that neither requires transcription nor translation [28]. In the first two scenarios (replication-coupled repair and transcription-coupled repair), the interstrand cross-link lesion causes a stall at the replication fork during DNA replication or transcription by a polymerase, followed by the removal and repair of the lesion via a combination of the aforementioned repair mechanisms. Alternatively, global genome repair mechanisms (previously discussed in the nucleotide excision repair section) can be used to sense DNA cross-links independent of DNA replication or transcription [28]. Deficiencies in the cross-link damage-sensing Fanconi anemia pathway result in organ defects, as well as a substantially elevated cancer risk [70], exemplifying the relevance of interstrand cross-link repair to cancer prevention.

Double-Stranded DNA Break Repair

As we discussed in an earlier section, double-stranded DNA breaks (DSB) represent a major threat to DNA integrity [71], preventing replication and potentially leading to deletions and loss of heterozygosity. There are two main mechanisms through which DSB repair operates: (1) non-homologous end joining and (2) homologous recombination [71]. The former mechanism (non-homologous end joining) simply links the broken ends of the DNA back together, in an enzymatic reaction [71]. However, this mechanism does not utilize a template strand for repair and thus is very error prone. Since it does not consider missing or added genetic information, it is occasionally associated with the gain or loss of several bases at the join point. The latter of the two mechanisms (homologous recombination) is much more complex and takes missing genetic information into account and therefore by contrast is considered to be far less susceptible to errors [9, 71]. The success of homologous recombination is based on the ability of single-stranded DNA to locate regions of perfect or near-perfect homology elsewhere in the genome. This is predominately carried out using the sister chromatid produced following DNA replication, although the same DNA molecule or a homologous chromosome may also be utilized [71]. Since homologous recombinant repair generally utilizes a sister chromatid as a source for the template, it is primarily constrained to the S and G2 phase of the cell cycle, when sister chromatids are available [71]. The importance of double-stranded break repair in protection from development of cancer-inducing aberrations is demonstrated by increased cancer incidence associated with several inherited conditions involving germline mutations in double-stranded break repair genes. Germline mutations in *BRCA1*/*BRCA2* genes, both of which play a role in homologous recombination pathways, are associated with a high lifetime risk for developing breast or ovarian cancer [72, 73]. Additionally, some radiation sensitivity syndromes arise as a result of germline mutations in damage-sensing genes involved in DNA double-stranded break repair. These include ataxia telangiectasia and Nijmegen breakage syndrome, which occur as a result of respective inherited germline mutations in the *ATM* and *NBS1*, both of which are involved in sensing double-stranded break damage and are associated with a substantial increase in cancer susceptibility [74].

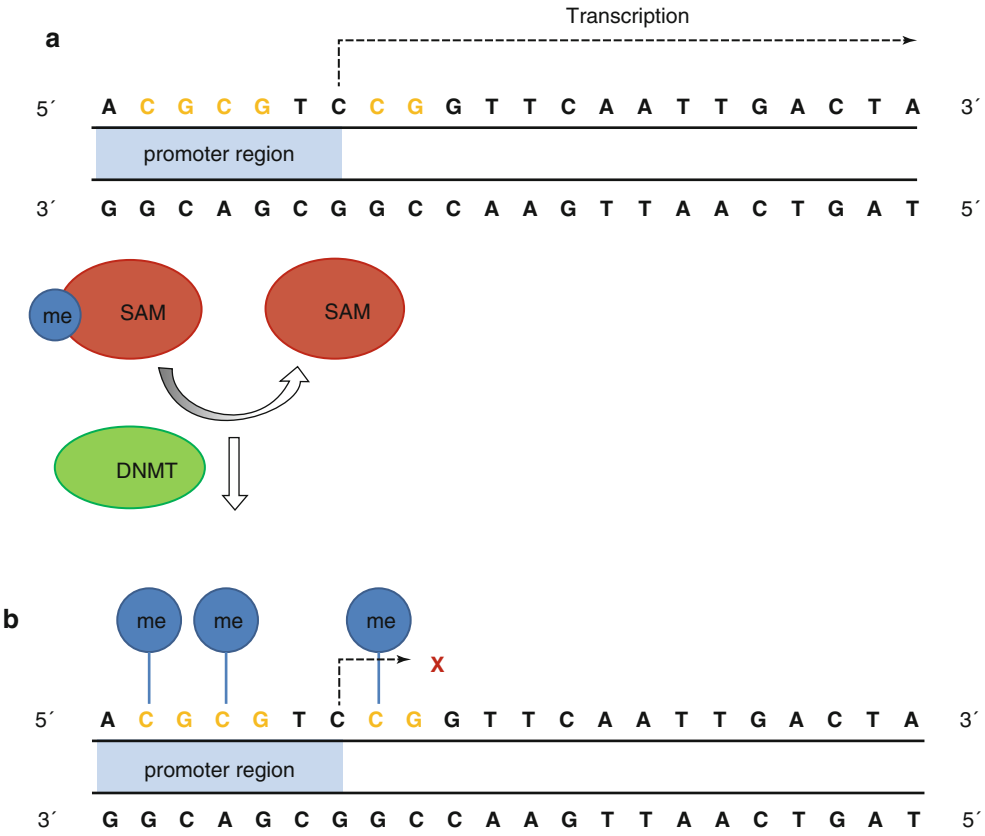


Fig. 3.1 Transcriptional silencing by DNA promoter methylation. (**a**) The CpGs in the promoter region of the gene are unmethylated, allowing the gene to be transcribed. (**b**) Methyl groups donated by S-adenosylmethionine are covalently attached to the 5-carbons on the pyrimidine rings of the cytosines on CpG dinucleotides in a CpG island in the promoter region in a reaction catalyzed by a DNA methyltransferase enzyme (DNMT), resulting in transcriptional repression. Abbreviations: *me* methyl groups, *SAM* S-adenosylmethionine, *DNMT* DNA methyltransferase

DNA Damage Tolerance

DNA damage tolerance is a way of bypassing DNA lesions that block the replication fork (translesion synthesis). This is a last resort mechanism that does not technically repair the DNA but rather is a mode of tolerance that allows the cell to survive despite the damage. There are two basic ways in which replication bypass of DNA lesions can occur: (1) DNA replication switch and (2) DNA template switch. In the first scenario, the DNA polymerase that is responsible for normal replication of the leading strand, which is the strand on which DNA synthesis is heading in the direction of the replication fork, stalls at the damage site. It is then replaced by one or any combination of specialized translesion polymerases (e.g., pol η, pol ι, pol κ, pol θ, pol ζ, or pol ν) to bypass the lesion, after which the regular polymerases take over again [75, 76]. The second method, involving a template switch, occurs on the lagging strand, where DNA synthesis heads away from the replication fork. The polymerase responsible for lagging-strand synthesis stalls at the damage site creating a gap, which can either be filled in via recombination using the newly synthesized leading strand as a template or, if the gap is only a single base, filled in with a single adenine [75, 76]. Both of these mechanisms are highly error prone, with potential for increased DNA mutations due to base-mispairing and/or recombinational events.

Epigenetics and Cancer

Mutations stemming from DNA damage are not the only form of somatic carcinogenic alteration; epigenetics also play a major role in cancer development. Epigenetics encompasses stable and heritable changes that either alter or have the potential to alter gene expression or phenotype [77]. There is mounting evidence that environmental exposures can alter epigenetic regulation of the genome, although the precise mechanisms remain largely unknown. A study of monozygotic twins reported that while identical twins are epigenetically indistinguishable early in life, their epigenetic profiles become increasingly different as they age [78], which is likely attributable to differences in environmental exposures over the course of a lifetime. The two main exposure periods in this regard are (1) in utero or neonatal, when cells are still developing increasing the chance of dissemination of epigenetic errors throughout the genome, (2) and during adult life, entailing a much longer period over which we encounter a wide variety of environmental exposures. In the ensuing sections, we will focus on three epigenetic mechanisms with

great relevance to cancer development: DNA methylation, histone modification, and miRNA.

DNA Methylation and Cancer

DNA methylation is a normal physiological process in which a methyl (CH_3) group is covalently attached to the 5-carbon of a cytosine pyrimidine ring forming 5-methylcytosine (5-meC) in a reaction catalyzed by a DNA methyltransferase enzyme (DNMT) [79, 80]. DNA methylation primarily occurs at CpG dinucleotides, which are two-base sequences where cytosine is upstream and adjacent to guanine.

CpG islands (CGI) are enriched regions that tend to be differentially located in the promoter regions of genes. Methylation of CGIs in promoter regions is generally associated with transcriptional repression (Fig. 3.1), which experimental evidence suggests operates through recruitment of transcriptional repressors that signal for changes in chromatin conformation through histone modification, and via interference with the binding of transcriptional activators [81]. The vast majority of CGIs are generally not methylated in non-pathologic cells [82]; however, exceptions exist, such as during the normal genomic processes of X-inactivation and imprinting [83] or tissue differentiation [84–88].

Although promoter regions are enriched for CpG dinucleotides, 70–90 % of all CpGs in the human genome are located outside of CpG islands and are methylated under normal conditions [89]. Methylation of individual CpGs located outside of CGIs, particularly those located in DNA sequence repeat and pericentromeric regions, helps to maintain genomic stability [90, 91]. In these regions, DNA methylation, in concert with chromatin conformational changes, represses the expression of *transposable elements* (TE) [92]. TEs are genomic sequences that have a singular ability to relocate to another chromosomal location in the genome [93]. Active transcription and reinsertion of the TEs can lead to genomic damage that can be propagated in somatic cells and, if it occurs during early embryogenesis or gametogenesis, can be passed on to future offspring [93]. Non-long terminal repeat (LTR) retrotransposable elements comprise the majority of TEs, which constitute about one-third of the human genome and include long interspersed elements (*LINE*); short interspersed elements (*SINE*), the most common of which are called *Alu* sequences; and mammalian-wide interspersed repeat (*MIR*) elements [94].

Altered methylation patterns are common findings in cancer and have thus far been the most often-studied epigenetic modification, in large part due to their stability and amenability to measurement. DNA methylation generally affects cancer development in three main ways: (1) through global hypomethylation, (2) promoter hypermethylation, and (3) induction of point mutations [80].

Cancer cells generally exhibit a genome-wide decrease in methylation levels (hypomethylation) [80, 83], with tumor cells losing between 20 and 60 % of their genomic 5-methylcytosine relative to normal tissue [95]. Hypomethylation is commonly an early event in carcinogenesis and becomes greater as tumors progress [83, 96]. This can potentially result in overexpression of oncogenes or oncogenic microRNAs (which will be described later in this chapter). In addition, hypomethylation may be associated with corresponding loss of genomic stability due to nucleosome repositioning as part of the reactivation of transposable elements, increasing the risk of chromosomal breaks, translocations, or allelic loss [80, 83, 91]. This is particularly true for hypomethylation of pericentric chromosomal regions, characteristic of many cancers, and may further increase the probability of chromosomal breakage [80].

In contrast to the genome-wide loss of methylation, cancer cells also frequently exhibit localized increases in methylation of sequences in or around promoter regions (hypermethylation), which, as previously discussed, are generally unmethylated in normal tissue [80, 83]. It is not as of yet fully appreciated if localized hypermethylation is a stochastic or targeted event and whether it occurs as a result of failed epigenetic machinery or random biochemical processes or in response to endogenous or exogenous stimuli. Promoter methylation is associated with transcriptional silencing, is at least as common as DNA mutation in the inactivation of tumor suppressor genes, and is considered to be a major event in carcinogenesis [83, 97]. It is estimated that most tumors contain 100–400 hypermethylated promoter regions [83]. Some genes are hypermethylated in multiple cancers, such as *RASSF1A* and *CDKN2A*, while others are cancer-specific [79]. Promoter hypermethylation can affect genes involved in cell-cycle control, DNA repair, carcinogen metabolism, cell-cell interactions, apoptosis, and angiogenesis [83, 98]. This often begins early in the genesis of cancers, even in normal-appearing tissue preceding frank malignancy, with the number of hypermethylated genes progressively increasing during carcinogenesis [83, 98, 99].

Numerous environmental and occupational exposures have been associated with alterations in DNA methylation, including physical agents and organic and inorganic chemical agents, many of which are reported to have a pleiotropic effect. Ionizing radiation due to occupational plutonium exposure has been associated with promoter hypermethylation and transcriptional silencing of the *CDKN2A* gene, which encodes the p16 tumor suppressor [100], while ultraviolet radiation exposure has been reported to induce global hypomethylation [101]. Airborne benzene exposure among gas station attendants and traffic police has also been associated with decreased levels of *LINE-1* and *Alu* methylation, hypermethylation of p15, and hypomethylation of *MAGE-1* [102]. An inverse association has been reported for *Alu* methylation levels in blood and exposure to persistent organic pollutants,

including dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), β-hexachlorocyclohexane (β-BHC), oxychordane, α-chlordane, mirex, and several forms of polychlorinated biphenyls (PCBs) [103]. There is also evidence that ever-use of hair dyes, the majority of which contain arylamines (along with other chemical agents) [104], is associated with DNA methylation in a CpG context-dependent manner in healthy individuals [105]. Among foundry workers, occupational exposure to particulate matter ≤10 μm in diameter (PM_{10}) has been associated with decreased methylation of *LINE-1* and *Alu* transposable elements and hypomethylation of the inducible nitrous oxide (*iNOS*) gene in blood-derived DNA [106]. Asbestos exposure has been associated with hypermethylation of 24 CpG loci in pleural tissue [107]. In experimental models, arsenic depletes S-adenosylmethionine (SAM), the primary methyl donor in DNA methylation, thus inducing global hypomethylation [108, 109], but has also been associated with promoter hypermethylation of *p53* [110] and *RASSF1A* [111]. Other metals such as chromium, cadmium, nickel, and zinc have been shown to reduce DNA methylation levels through the inhibition of DNA methyltransferase (DNMT) activity (enzymes responsible for catalyzing the transfer of methyl groups to DNA) [112–115].

CpG Methylation and Point Mutations

Another potential consequence of DNA methylation is induction of point mutations. If left unrepaired, methylated CpG sites can lead to alterations or loss of function of genes, potentially resulting in dysregulation of cellular processes. CpG methylation is capable of inducing point mutations through deamination of 5-meC or enhancement of exogenous carcinogens.

Methylated cytosine can undergo spontaneous hydrolytic deamination causing a C to T transition [80]. As a result, most of the human genome is depleted of CpG dinucleotides due to the relative instability of 5-meC [80]. The frequency of C to T methylation-associated transitions varies by tissue type, probably due to tissue-specific differences in mismatch repair [80]. Repair of a T-G mismatch stemming from deamination can also give rise to a T-A *transversion* (transversions involve an interchange of purine and pyrimidine bases) mutation [116]. More than 30 % of disease-related germline point mutations occur at CpG dinucleotides [80]. The p53 protein is a critical tumor suppressor gene, involved in damage-sensing, cell-cycle control, and DNA repair processes that is commonly inactivated during carcinogenesis [3]. Nearly half of all somatic and one-third of all germline p53 mutations take place at methylated CpGs, and many common p53 mutations that manifest in somatic cells are caused by C to T transitions, including "hot spot" mutations at codons 248, 273, and 282 [117]. The risk of p53 mutation at 5-meC is tenfold that of unmethylated cytosine, and CpG dinucleotides in these regions have been observed to be methylated in normal tissue [117].

Alternatively, DNA methylation can indirectly induce point mutations by enhancing the mutagenic effect of exogenous carcinogens [80]. An example of this is the affinity of benzo[α]pyrene diol epoxide (BPDE) for adduct formation on guanines adjacent to 5-meC, resulting in G to T transversions in aerodigestive tract cancers among smokers [118–120]. Similarly, acrolein has an affinity for binding 5-meC, instigating to C to T transitions [121]. Additionally, methylation alters the light absorption wavelength for cytosine, favoring the formation of covalent cross-link lesions in skin DNA upon UV exposure [80].

Histone Modifications

DNA methylation is not the sole epigenetic mechanism capable of altering gene expression but rather this process is part of a coordinated structural change manifested at the level of the DNA scaffold, termed the chromatin (specifically including the histone proteins). Modification of histone proteins can result in the alteration of overall chromatin structure, directly affecting gene transcription, DNA repair, DNA replication, and chromosomal organization [80, 83]. Histones are protein octamers (meaning that they are composed of eight protein subunits), containing two of each of H2A, H2B, H3, and H4 protein subunits, around which approximately 146 bp of DNA is wound, forming a structure called a *nucleosome* [80]. This is a recurring unit of eukaryotic DNA that makes up the chromosomes, condensing the DNA so that the entire genome can fit into the nucleus. Most chromatin exists as tightly compacted nucleosomes, called heterochromatin, which is transcriptionally incompetent. This is represented by the dark staining portion of the nucleus on light microscopy. Euchromatin has less compact nucleosomes, forming an open chromatin structure that can be readily transcribed. This appears as the lightly staining portion of the nucleus on light microscopy [80].

Histone modifications occur in different histone subunits and amino acid residues such as lysine, arginine, and serine. Modifications can involve acetylation, methylation, phosphorylation, glycosylation, sumoylation, ubiquitylation, or ADP ribosylation of the histone proteins at the N-terminal tails protruding from the nucleosomes [80, 83, 122].

Histone acetylation is generally associated with transcriptional activation (Fig. 3.2). It involves the attachment of acetyl groups to lysine residues in the N-terminal tail of histone proteins in a process catalyzed by histone acetyl transferases (HAT). These form a complex with transcription activator and coactivator proteins to initiate transcription. Conversely, histone deacetylases (HDAC) form complexes with methyl-CpG-binding proteins (MBD) and methylated cytosines in the

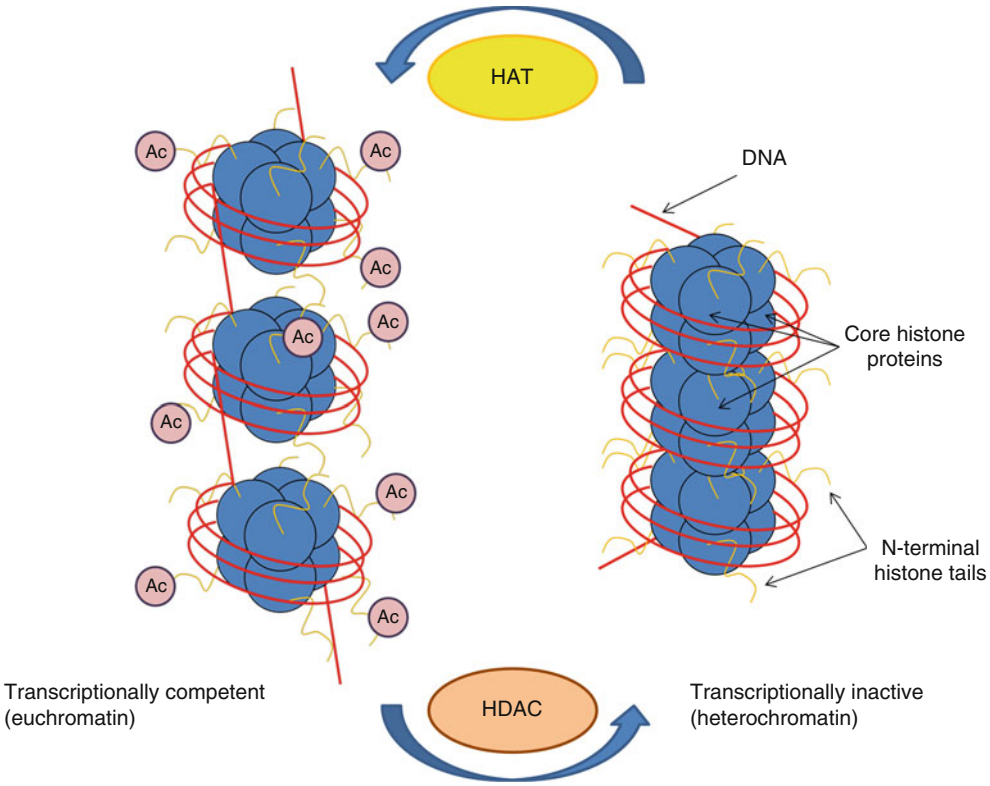


Fig. 3.2 Histone acetylation and transcriptional activation. Lysine residues on the N-terminal tails of histone proteins are acetylated in a reaction catalyzed by histone acetyl transferase enzymes (*HAT*), allowing the chromatin to exist in an open, transcriptionally active euchromatic state (depicted on the *left side* of the figure). The removal of the acetyl groups is catalyzed by histone deacetylases enzymes (*HDAC*), resulting in condensation of the nucleosome (heterochromatin) and transcriptional inactivation (*right side*). Abbreviations: *Ac* acetyl groups, *HAT* histone acetyltransferase, *HDAC* histone deacetylase

promoter, allowing them to remove acetyl groups from the N-terminal tails of the histones, causing condensation of the nucleosome, resulting in transcriptional inactivation [80, 83].

The effects of other histone modifications are complex and poorly understood, although they appear to vary dependent upon the position, location, and degree of modification. This complexity is exemplified by histone methylation. As with acetylation, histone methylation is a reversible process. Histone methylation is catalyzed by a class of enzymes called histone methyltransferases, while histone demethylases are responsible for demethylation [80, 123]. It can include mono-, di-, and trimethylation. Trimethylation of lysine at position 9, 27, or 36 of the N-terminal tail of H3 (H3-K9, H3-K27, or H3-K36) or lysine at position 20 on H4 (H4-K20) results in chromosomal structure alterations (heterochromatin) leading to transcriptional silencing. Trimethylation of lysine at position 4, 36, or 79 on H3 (H3-K4 or H3-K79) is associated with a euchromatin conformation and active transcription [123–125]. As previously mentioned, several other covalent methyl histone modifications have been identified, but their precise effects on transcription are presently unknown [80].

As is the case for DNA methylation, environmental and occupational exposures have been reported to alter histone modifications, particularly exposure to metals. Nickel can actuate de novo methylation of tumor suppressor genes through induction of heterochromatin conformation by suppressing H4 acetylation through interference with HAT enzymes [98, 126–128], increasing H3 lysine dimethylation via interference with histone demethylase enzymes [129], and H3 serine phosphorylation [130]. Chromium exposure can induce gene silencing via histone acetylation through interactions with histone HAT and HDAC enzymes [131]. Arsenic has been reported to increase dimethylation of lysine at the 9th position of H3 (H3K9) and reduce trimethylation of lysine at the 27th position of H3 (H3K27), both of which are associated with transcriptional repression, and increase trimethylation of the 4th lysine position on H3 (H3K4), which is associated with a transcriptionally active heterochromatic conformation [132].

MicroRNA

MicroRNAs (miRNA) are small, evolutionarily conserved, noncoding ribonucleic acid (RNA) molecules involved in posttranscriptional regulation of gene expression in essentially all eukaryotic organisms. Their mature transcripts are tiny in size, ranging from 18 to 25 nucleotides in length [133–137]. MicroRNAs are a relatively recent discovery, being first described in 1993 in the nematode *C. elegans* [138] with the identification of Lin-4, a small non-protein-coding RNA that represses expression of Lin-14 protein. Presently, there are 1,424 human miRNA sequences catalogued in the miRNA registry (miRBase) [139]. MicroRNAs are involved in control of crucial cellular functions, including proliferation, apoptosis, development, differentiation, and metabolism [134]. In fact, it is estimated that up to 30 %

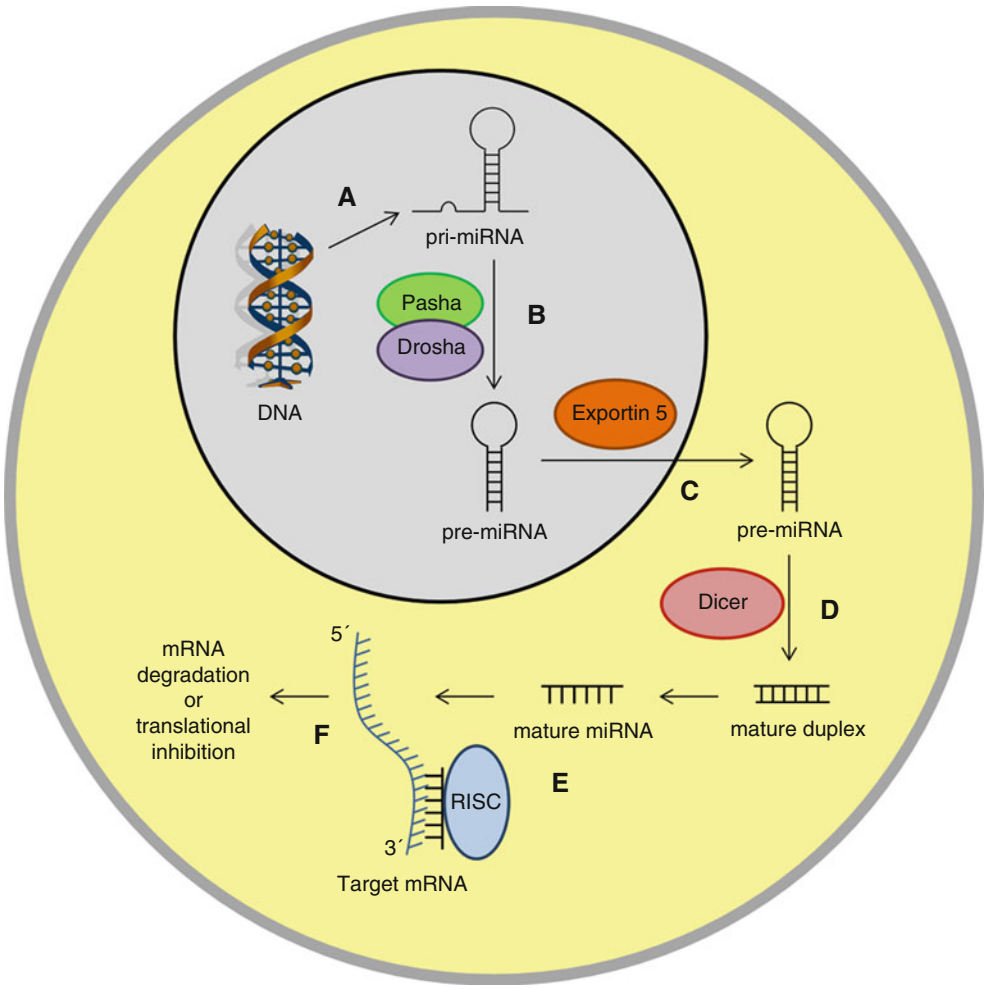


Fig. 3.3 MicroRNA processing and posttranscriptional regulation of gene expression. (*A*) MicroRNA (*miRNA*) is transcribed from DNA, giving rise to a primary miRNA transcript (*pri-miRNA*) containing a hairpin loop structure. (*B*) Pri-miRNA is cleaved in the nucleus by the Drosha/Pasha enzyme complex (Microprocessor) producing one or more small hairpin loop structures called precursor-miRNAs (*pre-miRNA*). (*C*) Pre-miRNA is exported from the nucleus by Exportin-5, (*D*) where it is further cleaved by the Dicer enzyme leaving an 18–25 bp miRNA duplex (two complementary strands). (*E*) One of the two strands of the duplex is retained and becomes the mature miRNA, which forms a complex with Argonaut protein (*Ago*) called the RNA-induced silencing complex (*RISC*). (*F*) The miRNA guides RISC to the target mRNA through base-pairing interactions at the 3′UTR of the target, resulting in degradation or translational inhibition

of human genes are regulated by miRNA expression [140]. Part of the critical regulatory importance of miRNA stems from the ability of a single miRNA to simultaneously control the expression of a multitude of genes, each potentially regulating up to 200 (or more) genes [135, 137]. They are tightly controlled and have been observed to show tissue-specific expression patterns during embryogenesis [133], though they are expressed in all tissues and at all stages of development [141].

MicroRNA expression is regulated by transcription factors and transcribed by RNA polymerase II (pol II), similar to protein-coding genes, although the precise mechanisms of transcriptional control of miRNAs are not entirely understood. While most miRNAs reside within intergenic (sequences containing few or no genes) noncoding regions [142], they can also be located in introns or exons of coding genes [135]. Many miRNAs are embedded close to other miRNAs in the genome, giving rise to miRNA clusters [142]. Single and clustered miRNAs can be transcribed from their own promoters, generally located within 500 base pairs of the 5′ end of the miRNA, individually or simultaneously as multiple miRNA (polycistron) transcriptional units, respectively [141, 142].

Following transcription, the miRNA undergoes a multistep posttranscriptional maturation process, which is depicted in Fig. 3.3. The primary transcript, called pri-miRNA, is typically 3–4 kb in length with a 5′ 7-methylguanosine (m^7G) cap and polyadenylated (poly-A) tail, similar to mRNA [143]. Following transcription, a stable hairpin structure of at least 30 bp is necessary to serve as the initiation signal for the processing steps [144]. The pri-miRNAs are cleaved in the nucleus by a multiprotein complex called Microprocessor, composed of the RNase III enzyme Drosha and double-stranded RNA-binding domain (dsRBD) protein DGCR8/Pasha, producing one or more precursor-miRNAs (pre-miRNA) [133–137]. DGCR8/Pasha recognizes the junction of single and double-stranded RNA at the base of the pri-miRNA hairpin, binding Microprocessor to it, allowing Drosha to cleave it [144]. Pri-miRNAs often contain several pre-miRNAs, known as clusters.

Pre-miRNAs are 65–100 nucleotides long with a hairpin structure containing a double-stranded RNA stem [144]. Exportin-5 (Exp5) recognizes the 3′ overhang, which is characteristic of pre-miRNA, and a portion of the RNA duplex structure [145, 146] and transports the pre-miRNA from the nucleus to the cytoplasm. Once in the cytoplasm,

the pre-miRNA is bound by the RISC-loading complex (RLC), which consists of another RNase III, called Dicer, along with Argonaut 2 and TAR RNA-binding proteins (TRBP) [133–137, 144]. Dicer recognizes the stem of the hairpin structure as double-stranded RNA and cleaves it on the loop side, leaving an 18–25 bp miRNA duplex [133–137, 141]. The strand of the duplex with its 5′ end on the less thermodynamically stable end of the duplex, termed the guide strand, is retained and becomes the mature miRNA [147, 148] in a process facilitated by Dicer [141].

The mature miRNA, in conjunction with an Argonaut (Ago) protein, forms a complex called the RNA-induced silencing complex (RISC) [133–137, 141], which it guides specifically to the target messenger RNA (mRNA) through base-pairing interactions generally at the 3′ UTR of the target. Nucleotides 2–7 in the 5′ region of the miRNA, called the seed region, bind the target mRNA through perfect or near-perfect base pairing [149]. The remainder of the miRNA binds the target mRNA with varying degrees of complementarity [149]. If the entire miRNA is a perfect or near-perfect complement, cleavage and degradation of the mRNA are induced through decapping of the 5′ m^7G cap or deadenylation of the poly(A) tail [133–137]. If it is a partial complement, RISC inhibits translation [133–137] through competitive m^7G cap binding by the Ago protein with the translational initiating factor eIF4E [150], preventing translation of the target mRNA into protein. These translationally silenced mRNA-RISC complexes remain in the cytoplasm and accumulate, forming processing bodies (P-bodies) [141]. P-bodies contain decapping proteins and exoribonuclease and therefore are capable of degrading the mRNAs. However, there are some indications that miRNA translational silencing may be reversible, allowing mRNAs to leave P-bodies and migrate to ribosomes for translation [151].

Among the first evidence of the association between aberrant miRNA expression and cancer was the 2002 study by Calin and colleagues reporting the downregulation and frequent deletion of miR-15a and miR-16-1 in chronic lymphocytic leukemia (CLL) [152]. Shortly after came the first description of altered miRNA expression in solid tumors, with a report of downregulation of miR-143 and miR-145 in colorectal carcinoma [153]. Given their involvement in development and key cellular functions, along with their potential to regulate as many as 200 target genes, one can see how miRNA alterations could have a major impact on cancer development.

Many miRNAs are differentially expressed in cancers relative to normal tissue in both a tissue of origin- and tumor-specific manner [134, 136, 137]. The majority of miRNAs are downregulated in cancer, although they can be upregulated as well [136], with alterations in expression starting early in carcinogenesis [141]. For instance, abnormal miRNA expression has been identified in premalignant tumors, including colonic and pituitary adenomas [153, 154]. MicroRNAs can function as either tumor suppressors or oncogenes. Those that target and regulate proto-oncogenes act as tumor suppressors, so when they are downregulated or silenced, the target oncogene is overexpressed [134]. Conversely, miRNAs that target tumor suppressor genes can act as oncogenes when overexpressed through the downregulation or inactivation of the tumor suppressor gene [134].

Environmental exposures can influence miRNA expression, which, as previously discussed, can have a profound effect on posttranscriptional regulation due to the multi-target potential of miRNAs. Several carcinogenic exposures have been associated with miRNA dysregulation in various human tissues, including anti-benzo[α]pyrene-7,8-diol-9,10-epoxide [155], arsenite [156], diethylstilbestrol (DES) [157], estradiol [158], reactive oxygen species (ROS) generated by aluminum sulfate and iron sulfate [159], cigarette smoking [160], and 12-O-tetradecanoylphorbol-13-acetate (TPA) [161–163].

References

1. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57–70.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
3. Weinberg RA. The biology of cancer. New York: Garland Science; 2007.
4. Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A. 1971;68(4):820–3.
5. Comings DE. A general theory of carcinogenesis. Proc Natl Acad Sci U S A. 1973;70(12):3324–8.
6. Berger AH, Knudson AG, Pandolfi PP. A continuum model for tumour suppression. Nature. 2011;476(7359):163–9.
7. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963–8.
8. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res. 2003;63(8):1727–30.
9. Weston A, Harris C. Chemical carcinogenesis. In: Bast RJ, Kufe D, Pollock R, Weichselbaum M, Holland J, Frei E, editors. Holland-Frei cancer medicine. 5th ed. Hamilton: BC Decker; 2000.
10. Vamvakas S, Vock EH, Lutz WK. On the role of DNA double-strand breaks in toxicity and carcinogenesis. Crit Rev Toxicol. 1997;27(2):155–74.
11. Yassi A, Kjellstrom T, de Kok T, Guidotti TL. Basic environmental health. New York: Oxford University Press; 2001.
12. Dextraze ME, Gantchev T, Girouard S, Hunting D. DNA interstrand cross-links induced by ionizing radiation: an unsung lesion. Mutat Res. 2010;704(1–3):101–7.
13. Peak JG, Peak MJ, MacCoss M. DNA breakage caused by 334-nm ultraviolet light is enhanced by naturally occurring nucleic acid components and nucleotide coenzymes. Photochem Photobiol. 1984;39(5):713–6.
14. Walrant P, Santus R. N-formyl-kynurenine, a tryptophan photooxidation product, as a photodynamic sensitizer. Photochem Photobiol. 1974;19(6):411–7.
15. McCormick JP, Fischer JR, Pachlatko JP, Eisenstark A. Characterization of a cell-lethal product from the photooxidation of

tryptophan: hydrogen peroxide. Science (New York, NY). 1976; 191(4226):468–9.
16. Krasnovsky Jr AA. Photoluminescence of singlet oxygen in pigment solutions. Photochem Photobiol. 1979;29:29–36.
17. Phillips JL, Singh NP, Lai H. Electromagnetic fields and DNA damage. Pathophysiology. Washington, DC. 2009;16(2–3):79–88.
18. Conney AH, Poirier MC, Surh YJ, Kadlubar FF. Elizabeth Cavert Miller: May 2, 1920–October 14, 1987; James A. Miller: May 27, 1915–December 24, 2000. Biographical memoirs; National Academy of Sciences, vol 90. National Academies Press; 2009. p. 1–38.
19. NTP Report on carcinogens, twelfth edition. Research Triangle: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program; 2011.
20. Irigaray P, Belpomme D. Basic properties and molecular mechanisms of exogenous chemical carcinogens. Carcinogenesis. 2010;31(2):135–48.
21. Williams D, Foye W, Lemke T, editors. Foye's principles of medicinal chemistry. 6th ed. Baltimore: Lippincott Williams & Wilkins; 2007.
22. Martelli A, Robbiano L, Gazzaniga GM, Brambilla G. Comparative study of DNA damage and repair induced by ten N-nitroso compounds in primary cultures of human and rat hepatocytes. Cancer Res. 1988;48(15):4144–52.
23. Wiencke JK, McDowell ML, Bodell WJ. Molecular dosimetry of DNA adducts and sister chromatid exchanges in human lymphocytes treated with benzo[a]pyrene. Carcinogenesis. 1990;11(9): 1497–502.
24. Vollhardt KPC, Schore NE. Organic chemistry: structure and function. 4th ed. New York: W.H. Freeman and Company; 2003.
25. Shrivastav N, Li D, Essigmann JM. Chemical biology of mutagenesis and DNA repair: cellular responses to DNA alkylation. Carcinogenesis. 2010;31(1):59–70.
26. Singer B. Sites in nucleic acids reacting with alkylating agents of differing carcinogenicity of mutagenicity. J Toxicol Environ Health. 1977;2(6):1279–95.
27. Gates KS. An overview of chemical processes that damage cellular DNA: spontaneous hydrolysis, alkylation, and reactions with radicals. Chem Res Toxicol. 2009;22(11):1747–60.
28. Hlavin EM, Smeaton MB, Miller PS. Initiation of DNA interstrand cross-link repair in mammalian cells. Environ Mol Mutagen. 2010;51(6):604–24.
29. Rothfuss A, Grompe M. Repair kinetics of genomic interstrand DNA cross-links: evidence for DNA double-strand break-dependent activation of the Fanconi anemia/BRCA pathway. Mol Cell Biol. 2004;24(1):123–34.
30. Sczepanski JT, Jacobs AC, Van Houten B, Greenberg MM. Double-strand break formation during nucleotide excision repair of a DNA interstrand cross-link. Biochemistry. 2009;48(32): 7565–7.
31. Wilson VL, Weston A, Manchester DK, et al. Alkyl and aryl carcinogen adducts detected in human peripheral lung. Carcinogenesis. 1989;10(11):2149–53.
32. van Schooten FJ, Hillebrand MJ, van Leeuwen FE, et al. Polycyclic aromatic hydrocarbon-DNA adducts in lung tissue from lung cancer patients. Carcinogenesis. 1990;11(9):1677–81.
33. Li D, Wang M, Dhingra K, Hittelman WN. Aromatic DNA adducts in adjacent tissues of breast cancer patients: clues to breast cancer etiology. Cancer Res. 1996;56(2):287–93.
34. Pfohl-Leszkowicz A, Grosse Y, Carriere V, et al. High levels of DNA adducts in human colon are associated with colorectal cancer. Cancer Res. 1995;55(23):5611–6.
35. Hamada K, Umemoto A, Kajikawa A, et al. Mucosa-specific DNA adducts in human small intestine: a comparison with the colon. Carcinogenesis. 1994;15(11):2677–80.
36. Wang M, Abbruzzese JL, Friess H, et al. DNA adducts in human pancreatic tissues and their potential role in carcinogenesis. Cancer Res. 1998;58(1):38–41.
37. Lu AL, Li X, Gu Y, Wright PM, Chang DY. Repair of oxidative DNA damage: mechanisms and functions. Cell Biochem Biophys. 2001;35(2):141–70.
38. Klaunig JE, Wang Z, Pu X, Zhou S. Oxidative stress and oxidative damage in chemical carcinogenesis. Toxicol Appl Pharmacol. 2011;254(2):86–99.
39. Kuchino Y, Mori F, Kasai H, et al. Misreading of DNA templates containing 8-hydroxydeoxyguanosine at the modified base and at adjacent residues. Nature. 1987;327(6117):77–9.
40. Schiestl RH, Aubrecht J, Yap WY, Kandikonda S, Sidhom S. Polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin induce intrachromosomal recombination in vitro and in vivo. Cancer Res. 1997;57(19):4378–83.
41. International Agency for Research on Cancer. Some metals and metalic compounds. IARC Monogr Eval Carcinog Risk Chem Hum. 1980;23:1–415.
42. International Agency for Research on Cancer. Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide. IARC Monogr Eval of Carcinog Risks Hum. 2006;86:1–294.
43. International Agency for Research on Cancer. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC Monogr Eval Carcinog Risks Hum. 1993;58:1–415.
44. Salnikow K, Zhitkovich A. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. Chem Res Toxicol. 2008;21(1):28–44.
45. Galanis A, Karapetsas A, Sandaltzopoulos R. Metal-induced carcinogenesis, oxidative stress and hypoxia signalling. Mutat Res. 2009;674(1–2):31–5.
46. Witkiewicz-Kucharczyk A, Bal W. Damage of zinc fingers in DNA repair proteins, a novel molecular mechanism in carcinogenesis. Toxicol Lett. 2006;162(1):29–42.
47. Barnes DE, Lindahl T. Repair and genetic consequences of endogenous DNA base damage in mammalian cells. Annu Rev Genet. 2004;38:445–76.
48. Bertram JS. The molecular biology of cancer. Mol Aspects Med. 2000;21(6):167–223.
49. Swenberg JA, Lu K, Moeller BC, et al. Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment. Toxicol Sci. 2011;120 Suppl 1: S130–45.
50. Cavalieri EL, Rogan EG. Unbalanced metabolism of endogenous estrogens in the etiology and prevention of human cancer. J Steroid Biochem Mol Biol. 2011;125(3–5):169–80.
51. Winters TA, Henner WD, Russell PS, McCullough A, Jorgensen TJ. Removal of 3′-phosphoglycolate from DNA strand-break damage in an oligonucleotide substrate by recombinant human apurinic/apyrimidinic endonuclease 1. Nucleic Acids Res. 1994;22(10):1866–73.
52. Dianov GL, Parsons JL. Co-ordination of DNA single strand break repair. DNA Repair (Amst). 2007;6(4):454–60.
53. Martinez MC, Andriantsitohaina R. Reactive nitrogen species: molecular mechanisms and potential significance in health and disease. Antioxid Redox Signal. 2009;11(3):669–702.
54. Blair IA. Lipid hydroperoxide-mediated DNA damage. Exp Gerontol. 2001;36(9):1473–81.
55. Lindahl T, Wood RD. Quality control by DNA repair. Science (New York, NY). 1999;286(5446):1897–905.
56. Hegi ME, Liu L, Herman JG, et al. Correlation of O6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity. J Clin Oncol. 2008;26(25):4189–99.
57. Brettel K, Byrdin M. Reaction mechanisms of DNA photolyase. Curr Opin Struct Biol. 2010;20(6):693–701.
58. Caldecott KW. Mammalian DNA, single-strand break repair: an X-ra(y)ted affair. Bioessays. 2001;23(5):447–55.

59. Svilar D, Goellner EM, Almeida KH, Sobol RW. Base excision repair and lesion-dependent subpathways for repair of oxidative DNA damage. Antioxid Redox Signal. 2011;14(12):2491–507.
60. Sung JS, Demple B. Roles of base excision repair subpathways in correcting oxidized abasic sites in DNA. FEBS J. 2006;273(8): 1620–9.
61. Kastrinos F, Syngal S. Recently identified colon cancer predispositions: MYH and MSH6 mutations. Semin Oncol. 2007;34(5): 418–24.
62. Rouillon C, White MF. The evolution and mechanisms of nucleotide excision repair proteins. Res Microbiol. 2011;162(1):19–26.
63. Rechkunova NI, Lavrik OI. Nucleotide excision repair in higher eukaryotes: mechanism of primary damage recognition in global genome repair. Subcell Biochem. 2010;50:251–77.
64. Kraemer KH, Patronas NJ, Schiffmann R, Brooks BP, Tamura D, DiGiovanna JJ. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype-phenotype relationship. Neuroscience. 2007;145(4):1388–96.
65. Kunz C, Saito Y, Schar P. DNA repair in mammalian cells: mismatched repair: variations on a theme. Cell Mol Life Sci. 2009;66(6):1021–38.
66. Marti TM, Kunz C, Fleck O. DNA mismatch repair and mutation avoidance pathways. J Cell Physiol. 2002;191(1):28–41.
67. Power DG, Gloglowski E, Lipkin SM. Clinical genetics of hereditary colorectal cancer. Hematol Oncol Clin N Am. 2010;24(5): 837–59.
68. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet. 2009;76(1):1–18.
69. Wood RD. Mammalian nucleotide excision repair proteins and interstrand crosslink repair. Environ Mol Mutagen. 2010;51(6): 520–6.
70. Kitao H, Takata M. Fanconi anemia: a disorder defective in the DNA damage response. Int J Hematol. 2011;93(4):417–24.
71. Mladenov E, Iliakis G. Induction and repair of DNA double strand breaks: the increasing spectrum of non-homologous end joining pathways. Mutat Res. 2011;711(1–2):61–72.
72. Shuen AY, Foulkes WD. Inherited mutations in breast cancer genes–risk and response. J Mammary Gland Biol Neoplasia. 2011;16(1):3–15.
73. Pruthi S, Gostout BS, Lindor NM. Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian cancer. Mayo Clin Proc. 2010;85(12):1111–20.
74. Frappart PO, McKinnon PJ. Ataxia-telangiectasia and related diseases. Neruomol Med. 2006;8(4):495–511.
75. Lange SS, Takata K, Wood RD. DNA polymerases and cancer. Nat Rev Cancer. 2011;11(2):96–110.
76. Friedberg EC. Suffering in silence: the tolerance of DNA damage. Nat Rev Mol Cell Biol. 2005;6(12):943–53.
77. Calvanese V, Lara E, Kahn A, Fraga MF. The role of epigenetics in aging and age-related diseases. Ageing Res Rev. 2009;8(4): 268–76.
78. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A. 2005;102(30):10604–9.
79. Das PM, Singal R. DNA methylation and cancer. J Clin Oncol. 2004;22(22):4632–42.
80. Gronbaek K, Hother C, Jones PA. Epigenetic changes in cancer. APMIS. 2007;115(10):1039–59.
81. Choudhuri S, Cui Y, Klaassen CD. Molecular targets of epigenetic regulation and effectors of environmental influences. Toxicol Appl Pharmacol. 2010;245(3):378–93.
82. Tost J. DNA methylation: an introduction to the biology and the disease-associated changes of a promising biomarker. Mol Biotechnol. 2010;44(1):71–81.
83. Esteller M. Epigenetics in cancer. N Engl J Med. 2008;358(11): 1148–59.
84. Eckhardt F, Lewin J, Cortese R, et al. DNA methylation profiling of human chromosomes 6, 20 and 22. Nat Genet. 2006;38(12): 1378–85.
85. Illingworth R, Kerr A, Desousa D, et al. A novel CpG island set identifies tissue-specific methylation at developmental gene loci. PLoS Biol. 2008;6(1):e22.
86. Rakyan VK, Down TA, Thorne NP, et al. An integrated resource for genome-wide identification and analysis of human tissue-specific differentially methylated regions (tDMRs). Genome Res. 2008;18(9):1518–29.
87. Rakyan VK, Hildmann T, Novik KL, et al. DNA methylation profiling of the human major histocompatibility complex: a pilot study for the human epigenome project. PLoS Biol. 2004;2(12): e405.
88. Schilling E, Rehli M. Global, comparative analysis of tissue-specific promoter CpG methylation. Genomics. 2007;90(3): 314–23.
89. Miranda TB, Jones PA. DNA methylation: the nuts and bolts of repression. J Cell Physiol. 2007;213(2):384–90.
90. Ehrlich M. DNA hypomethylation, cancer, the immunodeficiency, centromeric region instability, facial anomalies syndrome and chromosomal rearrangements. J Nutr. 2002;132(8 Suppl):2424S–9.
91. Hoffmann MJ, Schulz WA. Causes and consequences of DNA hypomethylation in human cancer. Biochem Cell Biol. 2005;83(3): 296–321.
92. Wilson AS, Power BE, Molloy PL. DNA hypomethylation and human diseases. Biochim Biophys Acta. 2007;1775(1):138–62.
93. Levin HL, Moran JV. Dynamic interactions between transposable elements and their hosts. Nat Rev Genet. 2011;12(9):615–27.
94. Cordaux R, Batzer MA. The impact of retrotransposons on human genome evolution. Nat Rev Genet. 2009;10(10):691–703.
95. Lujambio A, Esteller M. How epigenetics can explain human metastasis: a new role for microRNAs. Cell Cycle. 2009;8(3): 377–82.
96. Fraga MF, Herranz M, Espada J, et al. A mouse skin multistage carcinogenesis model reflects the aberrant DNA methylation patterns of human tumors. Cancer Res. 2004;64(16):5527–34.
97. Baylin SB. DNA methylation and gene silencing in cancer. Nat Clin Pract Oncol. 2005;2 Suppl 1:S4–11.
98. Davis CD, Uthus EO. DNA methylation, cancer susceptibility, and nutrient interactions. Exp Biol Med (Maywood). 2004;229(10): 988–95.
99. Shi H, Wang MX, Caldwell CW. CpG islands: their potential as biomarkers for cancer. Expert Rev Mol Diagn. 2007;7(5): 519–31.
100. Belinsky SA, Klinge DM, Liechty KC, et al. Plutonium targets the p16 gene for inactivation by promoter hypermethylation in human lung adenocarcinoma. Carcinogenesis. 2004;25(6):1063–7.
101. Herceg Z. Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. Mutagenesis. 2007;22(2):91–103.
102. Bollati V, Baccarelli A, Hou L, et al. Changes in DNA methylation patterns in subjects exposed to low-dose benzene. Cancer Res. 2007;67(3):876–80.
103. Rusiecki JA, Baccarelli A, Bollati V, Tarantini L, Moore LE, Bonefeld-Jorgensen EC. Global DNA hypomethylation is associated with high serum-persistent organic pollutants in Greenlandic Inuit. Environ Health Perspect. 2008;116(11):1547–52.
104. Nohynek GJ, Antignac E, Re T, Toutain H. Safety assessment of personal care products/cosmetics and their ingredients. Toxicol Appl Pharmacol. 2010;243(2):239–59.
105. Langevin SM, Houseman EA, Christensen BC, et al. The influence of aging, environmental exposures and local sequence features on the variation of DNA methylation in blood. Epigenetics. 2011;6(7):908–19.
106. Tarantini L, Bonzini M, Apostoli P, et al. Effects of particulate matter on genomic DNA methylation content and iNOS promoter methylation. Environ Health Perspect. 2009;117(2):217–22.

107. Christensen BC, Houseman EA, Marsit CJ, et al. Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. PLoS Genet. 2009;5(8):e1000602.
108. Chen H, Liu J, Zhao CQ, Diwan BA, Merrick BA, Waalkes MP. Association of c-myc overexpression and hyperproliferation with arsenite-induced malignant transformation. Toxicol Appl Pharmacol. 2001;175(3):260–8.
109. Zhao CQ, Young MR, Diwan BA, Coogan TP, Waalkes MP. Association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Proc Natl Acad Sci U S A. 1997;94(20):10907–12.
110. Davis CD, Uthus EO, Finley JW. Dietary selenium and arsenic affect DNA methylation in vitro in Caco-2 cells and in vivo in rat liver and colon. J Nutr. 2000;130(12):2903–9.
111. Marsit CJ, Houseman EA, Schned AR, Karagas MR, Kelsey KT. Promoter hypermethylation is associated with current smoking, age, gender and survival in bladder cancer. Carcinogenesis. 2007;28(8):1745–51.
112. Shiao YH, Crawford EB, Anderson LM, Patel P, Ko K. Allele-specific germ cell epimutation in the spacer promoter of the 45S ribosomal RNA gene after Cr(III) exposure. Toxicol Appl Pharmacol. 2005;205(3):290–6.
113. Salnikow K, Costa M. Epigenetic mechanisms of nickel carcinogenesis. J Environ Pathol Toxicol Oncol. 2000;19(3):307–18.
114. Poirier LA, Vlasova TI. The prospective role of abnormal methyl metabolism in cadmium toxicity. Environ Health Perspect. 2002;110 Suppl 5:793–5.
115. Takiguchi M, Achanzar WE, Qu W, Li G, Waalkes MP. Effects of cadmium on DNA-(Cytosine-5) methyltransferase activity and DNA methylation status during cadmium-induced cellular transformation. Exp Cell Res. 2003;286(2):355–65.
116. Sved J, Bird A. The expected equilibrium of the CpG dinucleotide in vertebrate genomes under a mutation model. Proc Natl Acad Sci U S A. 1990;87(12):4692–6.
117. Rideout 3rd WM, Coetzee GA, Olumi AF, Jones PA. 5-Methylcytosine as an endogenous mutagen in the human LDL receptor and p53 genes. Science. 1990;249(4974):1288–90.
118. Chen JX, Zheng Y, West M, Tang MS. Carcinogens preferentially bind at methylated CpG in the p53 mutational hot spots. Cancer Res. 1998;58(10):2070–5.
119. Denissenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. Science. 1996;274(5286):430–2.
120. Yoon JH, Smith LE, Feng Z, Tang M, Lee CS, Pfeifer GP. Methylated CpG dinucleotides are the preferential targets for G-to-T transversion mutations induced by benzo[a]pyrene diol epoxide in mammalian cells: similarities with the p53 mutation spectrum in smoking-associated lung cancers. Cancer Res. 2001;61(19):7110–7.
121. Feng Z, Hu W, Hu Y, Tang MS. Acrolein is a major cigarette-related lung cancer agent: preferential binding at p53 mutational hotspots and inhibition of DNA repair. Proc Natl Acad Sci U S A. 2006;103(42):15404–9.
122. Suganuma T, Workman JL. Crosstalk among histone modifications. Cell. 2008;135(4):604–7.
123. Bartova E, Krejci J, Harnicarova A, Galiova G, Kozubek S. Histone modifications and nuclear architecture: a review. J Histochem Cytochem. 2008;56(8):711–21.
124. Lachner M, O'Carroll D, Rea S, Mechtler K, Jenuwein T. Methylation of histone H3 lysine 9 creates a binding site for HP1 proteins. Nature. 2001;410(6824):116–20.
125. Santos-Rosa H, Schneider R, Bannister AJ, et al. Active genes are tri-methylated at K4 of histone H3. Nature. 2002;419(6905):407–11.
126. Broday L, Cai J, Costa M. Nickel enhances telomeric silencing in Saccharomyces cerevisiae. Mutat Res. 1999;440(2):121–30.
127. Chen H, Ke Q, Kluz T, Yan Y, Costa M. Nickel ions increase histone H3 lysine 9 dimethylation and induce transgene silencing. Mol Cell Biol. 2006;26(10):3728–37.
128. Ke Q, Davidson T, Chen H, Kluz T, Costa M. Alterations of histone modifications and transgene silencing by nickel chloride. Carcinogenesis. 2006;27(7):1481–8.
129. Chen H, Giri NC, Zhang R, et al. Nickel ions inhibit histone demethylase JMJD1A and DNA repair enzyme ABH2 by replacing the ferrous iron in the catalytic centers. J Biol Chem. 2010;285(10):7374–83.
130. Ke Q, Li Q, Ellen TP, Sun H, Costa M. Nickel compounds induce phosphorylation of histone H3 at serine 10 by activating JNK-MAPK pathway. Carcinogenesis. 2008;29(6):1276–81.
131. Weidman JR, Dolinoy DC, Murphy SK, Jirtle RL. Cancer susceptibility: epigenetic manifestation of environmental exposures. Cancer J. 2007;13(1):9–16.
132. Zhou X, Sun H, Ellen TP, Chen H, Costa M. Arsenite alters global histone H3 methylation. Carcinogenesis. 2008;29(9):1831–6.
133. Dalmay T. MicroRNAs and cancer. J Intern Med. 2008;263(4):366–75.
134. Garzon R, Fabbri M, Cimmino A, Calin GA, Croce CM. MicroRNA expression and function in cancer. Trends Mol Med. 2008;19(7–8):517–25.
135. Rouhi A, Mager DL, Humphries RK, Kuchenbauer F. MiRNAs, epigenetics, and cancer. Mamm Genome. 2008;19:517–25.
136. Weber B, Stresemann C, Brueckner B, Lyko F. Methylation of human microRNA genes in normal and neoplastic cells. Cell Cycle. 2007;6(9):1001–5.
137. Yang N, Coukos G, Zhang L. MicroRNA epigenetic alterations in human cancer: one step forward in diagnosis and treatment. Int J Cancer. 2008;122(5):963–8.
138. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75(5):843–54.
139. miRbase. 2011 http://microrna.sanger.ac.uk/sequences/. Accessed 19 Sept 2011.
140. Rajewsky N, Socci ND. Computational identification of microRNA targets. Dev Biol. 2004;267(2):529–35.
141. Hudder A, Novak RF. miRNAs: effectors of environmental influences on gene expression and disease. Toxicol Sci. 2008;103(2):228–40.
142. Lujambio A, Esteller M. CpG island hypermethylation of tumor suppressor microRNAs in human cancer. Cell Cycle. 2007;6(12):1455–9.
143. Wang Y, Lee CG. MicroRNA and cancer - focus on apoptosis. J Cell Mol Med. 2009;13(1):12–23.
144. Lau PW, Macrae IJ. The molecular machines that mediate microRNA maturation. J Cell Mol Med. 2009;13(1):54–60.
145. Zeng Y, Cullen BR. Structural requirements for pre-microRNA binding and nuclear export by exportin 5. Nucleic Acids Res. 2004;32(16):4776–85.
146. Lund E, Dahlberg JE. Substrate selectivity of exportin 5 and Dicer in the biogenesis of microRNAs. Cold Spring Harb Symp Quant Biol. 2006;71:59–66.
147. Khvorova A, Reynolds A, Jayasena SD. Functional siRNAs and miRNAs exhibit strand bias. Cell. 2003;115(2):209–16.
148. Schwarz DS, Hutvagner G, Du T, Xu Z, Aronin N, Zamore PD. Asymmetry in the assembly of the RNAi enzyme complex. Cell. 2003;115(2):199–208.
149. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005;120(1):15–20.
150. Kiriakidou M, Tan GS, Lamprinaki S, De Planell-Saguer M, Nelson PT, Mourelatos Z. An mRNA m7G cap binding-like motif within human Ago2 represses translation. Cell. 2007;129(6):1141–51.
151. Bhattacharyya SN, Habermacher R, Martine U, Closs EI, Filipowicz W. Stress-induced reversal of microRNA repression and mRNA P-body localization in human cells. Cold Spring Harb Symp Quant Biol. 2006;71:513–21.

152. Calin GA, Dumitru CD, Shimizu M, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A. 2002;99(24):15524–9.
153. Michael MZ, O'Connor SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res. 2003;1(12):882–91.
154. Bottoni A, Piccin D, Tagliati F, Luchin A, Zatelli MC, degli Uberti EC. miR-15a and miR-16-1 down-regulation in pituitary adenomas. J Cell Physiol. 2005;204(1):280–5.
155. Shen YL, Jiang YG, Greenlee AR, Zhou LL, Liu LH. MicroRNA expression profiles and miR-10a target in anti-benzo[a] pyrene-7, 8-diol-9, 10-epoxide-transformed human 16HBE cells. Biomed Environ Sci. 2009;22(1):14–21.
156. Marsit CJ, Eddy K, Kelsey KT. MicroRNA responses to cellular stress. Cancer Res. 2006;66(22):10843–8.
157. Cheng AS, Culhane AC, Chan MW, et al. Epithelial progeny of estrogen-exposed breast progenitor cells display a cancer-like methylome. Cancer Res. 2008;68(6):1786–96.
158. Bhat-Nakshatri P, Wang G, Collins NR, et al. Estradiol-regulated microRNAs control estradiol response in breast cancer cells. Nucleic Acids Res. 2009;37(14):4850–61.
159. Lukiw WJ, Pogue AI. Induction of specific micro RNA (miRNA) species by ROS-generating metal sulfates in primary human brain cells. J Inorg Biochem. 2007;101(9):1265–9.
160. Schembri F, Sridhar S, Perdomo C, et al. MicroRNAs as modulators of smoking-induced gene expression changes in human airway epithelium. Proc Natl Acad Sci U S A. 2009;106(7):2319–24.
161. Navarro F, Gutman D, Meire E, et al. miR-34a contributes to megakaryocytic differentiation of K562 cells independently of p53. Blood. 2009;114(10):2181–92.
162. Kasashima K, Nakamura Y, Kozu T. Altered expression profiles of microRNAs during TPA-induced differentiation of HL-60 cells. Biochem Biophys Res Commun. 2004;322(2):403–10.
163. Chen A, Luo M, Yuan G, et al. Complementary analysis of microRNA and mRNA expression during phorbol 12-myristate 13-acetate (TPA)-induced differentiation of HL-60 cells. Biotechnol Lett. 2008;30(12):2045–52.

Cancer of the Oral Cavity, Pharynx, and Nasopharynx

4

Victor Wünsch Filho

Keywords
Oral cancer • Pharyngeal cancer • Occupation • Asbestos • Diesel engine exhaust • Leather dust • Cotton dust • Occupational risk factors • Formaldehyde • Wood dust • Welding fumes

Overview

Oral Cavity and Pharynx Cancer

Cancer of the oral cavity and pharynx is one of the ten most common in the world. In 2008, the age-standardized incidence rate was 8.7 per 100,000 men and 3.4 per 100,000 women, and mortality rate was 7.0 per 100,000 men and 1.7 per 100,000 women [1]. About 90 % of oral cavity and pharynx tumors are histological squamous cell type. Incidence increases with age and peaks between ages of 50 and 70 years. Incidence is higher in more developed regions for males than less developed regions, while mortality is similar between the more and less developed regions. In women, incidence and mortality are higher in less developed regions [2]. In India, these tumors are a heavy health burden in both urban and rural areas. They are responsible for the highest cancer mortality rates in men and are third after breast and uterine cervix tumors in women [1]. Other high-incidence areas are Eastern, Western, and Southern Europe, Australia and New Zealand, and Melanesia [3]. Latin America and the Caribbean have intermediate incidence rates of oral and pharynx cancers; however, rates vary widely between countries in the region and even within those countries [4, 5]. In Brazil, mortality rates from oral cavity cancer are stable in both men and women; however, pharynx cancer is increasing [6].

V. Wünsch Filho, MD, PhD
Department of Epidemiology,
University of São Paulo School of Public Health,
Av. Dr. Arnaldo, 715, São Paulo, SP 01246-904, Brazil
e-mail: wunsch@usp.br

Increasing incidence of oral and pharynx cancers has been observed in some Western Europe countries [7–10]. Incidence of oral cavity and pharynx tumors in the United States has been decreasing over the last 30 years [11]. However, increasing incidence in cancer of the tongue, base of the tongue, and the tonsils has been observed in patients under 45 years of age [12, 13]. Nordic countries have also shown increasing incidence of tongue cancer in both male and female young adults [14, 15].

Nasopharynx Cancer

Incidence of nasopharynx cancer is higher for those in their 50s. Worldwide incidence rates are about 1.7 per 100,000 in men and 0.8 per 100,000 in women, and mortality rates are 1.1 and 0.4 per 100,000, respectively, in men and women [1]. However, incidence is much higher in Southern China, Southeast Asia, the Middle East, and North Africa. In some regions of Southern China, such as Hong Kong, incidence in men reached levels higher than 20 per 100,000, but there has been a remarkable continuous downward trend for these tumors [16–18]. This can mainly be attributed to changes in environmental risk factors within the Chinese population, such as a diet that has been changing to a more Western style; thus, preserved salted fish is no longer a common food for most Chinese households [16]. This downward trend has also been seen in the United States among Chinese Americans living in California [19, 20]. The World Health Organization classifies nasopharyngeal carcinoma into three types according to histology: squamous cell carcinoma (Type I), nonkeratinizing carcinoma (Type II), and undifferentiated carcinoma (Type III). Nonkeratinizing and undifferentiated

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_4,

carcinomas are the most common (>90 %) in high-incidence areas [20–22], and squamous cell carcinoma is the most common (>70 %) in low-incidence regions [20, 21, 23].

Nonoccupational Risk Factors

Oral Cavity and Pharynx Cancer

For a long time, tobacco smoking and alcohol consumption have been recognized as the main causal factors for oral cavity and pharynx tumors; recent pooled analysis and multicenter studies have confirmed this [24–26]. Tobacco smoking and alcohol intake have a dose-response relationship in the occurrence of these tumors; there is also an evident interaction between these two risk factors [27]. Environmental exposure to tobacco smoke in homes and workplace is also associated with oral cavity and pharynx tumors. A pooled analysis of case-control studies has shown the carcinogenic effect of involuntary smoking on head and neck anatomical sites, particularly the pharynx and larynx [28]. Incidence of oral cavity and pharynx cancer is higher among groups of low socioeconomic status [29]. This can be partly explained by higher prevalence of smoking and alcohol consumption in individuals from socially disadvantaged groups [30]. Other factors related to these tumors have also been reported: for instance, diet, where consumption of fruit and vegetables is inversely associated to the risk of these tumors [31]; being underweight, where individuals with low BMI are at increased risk of head and neck cancer (including oral cavity, pharynx, and larynx) [32, 33]; chewing betel quid with or without tobacco, where products commercially available in India are considered carcinogenic to humans, affecting the oral cavity and pharynx with tobacco and just the oral cavity without tobacco [34–36]; and periodontal disease and regular gum bleeding, as well as daily mouthwash use, which may be independent risk factors for oral cavity and pharynx cancer [37, 38]. Poor mouth condition and missing teeth indicate low mouth health care and limited access to dental assistance, both correlated with low socioeconomic status. Human papillomavirus (HPV), particularly HPV16, is associated with oropharyngeal cancer [39]. Increasing incidence of tongue and tonsil tumors seen among those under 45 has been attributed to increasing prevalence of HPV infection in developing countries, practice of oral sex, and number of sexual partners [2, 40, 41]. In addition to environmental factors, familial clustering of oral cavity and pharynx cancer is related to increased risk of oral cavity and pharynx cancer [42].

Nasopharynx Cancer

Nasopharynx cancer is a complex disease; some environmental factors are involved in its origin, probably interacting, and there is also some type of genetic susceptibility. Consumption of salted fish starting in childhood is an important cause of nasopharyngeal cancer in the Chinese population [35, 36], but in contrast to salted fish and other preserved foods, frequent consumption of fresh fruit and vegetables has been linked to a lower risk [21]. Epstein-Barr virus is associated with nasopharynx cancer, but other cofactors must also be present for the disease to manifest [20, 39, 43]. Other factors also associated with nasopharynx cancer are previous chronic ear or nose diseases, such as chronic rhinitis or otitis media [23, 44]; active and passive smoking [23, 36, 44–47]; and the use of Chinese nasal oil and traditional herbal medicine [45, 48]. Additionally, family history of nasopharynx cancer has also been related to increased risk of nasopharynx cancer [44, 45, 49].

Occupational Risk Factors

Oral Cavity and Pharynx Cancer

Some studies have investigated the relationship between occupation and oral cavity and pharynx cancer considering broad categories; Garrote et al. [50] divided subjects into white-collar and blue-collar workers, farmers and housewives, and others, and Menvielle et al. [51] classified their study population into three groups, manual, nonmanual, and agricultural. Tables 4.1 and 4.2 describe 20 case-control and 24 cohort studies which reported an association between specific occupations and industries and oral cavity and pharynx cancer. Several occupations, work in specific industries, and exposure to specific agents have been screened for their carcinogenic potential.

Formaldehyde

Formaldehyde is widely used to manufacture building materials and household products. Most of formaldehyde production is for manufacture of resins, used to make adhesives for pressed wood products. Formaldehyde is also used as a preservative in medical laboratories and mortuaries.

Three of the four case-control studies in Table 4.1, which examined the effect of exposure to formaldehyde in oral and pharynx cancers, found relative risks (RR) of around 1.0 [52–54], whereas Vlajinac et al. [55] found a high risk (RR 4.4, 95 % confidence interval [95 % CI] 0.6–31.6). In a cohort study of workers from ten formaldehyde-producing or formaldehyde-using plants in the United States, Blair et al. [56] found standardized mortality ratio (SMR) of 443 ($p<0.05$) for oropharynx cancer in those exposed to cumulative doses of 0.5 parts per million-years (ppm-years) or less; however, SMRs were lower than 100 for those exposed to higher cumulative dose levels. Gardner et al. [57] in a cohort study of six formaldehyde-producing companies in the United Kingdom observed increased SMRs for oral and pharynx cancers in those employed before 1965 and for

Table 4.1 Case-control studies on occupation and cancer of the oral cavity and pharynx

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Decoufle [74], United States, 1956–1965	Oral cavity and pharynx cancer patients from a single New York clinical center	Patients without cancer conditions	Employment in the leather industry	Men			RR adjusted for tobacco smoking	
				Ever	18 (?)	3.22 ($p<0.01$)		
				employed at least for 5 years	12 (?)	3.58 ($p<0.01$)		
Winn et al. [88], United States, 1975–1978	232 women with oral and pharynx cancer residents in certain central North Carolina counties (156 from 5 hospitals and 99 from death certificates)	502 controls matched by admission date, age, race, and county of residence (from the same institutions as cases and from death certificate lists). Controls were not eligible if they had a diagnosis of mental disorder; neoplasms of the oral cavity or pharynx, esophagus, or larynx; or other noninfectious oral or pharyngeal diseases	Employment in textile, apparel, and hosiery industries. It was examined also exposure to dust in textile industry	*Textile*			RR crude. Authors referred that adjusting for smoking and snuff consumption did not appreciably reduce the association	
				No	192 (344)	1.0		
				Yes	40 (66)	1.1 (0.7–1.7)		
				1–4 years	13 (16)	1.5 (0.7–3.1)		
				5–9 years	6 (9)	1.2 (0.4–3.4)		
				10–19 years	6 (18)	0.6 (0.3–1.6)		
				20 years or more	13 (16)	1.5 (0.7–3.1)		
				Apparel				
				No	233 (392)	1.0		
				Yes	9 (18)	0.9 (0.4–2.0)		
				1–4 years	3 (7)	0.8 (0.2–3.0)		
				5–9 years	1 (4)	0.6 (0.1–3.7)		
				10 years or more	4 (5)	1.4 (0.4–5.1)		
				Hosiery				
				No	225 (384)	1.0		
				Yes	7 (26)	0.5 (0.2–1.1)		
				1–4 years	3 (7)	0.8 (0.2–2.9)		
				5–9 years	2 (5)	0.8 (0.2–3.5)		
				10 years or more	1 (11)	0.2 (0.0–1.2)		
				Textile dust				
				Never (work <6 months)	204 (373)	1.0		
				1–4 years	9 (4)	3.9 (1.2–12.0)		
				5–9 years	4 (5)	1.5 (0.4–5.3)		
				10 + years	14 (26)	1.0 (0.5–1.9)		

(continued)

Table 4.1 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Vaughan et al. [114], United States, 1980–1983	285 cases (186 men, 99 women) of oro- and hypopharynx cancer ($n=205$), nasopharynx ($n=27$), sinus, and nasal cavity ($n=53$) selected from a population-based cancer registry	552 controls (327 men, 225 women) were identified via random digit dialing	Occupational formaldehyde exposure was assessed via a job-exposure matrix	*Oro-hypopharynx*			Odds ratio adjusted for age, sex, cigarette smoking, and alcohol consumption	
				Exposure level				
				Background	147 (381)	1.0		
				Low	41 (121)	0.8 (0.5–1.4)		
				Medium	13 (42)	0.8 (0.4–1.7)		
				High	4 (8)	0.6 (0.1–2.7)		
				Number of years exposed				
				0	147 (381)	1.0		
				1–9	32 (127)	0.6 (0.3–1.0)		
				10+	26 (44)	1.3 (0.7–2.5)		
				Exposure score (all years)				
				0–4	170 (464)	1.0		
				5–19	14 (59)	0.6 (0.3–1.2)		
				20+	21 (29)	1.5 (0.7–3.0)		
				Exposure score induction (excluding 15 years before diagnosis)				
				0–4	174 (490)	1.0		
				5–19	16 (40)	0.9 (0.4–1.8)		
				20+	15 (22)	1.3 (0.6–3.1)		
Oreggia et al. [96], Uruguay, 1977–1981	242 cases of men with oral cavity, pharynx, and hypopharynx cancer ($n=236$) and larynx cancer ($n=6$) selected in a single center	322 controls matched by age among patients from the same hospital of cases, excluding those with lung, bladder, pancreas, and kidney cancer	Occupation with the longest duration was codified according to the International Classification of Occupations	*Oro-hypopharynx*			RR adjusted for tobacco smoking and alcohol consumption	Reference category: administrative, commerce, and professional workers
				Farmers	16 (72)	0.9 (0.3–2.2)		
				Baristas	2 (6)	1.0 (0.1–7.0)		
				Mechanics workers	2 (7)	1.5 (0.3–9.3)		
				Agriculture workers	2 (6)	1.9 (0.3–10.7)		
				Butchers	7 (8)	2.0 (0.4–9.5)		
				Blacksmiths	3 (3)	2.8 (0.5–16.0)		
				Bricklayers	18 (23)	2.8 (1.1–7.6)		
				Drivers	6 (13)	3.1 (0.7–14.0)		
				Telephone Operators	3 (2)	4.2 (0.5–34.9)		
				Electricians	2 (2)	5.5 (0.7–40.2)		
				Railwaymen	2 (1)	5.7 (0.6–51.3)		
Franco et al. [75], Brazil, 1986–1988	232 cases (201 men, 31 women) with oral cavity cancer from three clinical centers in three Brazilian cities	Controls selected among patients of the same hospitals of cases or from neighboring general hospitals, matched to cases by sex, age, and period of hospital admission	Never/ever employed in selected occupational settings	Textile	12 (40)	0.5 (0.3–1.1)	Adjusted for tobacco smoking and alcohol consumption	Reference category: never exposed
				Wood	27 (39)	1.2 (0.7–2.2)		
				Paper	6 (5)	2.1 (0.6–7.3)		
				Mining	10 (27)	0.8 (0.3–1.8)		
				Leather	7 (13)	1.3 (0.4–3.7)		
				Metal	23 (70)	0.6 (0.3–1.0)		
				Sugar/alcohol	7 (11)	0.9 (0.3–2.5)		
				Rubber	7 (11)	1.5 (0.5–4.8)		

Vaughan [82], United States, 1980–1983	183 cases (121 men, 62 women) of oro- and hypopharynx squamous cell carcinoma selected from a population-based cancer registry	552 controls (327 men, 225 women) were identified via random digit dialing, matched on age and gender	Jobs were broadly classified into 31 industrial and 59 occupations classified via the US Census Bureau. Never/ever considering all years and induction period (excluding 15 years before diagnosis). Presented here are only the odds ratios equal or higher than 1.5 for both situations "all years" and "induction period"	*OR (all years)*			Adjusted for age, gender, race, and smoking	Induction period = duration in job calculated after excluding the most recent 15 years before reference date (diagnosis for cases, interview for controls)
				Occupation/industry				
				Writers, entertainers, athletes in entertainment and recreation	8 (8)	3.6 (0.9–13.9)		
				Administrative support in personal services	3 (4)	2.2 (0.8–6.0)		
				Food service in transportation and communication	3 (1)	3.8 (0.2–57.2)		
				Food service in retail trade	41 (67)	1.9 (1.0–3.6)		
				Personal service in personal services	4 (10)	2.0 (0.4–9.2)		
				Personal service in professional services	4 (9)	3.5 (0.8–14.5)		
				Vehicle mechanics in repair services	5 (9)	2.5 (0.8–8.3)		
				Industrial mechanics in all industries	4 (1)	31.0 (3.0–315.1)		
				Carpenters in construction	10 (17)	1.5 (0.7–3.4)		
				Painters in all industries	4 (5)	2.3 (0.4–14.4)		
				Painters in construction	3 (4)	2.2 (0.3–14.3)		
				Other construction in construction	6 (10)	1.5 (0.4–5.6)		
				Precision metal workers in all industries	13 (33)	1.7 (0.8–3.7)		
				Precision metal workers in metal product manufacturing	3 (3)	4.6 (1.0–21.8)		
				Precision metal workers in public administration	5 (4)	9.7 (1.6–59.9)		
				Metal working machine operator in metal product manufacturing	3 (3)	3.3 (0.6–19.7)		
				Other machine operators in agriculture, forestry, and fisheries	6 (11)	1.6 (0.5–5.3)		
				Other machine operators in lumber and wood product manufacturing	4 (3)	4.4 (0.7–28.3)		
				Motor vehicle operators in public administration	4 (3)	5.4 (1.0–28.4)		
				Other transportation workers in transportation communication	8 (9)	1.7 (0.7–4.5)		
				Handlers, cleaners, and laborers in lumber and wood product manufacturing	8 (18)	1.6 (0.6–4.7)		

(continued)

Table 4.1 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
				OR (induction period)				
				Occupation/industry				
				Writers, entertainers, and athletes in entertainment and recreation	8 (8)	4.0 (1.0–16.1)		
				Administrative support in personal services	3 (4)	3.0 (1.1–7.9)		
				Food service in transportation and communication	3 (1)	3.8 (0.2–57.2)		
				Food service in retail trade	41 (67)	2.1 (1.1–4.0)		
				Personal service in personal services	4 (10)	2.2 (0.5–10.4)		
				Personal service in professional services	4 (9)	9.1 (1.9–44.8)		
				Vehicle mechanics in repair services	5 (9)	2.6 (0.8–8.8)		
				Industrial mechanics in all industries	4 (1)	31.0 (3.0–315.1)		
				Carpenters in construction	10 (17)	1.8 (0.7–4.8)		
				Painters in all industries	4 (5)	2.3 (0.4–14.4)		
				Painters in construction	3 (4)	2.2 (0.3–14.3)		
				Other construction in construction	6 (10)	1.7 (0.4–6.4)		
				Precision metal workers in all industries	13 (33)	1.7 (0.8–3.7)		
				Precision metal workers in metal product manufacturing	3 (3)	4.6 (1.0–21.8)		
				Precision metal workers in public administration	5 (4)	7.6 (1.1–54.0)		
				Metal working machine operator in metal product manufacturing	3 (3)	3.3 (0.6–19.7)		
				Other machine operators in agriculture, forestry, and fisheries	6 (11)	1.6 (0.5–5.4)		
				Other machine operators in lumber and wood product manufacturing	4 (3)	2.8 (0.3–24.0)		
				Motor vehicle operators in public administration	4 (3)	5.4 (1.0–28.4)		
				Handlers, cleaners, and laborers in lumber and wood product manufacturing	8 (9) 8 (18)	1.5 (0.6–4.0) 1.6 (0.6–4.7)		

Haguenoer et al. [78], France, 1983	283 men with nose ($n=14$), lips ($n=16$), oral cavity ($n=64$), pharynx ($n=114$) and larynx ($n=54$), and other and multiple site ($n=21$) cancer diagnosed in the 1st semester of 1983 in a regional cancer center in North of France	Two controls per case were chosen from patients without cancer in general hospitals in the same geographical area, matched by age, gender, ethnic group, area of residence, and smoking and alcohol drinking history	Types of occupation classified in 11 groups	*Oral cavity*		
				Mining	11 (11)	3.5 ($p<0.5$)
				Building industry	12 (14)	1.9 ($p>0.5$)
				Metal work and mechanics	13 (22)	1.2 ($p>0.5$)
				Agriculture	1 (7)	0.3 ($p>0.5$)
				Road transport	4 (10)	0.8 ($p>0.5$)
				Shipping and seamen	3 (9)	0.5 ($p>0.5$)
				Textile industry	2 (5)	0.7 ($p>0.5$)
				Woodwork	2 (3)	1.3 ($p>0.5$)
				Road works	5 (5)	2.2 ($p>0.5$)
				Service	11 (39)	0.5 ($p>0.5$)
				Others	1 (3)	0.7 ($p>0.5$)
				Pharynx		
				Mining	17 (28)	1.4 ($p>0.5$)
				Building industry	21 (23)	2.0 ($p<0.5$)
				Metal work and mechanics	16 (42)	0.7 ($p>0.5$)
				Agriculture	4 (15)	0.5 ($p>0.5$)
				Road transport	6 (15)	0.8 ($p>0.5$)
				Shipping and seamen	5 (10)	1.0 ($p>0.5$)
				Textile industry	12 (11)	2.4 ($p<0.5$)
				Woodwork	4 (1)	–
				Road works	5 (6)	1.8 ($p>0.5$)
				Service	20 (67)	0.5 ($p<0.5$)
				Others	5 (10)	1.0 ($p>0.5$)

(continued)

Table 4.1 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Merletti et al. [53], Italy, 1982–1984	86 men with oral cavity and pharynx cancer diagnosed among residents of Turin	Random sample stratified by gender and age from the files of residents of the city of Turin (1980–1984)	Job titles and economic activities were coded according to the International Standard Classification of Occupations of the International Labour Office and the International Standard Industrial Classification of the United Nations, respectively. For each occupational category and each industry, the subjects were classified as ever versus never employed. Duration was calculated for each period of employment. A latency analysis was also carried; then, occupational history after 1967 was ignored. A job-exposure matrix for 13 agents which are or may be related to respiratory cancer and three nonspecific exposures was applied to this database. Presented here are only the odds ratios (OR) with 95 % confidence intervals included	*Occupation* Service workers Working proprietors Cooks, waiters, and bartenders Service workers Production and related workers and transport equipment Chemical processers and related workers Tailors, dressmakers, and sewers Machinery fitters and assemblers and precision instrument makers (except electrical) Plumbers and pipe fitters *Activity branch* Railway equipment production Building industry Restaurant, bars, and hotels Social services Recreational and cultural private services	 15 (36) 3 (1) 3 (3) 3 (4) 69 (235) 4 (2) 3 (8) 18 (43) 6 (5) 3 (2) 29 (67) 6 (4) 10 (26) 3 (1)	 2.7 (1.0–4.6) 14.7 (1.0–206.5) 10.3 (1.3–81.2) 5.9 (1.0–35.4) 2.3 (1.1–5.0) 8.3 (1.3–55.0) 6.8 (1.4–38.7) 2.0 (1.0–4.0) 5.0 (1.8–21.5) 7.7 (1.0–63.2) 2.5 (1.3–4.5) 14.5 (2.8–75.7) 2.8 (1.1–6.7) 34.6 (2.3–524.0)	Odds ratios adjusted for age, education, area of birth, tobacco smoking, and alcohol drinking	Analysis considering probable or definitive exposure to asbestos, polycyclic aromatic hydrocarbons, chromium, nickel, arsenic, man-made mineral fibers, wood dust, leather dust, isopropyl alcohol, dimethyl sulfate, naphthalene, sulfuric acid, formaldehyde, dusts, gases, and solvents were conducted, but all RR had 95 % confidence intervals excluded

Vaughan and Davis [79], United States, 1983–1987	183 cases of oropharynx squamous cell carcinoma diagnosed in a single center	Controls were selected by random digit dialing matched to the cases by age and sex	Lifetime occupational histories were obtained, including a description of the duties involved in each job, as well as the associated industry. Jobs considered to entail significant exposure to wood dust included carpenters, forestry and logging workers, precision woodworkers (including patternmakers, cabinetmakers, and other furniture makers and finishers), and woodworking machine operators	Ever employed in wood-related occupations	14	0.6 (0.3–1.1)	RR adjusted for age, sex, cigarette smoking, and race	Reference category: never exposed
				Employed in wood-related occupations >15 years before diagnosis	12	0.5 (0.2–1.2)		
				Employment for 10 or more years taking place at least 15 years before the reference date	No information	1.5 (0.4–5.5)		

(continued)

Table 4.1 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Huebner et al. [83], United States, 1984–1985	1,114 incident cases of the oral cavity and oropharynx (762 men, 352 women) of ages 18–79 years	1,268 controls (837 men, 431 women) matched by gender, race, age, and study area	Employment history information was coded using four-digit job and industry codes (respectively, Standard Occupational Classification and Standard Industrial Classification). A list of 14 suspected high-risk jobs was elaborated; also a list of employment categories was examined according to specific anatomical sites. Ever/never employment or job was considered	*Suspected high-risk jobs*			RR adjusted for age, race, smoking, alcohol, and study location	Self-reported exposures to formaldehyde and to asbestos were also analyzed. But low OR were observed among men (formaldehyde 0.73, asbestos 0.82) and women (formaldehyde 0.36, asbestos 0.71)
				Men				
				Carpet installer	23 (4)	7.68 (2.37–24.9)		
				Semiconductor manufacturing	12 (10)	2.27 (0.83–6.19)		
				Resistor/transistor manufacturing	14 (10)	1.43 (0.56–3.65)		
				Brake repair work	41 (42)	1.15 (0.68–1.92)		
				Embalming fluid use/ manufacturing	16 (15)	1.09 (0.48–1.52)		
				Urea/phenol/resin manufacturing	6 (8)	1.02 (0.30–3.55)		
				Paint/varnish use/ manufacturing	125 (116)	0.99 (0.71–1.38)		
				Telegraph/telephone power work	24 (28)	0.79 (0.41–1.52)		
				TV/radio tube manufacturing	8 (11)	0.71 (0.25–2.03)		
				Other TV/radio parts manufacturing	7 (12)	0.60 (0.20–1.81)		
				Insulation manufacturing/ work	31 (44)	0.54 (0.31–0.97)		
				Women				
				Other TV/radio parts manufacturing	6 (7)	1.06 (0.29–3.90)		
				Resistor/transistor manufacturing	5 (6)	0.94 (0.23–3.82)		
				Paint/varnish use manufacturing	13 (17)	0.89 (0.37–2.14)		

Employment categories		
Tongue		
Males		
Boiler/furnace operator	6 (14)	2.32 (0.80–6.79)
Furniture/fixture industry worker	3 (26)	0.57 (0.16–2.04)
Iron/steel worker	6 (17)	1.23 (0.41–3.70)
Machinist	10 (31)	1.22 (0.51–2.93)
Painter	5 (18)	0.97 (0.33–2.84)
Petroleum industry worker	8 (11)	3.20 (1.15–8.90)
Primary metal industry worker	8 (35)	0.75 (0.30–1.89)
Transportation worker	23 (82)	0.92 (0.52–1.64)
Woodworking machine worker	1 (9)	0.34 (0.04–3.28)
Women		
Transportation equipment manufacturing worker	3 (27)	0.66 (0.19–2.34)
Mouth		
Males		
Boiler/furnace operator	8 (14)	1.67 (0.58–4.84)
Furniture/fixture industry worker	8 (26)	0.94 (0.37–2.40)
Iron/steel worker	6 (17)	1.08 (0.36–3.20)
Machinist	11 (31)	1.15 (0.51–2.59)
Painter	5 (18)	0.71 (0.22–2.34)

(continued)

Table 4.1 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
				Petroleum industry worker	1 (11)	0.41 (0.05–3.46)		
				Primary metal industry worker	13 (35)	1.03 (0.47–2.23)		
				Transportation worker	41 (82)	1.65 (1.04–2.61)		
				Woodworking machine worker	2 (9)	0.51 (0.09–2.96)		
				Women				
				Transportation equipment manufacturing worker	8 (27)	0.76 (0.29–1.98)		
				Pharynx				
				Males				
				Boiler/furnace operator	8 (14)	1.92 (0.63–5.83)		
				Furniture/fixture industry worker	14 (26)	2.17 (1.01–4.66)		
				Iron/steel worker	12 (17)	2.03 (0.83–5.13)		
				Machinist	15 (31)	1.93 (0.93–4.00)		
				Painter	12 (18)	2.03 (0.87–4.71)		
				Petroleum industry worker	7 (11)	2.31 (0.75–7.15)		
				Primary metal industry worker	22 (35)	2.22 (1.16–4.25)		
				Transportation worker	22 (82)	0.65 (0.36–1.18)		
				Woodworking machine worker	6 (9)	2.27 (0.69–7.44)		
				Women				
				Transportation equipment manufacturing worker	13 (27)	2.75 (1.13–6.66)		
Tisch et al. [126], Germany, 1988–1991	100 incident cases of oral cavity cancer	400 randomized controls	Ever/never employment as machine workers	Exposed or nonexposed as machine workers	22/34	3.4 (1.7–7.0)	Adjusted for tobacco and alcohol consumption	

Gustavsson et al. [54], Sweden, 1988–1990	Incident cases of cancers of the oral cavity ($n = 128$), pharynx ($n = 138$), esophagus ($n = 122$), and larynx ($n = 157$) of all Swedish men aged 40–79 years living in two regions of Sweden	641 controls were selected stratified by age and region as a random sample of the population base	Occupational history included all jobs held for more than 1 year over lifetime, recording the times of starting and stopping, job title, job tasks, and company for each job. An occupational hygienist examined the intensity and probability of the exposure to 17 specific occupational exposure factors	*Oral cavity*			Adjusted for geographical region, age, alcohol consumption, and tobacco smoking
				PAHs			
				Low	25	0.99 (0.57–1.73)	
				High	41	1.39 (0.86–2.25)	
				Asbestos			
				Low	17	0.64 (0.35–1.20)	
				High	16	0.67 (0.36–1.25)	
				Dust			
				Low	21	1.76 (0.98–3.16)	
				High	16	1.35 (0.70–2.60)	
				Wood dust	16	0.70 (0.38–1.29)	
				Quartz	20	0.85 (0.48–1.50)	
				Metal dust	19	0.76 (0.43–1.36)	
				Oil mist	15	0.69 (0.37–1.29)	
				Welding fumes	18	0.88 (0.48–1.60)	
				Formaldehyde	14	1.28 (0.64–2.54)	
				MMMF	6	0.51 (0.20–1.32)	
				Paper dust	6	0.63 (0.24–1.64)	
				Textile dust	4	0.80 (0.26–2.48)	
				Chromium	7	1.60 (0.63–4.06)	
				Phenoxy acids	7	1.61 (0.61–4.24)	
				Nickel	6	1.53 (0.57–4.16)	
				Acid mist	3	1.39 (0.34–5.58)	
				Leather dust	3	2.15 (0.54–8.67)	

(continued)

Table 4.1 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
				Pharynx				
				PAHs				
				Low	28	1.06 (0.61–1.82)		
				High	44	1.52 (0.94–2.45)		
				Asbestos				
				Low	24	1.01 (0.57–1.80)		
				High	22	1.08 (0.62–1.91)		
				Dust				
				Low	15	1.06 (0.55–2.05)		
				High	17	1.42 (0.74–2.72)		
				Wood dust	14	0.52 (0.27–0.99)		
				Quartz	27	1.29 (0.77–2.18)		
				Metal dust	31	1.40 (0.84–2.33)		
				Oil mist	19	0.78 (0.43–1.41)		
				Welding fumes	28	1.57 (0.91–2.71)		
				1–8 years		1.12 (0.53–2.35)		
				>8 years		2.26 (1.09–3.69)		
				Formaldehyde	13	1.01 (0.49–2.07)		
				MMMF	7	0.56 (0.23–1.38)		
				Paper dust	7	0.68 (0.27–1.69)		
				Textile dust	3	0.53 (0.14–1.93)		
				Chromium	3	0.66 (0.18–2.41)		
				Phenoxy acids	0	–		
				Nickel	2	0.45 (0.10–2.11)		
				Acid mist	4	1.21 (0.35–4.23)		
				Leather dust	5	2.83 (0.79–10.20)		

Schildt et al. [84], Sweden, 1980–1988	410 cases (276 men, 134 women) of squamous cell carcinoma of the oral cavity diagnosed and reported to Cancer Registry in four most northern counties in Sweden	410 controls matched by age, sex, and of the same county as cases	A questionnaire covered lifetime occupational history up to date of diagnosis and asked about exposure for some agents. All occupations were classified according to the Nordic Working Classification system	*OR*		
				Occupations (10 or more subjects)		
				Secretary and typist	4 (10)	0.4 (0.1–1.3)
				Miner and rock blaster	5 (11)	0.4 (0.1–1.4)
				Delivery boy	4 (9)	0.4 (0.1–1.5)
				Welder	7 (3)	2.3 (0.6–9.1)
				Wood and wood product workers	12 (3)	5.5 (1.2–25)
				Pulp industry worker	18 (6)	4.0 (1.3–12)
				Storemen	10 (5)	2.2 (0.6–7.4)
				Agents (10 or more subjects)		
				Organic solvents	69 (60)	1.2 (0.8–1.8)
				All pesticides	49 (43)	1.2 (0.7–1.8)
				Phenoxyacetic acids	20 (12)	1.7 (0.8–3.5)
				Herbicides	4 (6)	0.7 (0.1–2.4)
				DDT	8 (12)	0.6 (0.2–1.7)
				Mercurial seed dressing	6 (4)	1.5 (0.4–5.3)
				Impregnating agents	17 (16)	1.1 (0.5–2.3)
				Diesel oil	8 (8)	1.0 (0.3–2.7)
				Oil	7 (11)	0.6 (0.2–1.7)
				Chlorine	4 (6)	0.6 (0.1–2.6)
				Producer gas	6 (6)	1.0 (0.3–3.2)
				Sulfur compounds	7 (6)	1.2 (0.3–3.5)
				Plastics	7 (7)	1.0 (0.3–2.9)

(continued)

Table 4.1 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Marchand et al. [100], France, 1989–1991	206 incident cases of hypopharynx cancer in men recruited from 15 hospitals in six French cities	305 men hospital-based controls with other (non-respiratory) cancers	Subjects' past occupational exposure to asbestos and to four types of MMVF (mineral wool, refractory ceramic fibers, glass filaments, and microfibers) was evaluated through a job-exposure matrix	Asbestos			RR adjusted for age, smoking, and alcohol consumption. In the analysis of joint effect of exposure to asbestos and smoking, RR adjusted for age and alcohol consumption	
				Never exposed	40 (110)	1.0		
				Ever exposed	161 (185)	1.80 (1.08–2.99)		
				Cumulative level				
				Low	52 (67)	1.92 (1.03–3.57)		
				Intermediate	52 (67)	1.40 (0.74–2.63)		
				High	57 (51)	2.14 (1.14–4.01)		
				Asbestos				
				None/low and smoking <30 pack-years		1.0		
				None/low and smoking >30 pack-years		3.95 (2.16–7.24)		
				Intermediate/high and smoking <30 pack-years		1.19 (0.61–2.32)		
				Intermediate/high and smoking >30 pack-years		6.22 (3.41–11.36)		
				Mineral wools				
				Ever exposed	99 (99)	1.55 (0.99–2.41)		
				Ceramic fibers				
				Ever exposed	7 (9)	0.78 (0.26–2.38)		
				Glass filaments				
				Ever exposed	8 (11)	0.91 (0.30–2.76)		
				Microfibers				
				Ever exposed	7 (9)	0.78 (0.26–2.38)		
Garrote et al. [50], Cuba, 1996–1999	200 incident cases of oral cavity and oropharynx cancer (143 men, 57 women)	200 hospital controls (136 men, 64 women) matched by age and gender with cases	Four major occupational groups	White collar	51 (85)	1.0	Adjusted for gender, age, area of residence, education, smoking, and drinking habits	
				Blue collar	68 (57)	1.73 (0.97–3.09)		
				Farmers	37 (19)	2.22 (0.97–5.10)		
				Housewives	35 (30)	1.94 (0.87–4.33)		

Coble et al. [127], Puerto Rico, 1992–1995	327 incident cases (286 men, 41 women) of oral cavity and pharynx cancer among Puerto Rican residents aged 21–79 years	499 population-based controls (413 men, 86 controls) matched on age, gender, and area of residence with cases	Occupation classified according to industry categories and occupation categories. A job-exposure matrix was used to examine the potential exposure to dusts, metals, and solvents	*Oral cavity* Agriculture industry Sugarcane industry Sugarcane farmers *Pharynx* Agriculture industry Sugarcane industry Sugarcane farmers *Oral cavity and pharynx* Dusts None Low Medium High Metals None Low Medium High Solvents None Low Medium High	 36 (64) 16 (13) 14 (10) 24 (64) 5 (13) 3 (10) 119 (197) 25 (51) 60 (70) 82 (94) 234 (350) 20 (23) 24 (32) 8 (7) 205 (321) 28 (33) 41 (54) 12 (4)	 1.4 (0.8–2.6) 3.4 (1.2–9.4) 4.4 (1.4–13.6) 1.6 (0.8–3.2) 1.0 (0.3–3.8) 0.8 (0.2–4.0) 1.0 0.5 (0.3–1.0) 1.3 (0.7–2.1) 1.1 (0.7–1.7) 1.0 1.1 (0.5–2.6) 1.2 (0.6–2.5) 2.7 (0.7–10.6) 1.0 1.0 (0.5–2.1) 1.6 (0.9–2.9) 3.2 (0.8–12.6)	Adjusted for age, smoking, and alcohol consumption. P-value for trend: dusts 0.5, metals 0.2, and solvents 0.03	
Menvielle et al. [51], France, 1989–1991	504 incident cases of hypopharynx ($n=201$) and larynx cancer ($n=303$) in men from 15 French hospitals in six cities	242 hospital-based controls, men with non-respiratory cancers	Occupation classified in ever manual or never manual	*Hypopharynx* Never manual Ever manual Adjusted Age + alcohol and tobacco + occupational exposure	 27 174 	 1.0 3.50 (2.14–5.73) 2.65 (1.51–4.66) 1.84 (0.97–3.48)	RR adjusted by alcohol intake, smoking, and occupational exposures: asbestos, coal dust (ever/never), and formaldehyde (maximal probability of exposure)	
Andreotti et al. [80], Brazil, 1999–2001	325 incident cases of oral cavity and pharynx (274 men, 51 women) from seven hospitals in the city of Sao Paulo	362 hospital-based controls without cancer, matched by age and gender	Occupation classified according to industry categories and occupation categories and considering periods of exposure in each category (>10 years, >10 years, and >20 years of latency)	*Working in vehicle maintenance shop* Ever exposed >10 years >10 years and >20 latency years *Vehicle repair worker* Ever exposed >10 years >10 years and >20 latency years	 26 (12) 21 (3) 19 (3) 14 (7) 13 (1) 11 (1)	 2.45 (1.14–5.27) 7.90 (2.03–30.72) 7.38 (1.88–28.98) 2.10 (0.78–5.68) 26.21 (2.34–294.06) 24.46 (2.10–284.60)	Adjusted for age, smoking, and alcohol consumption	Analysis conducted only with men workers. We reported only the occupation or industry with RR statistically significant

(continued)

Table 4.1 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Vlajinac et al. [55], Serbia and Montenegro, 1998–2000	100 incident cases (89 men, 11 women) of oropharynx cancer (including base of the tongue, neoplasm of the palate, neoplasm of the tonsils) recruited in a single center	100 controls recruited among patients treated in the same period as cases of some nonmalignant diseases of head and neck matched with cases according to age, sex, and place of residence	Occupational exposure was assessed by asking the participants whether they have ever been exposed to the items listed	*OR*			OR adjusted for education, BMI, smoking, alcohol consumption, and family history of oropharynx cancer	
				High temperature	49 (52)	0.51 (0.12–2.09)		
				Low temperature	56 (56)	0.82 (0.42–1.58)		
				High humidity	52 (45)	1.04 (0.53–2.05)		
				Dry air	57 (73)	0.30 (0.14–0.64)		
				Coal dust	16 (14)	0.88 (0.36–2.14)		
				Cement dust	16 (12)	1.58 (0.58–4.33)		
				Aniline dyes	11 (7)	1.41 (0.44–4.44)		
				Wood dust	22 (12)	2.33 (0.96–5.66)		
				Metal dust	23 (30)	0.57 (0.27–1.18)		
				Chemical dust or smoke	24 (30)	0.71 (0.34–1.48)		
				Nickel and chromium	6 (5)	1.33 (0.30–5.90)		
				Mortar	16 (11)	1.68 (0.57–4.97)		
				Formaldehyde	8 (2)	4.48 (0.63–31.63)		
Jayaprakash et al. [81], United States, 1982–1988	1,522 men of upper aerodigestive and respiratory cancers (241 oral and pharynx)	1,522 controls matched on age and smoking, selected from hospital visitors with a cancer suspicion and those who were screened as outpatients in the same hospital of cases, but not diagnosed with any malignant or benign tumors	Wood dust exposure was assessed through several questions about prior exposure at work. If exposed, they were queried about the frequency and duration exposure and also the year of first exposure	*Oral and pharynx cancers*			RR adjusted for age, pack-years of smoking, body mass index, smoking status, education, and alcoholic drinks per week and year of enrolment	
				Wood dust exposure				
				Never	188 (1.153)	1.0		
				Occasionally	32 (262)	0.72 (0.48–1.08)		
				Regularly	21 (107)	1.14 (0.68–1.92)		
				Squamous cell carcinoma of oral cavity and pharynx				
				Wood dust exposure				
				Never	169 (1.153)	1.0		
				Occasionally	28 (262)	0.68 (0.44–1.06)		
				Regularly	21 (107)	1.27 (0.76–2.14)		

Table 4.2 Cohort studies on occupation and cancer of the oral cavity and pharynx

Reference, location	Cohort description	Exposure assessment	Tumor site	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Moulin et al. [98], France	1,374 men workers of a single man-made mineral fibers present at the factory (1975–1984) and who had been working for at least one full year. No clear definition of period of beginning of exposure, but the first production lines started in 1940. Cancer incidence follow-up (1975–1984)	Environmental surveys were performed in 1981 in order to measure the pollution by fibers	Oral cavity and pharynx		*SIR*			Both SIR estimates were not statistically significant
				Oral cavity				
				9		3.01		
				Pharynx				
				5		1.40		
Blair et al. [56], United States	26,561 workers first employed in 10 formaldehyde-producing or formaldehyde-using plants before 1996. Mortality follow-up (1980)	A job-exposure matrix was prepared for industrial hygienists considering each job-work area-calendar year combination. Measures of exposure to formaldehyde used in the analysis included level or intensity, duration, average, cumulative or peak exposure, presence of particulates, and measures that excluded recent exposures from the exposure index		Several tumors	*SMR* Oral cavity and pharynx			Black women were excluded from analysis because of small numbers ($n=26$). SMR based on US national rates. NS = nonstatistically significant
					White men			
				18	Exposed	96 (57–152)		
				3	Nonexposed	54 (11–157)		
					White women			
				0	Exposed	–		
				0	Nonexposed	–		
					Black men			
				3	Exposed	–		
				3	Nonexposed	–		
					Intensity of exposure (white men)			
				2	0	89 (NS)		
				1	>0–<0.1	30 (NS)		
				4	0.1–0.4	59 (NS)		
				14	0.5–1.9	130 (NS)		
				0	>2.0	–		
					Lip			
				0	Cumulative formaldehyde exposure			

(continued)

Table 4.2 (continued)

Reference, location	Cohort description	Exposure assessment	Tumor site	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
				1	0 ppm-year	–		
				0	<0.5 ppm-year	477 (NS)		
				1	0.51–5.5 ppm-year	–		
					>5.5 ppm-year	764 (NS)		
					Tongue			
				0	Cumulative formaldehyde exposure			
				0	0 ppm-year	–		
				2	<0.5 ppm-year	–		
				0	0.51–5.5 ppm-year	96 (NS)		
					>5.5 ppm-year	–		
					Gum, floor, and other mouth sites			
					Cumulative formaldehyde exposure			
				0	0 ppm-year	–		
				1	<0.5 ppm-year	66 (NS)		
				0	0.51–5.5 ppm-year	–		
				1	>5.5 ppm-year	88 (NS)		
					Oropharynx			
					Cumulative formaldehyde exposure			
				0	0 ppm-year	–		
				4	<0.5 ppm-year	443 ($p < 0.05$)		
				1	0.51–5.5 ppm-year	95 (NS)		
				0	>5.5 ppm-year	–		
					Hypopharynx			
					Cumulative formaldehyde exposure			
				1	0 ppm-year	594 (NS)		
				1	<0.5 ppm-year	172 (NS)		
				0	0.51–5.5 ppm-year	–		
				0	>5.5 ppm-year	–		
					Other pharynx			
					Cumulative formaldehyde exposure			
				0	0 ppm-year	–		
				1	<0.5 ppm-year	73 (NS)		
				0	0.51–5.5 ppm-year	–		
				0	>5.5 ppm-year	–		

Stayner et al. [62], United States	11,030 workers from three garment manufactures who had been working for at least 3 months (1955–1977). Mortality follow-up until end of 1982	Workers of the cohort were compared with the US population. Exposure assessment considered duration of employment, latency, and first-year exposure	All tumors		*SMR*		Workers who were employed only in clerical or administrative positions were excluded from the analysis. We reported here only risk estimates for oral cavity and pharynx tumors. NS = nonstatistically significant
					Oral cavity		
				4	White men	343 (118–786)	
				0	White women	–	
				4	Nonwhite men	485 ($p<0.01$)	
					Nonwhite women	–	
				0	Plant 1	–	
				2	Plant 2	306 (NS)	
				2	Plant 3	886 ($p<0.01$)	
				0	Latency period (3 months–9 years)	–	
					Duration of exposure		
				0	3 months–3 years	–	
				0	4–9 years	–	
				0	10 + years	–	
				0	Overall latency period (10–19 years)	–	
					Duration of exposure		
				0	3 months–3 years	–	
				0	4–9 years	–	
				2	10 + years	822 ($p<0.01$)	
				2	Overall latency period (20 + years)	357 (NS)	
					Duration of exposure		
				0	3 months–3 years	–	
				1	4–9 years	315 (NS)	
				1	10 + years	654 (NS)	
				2	Overall year of first exposure	705 ($p<0.01$)	
				0	1955–1962		
				0	1963–1970		
				4	1971–1978	440 ($p<0.01$)	
					Pharynx		
				2	White men	–	
				1	White women	359 (NS)	
				1	Nonwhite men	239 (NS)	
				0	Nonwhite women	86 (NS)	
				0	Plant 1	–	
				1	Plant 2	100 (NS)	
				0	Plant 3	–	
				0	Latency period (3 months–9 years)	–	
					Duration of exposure		
				0	3 months–3 years	–	
				0	4–9 years	–	
				0	10 + years	–	
				0	Overall latency period (10–19 years)	–	
					Duration of exposure		
				1	3 months–3 years	368 (NS)	
				1	4–9 years	490 (NS)	
				0	10 + years	–	
				0	Overall latency period (20 + years)	233 (NS)	
					Duration of exposure		
				0	3 months–3 years	–	
				0	4–9 years	–	
				0	10 + years	–	
					Overall year of first exposure	–	
				1	1955–1962	76 (NS)	
				1	1963–1970	273 (NS)	
				0	1971–1978	–	

(continued)

Table 4.2 (continued)

Reference, location	Cohort description	Exposure assessment	Tumor site	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Lynge and Thygesen [128], Denmark	Cohort included people aged 20–64 years at the census on 9 November 1970. Ten-year follow-up for cancer incidence (1970–1980)	Industry and occupation were recorded only for people economically active at the time of census, through the International Standard Industrial Classification and a special Danish code, respectively	Pharynx cancer		*RR*			Here we reported only RR with 95 % confidence interval excluded 1
					Occupation/industry			
				12	Waiter	12.08 (6.26–21.17)		
				8	Bricklayer	2.69 (1.16–5.31)		
				6	Painter	3.30 (1.21–7.18)		
				5	Dock laborer	5.23 (1.69–12.16)		
				4	Self-employed/groceries	3.89 (1.06–9.94)		
				3	Chief engineer at sea	5.00 (1.03–14.62)		
				3	Cashier	8.94 (1.82–25.79)		
				2	Other banking staff	9.90 (1.21–36.10)		
					Selected occupational groups			
				1	Skilled workers and painter in metal industry	1.95 (0.05–10.92)		
				6	Skilled workers and painter in paint workshop	3.30 (1.21–7.18)		
				0	Skilled workers and painter/other industries	–		
				3	Self-employed and painter in paint workshop	1.73 (0.34–5.07)		
				10	All painters	2.27 (1.09–4.18)		
Gardner et al. [57], United Kingdom	14,017 men employed in six of formaldehyde-producing or formaldehyde-using plants (7,660 first employed before 1965, 6,357 first employed after 1964); mortality follow-up until the end of 1989	Exposure to formaldehyde was on the basis of recorded titles of jobs undertaken by each of the men before 1982. Exposures have been qualitatively classified after detailed discussions on past working conditions	All tumors		*SMR*			Here we reported only the risks for oral cavity and pharynx cancer
					Employed before 1965			
				3	Oral cavity	137 (28–401)		
				7	Pharynx	147 (59–303		
					Employed after 1964			
				1	Oral cavity	190 (5–10.59)		
				0	Pharynx	–		
Johnson [94], United States	Cohort with 10,841 members of meatcutter union in Baltimore (6,906 men, 3,935 women) employed for at least 1 year; mortality follow-up (1949–1989)	Subjects who ever worked in the meat department of supermarkets or grocery stores	Oral cavity and pharynx		*SMR*			
					Meat department			
					Men	1.8 (1.0–3.0)		
					Women	1.5 (0.3–4.4)		
					Other departments			
					Men	1.7 (0.8–3.2)		
					Women	0.5 (0.0–2.6)		

Pukkala et al. [86], Finland	Cohort of persons born in Finland during 1906–1945. Follow-up (1971–1985) detected 3,178 cases (2,369 in men, 809 in women) of cancer of the lip, tongue, oral cavity, and pharynx	Occupations were coded at Statistics Finland using a modified Nordic Classification of Occupations	Oral cavity (lip, tongue) and pharynx		*SIR*		SIR adjusted for social class	We reported here only SIR with 95 % confidence interval excluded 1
					Tongue (men only)			
				3	Journalists	6.84 (1.41–20.0)		
					Oral cavity (men/women)			
				16	Services	1.82 (1.04–2.96)		
				48	Economically inactive	1.62 (1.20–2.15)		
					Oral cavity (men)			
				5	Civilian guards	4.13 (1.34–9.63)		
				10	Electrical workers	2.29 (1.10–4.21)		
					Oral cavity (females)			
				2	Railway traffic supervisors	13.64 (1.65–49.3)		
				3	Vocational teachers	8.28 (1.71–24.2)		
				6	Waitresses	3.01 (1.11–6.56)		
					Pharynx (men/women)			
				97	Economically inactive	7.81 (1.61–22.8)		
					Pharynx (men)			
				3	Electronics and telefitters	5.18 (1.07–15.1)		
				3	Administrative managers	5.18 (1.07–15.1)		
				8	Artistic/literary workers	3.20 (1.38–6.31)		
					Pharynx (women)			
				8	Cutting/sewing workers	2.34 (1.01–4.61)		
				15	Farmers	1.80 (1.01–2.98)		
Andjelkovich et al. [58], United States	3,929 men with potential exposure to formaldehyde for at least 6 months between 1960 and 1987 at an automotive iron foundry; mortality follow-up until end of 1989. An internal referent population of 2,032 men who had worked in jobs with no exposure to formaldehyde during the same period was selected for comparison	Work history of each subject, including all jobs, department number, and job title, was examined by an industrial hygienist as associated with high, medium, and low or no formaldehyde and silica exposure	All malignant tumors		*SMR*			We reported only risks for oral cavity and pharynx cancer. Reference group for RR estimates consists of white nonsmokers with nonexposure to formaldehyde and cumulative silica exposure in first quartile
					Oral cavity and pharynx			
				6	Exposed	131(48–286)		
				5	Smokers	191 (NS)		
				0	Nonsmokers	–		
				5	Unexposed	169 (54–395)		
				1	Smoker	71 (NS)		
				2	Nonsmokers	392 (NS)		
					RR			
					Formaldehyde			
					Exposed	0.59 (0.14–2.93)		
					Quartile 3 + Quartile 4	1.16 (0.20–6.51)		
					Nonwhite	4.41 (1.004–22.7)		
					Ever smoking	1.00 (0.23–6.84)		
					Silica			
					Quartile 2	0.43 (0.02–4.54)		
					Quartile 3	0.48 (0.06–4.00)		
					Quartile 4	0.37 (0.06–2.91)		
Coggon and Wield [97], England and Wales	Cohort of men, 4,018 butchers and 2,062 cooks, identified from 1961 Census; mortality follow-up until the end of 1992 (79.9 % of the cohort)		Oral cavity and pharynx		*SMR*			
					Butchers			
				1	Oral cavity	0.55 (0.01–3.08)		
				2	Pharynx	0.53 (0.06–1.91)		
					Cooks			
				4	Oral cavity	5.57 (1.52–14.26)		
				4	Pharynx	2.66 (0.73–6.81)		

(continued)

Table 4.2 (continued)

Reference, location	Cohort description	Exposure assessment	Tumor site	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Boffetta et al. [99], Denmark, Finland, Norway, Sweden	6,296 workers employed >1 year in 9 factories (3,685 rock-slag wool; 2,611 glass wool) (1933–1961); follow-up (1995) (94.2 % of the cohort)		Oral cavity and pharynx		*SIR*			
				38	Total cohort	1.65 (1.17–2.26)		
				27	Rock-slag wool	1.84 (1.22–2.68)		
				11	Glass wool	1.31 (0.65–2.34)		
		Medium and high exposure to wood dust; employment duration: <10 years, 10–19 years, > and 20 years; formaldehyde exposure (no/possible)	Oral cavity or pharynx		*SIR*			
					Men			
				12	Oral cavity	1.22 (0.63–2.13)		
				9	Pharynx	1.82 (0.83–3.46)		
					Medium exposure			
				5	Oral cavity	3.66 (1.19–8.55)		
				3	Pharynx	4.02 (0.83–11.75)		
					High exposure			
				6	Oral cavity	0.76 (0.28–1.65)		
				6	Pharynx	1.51 (0.58–3.29)		
					<10 years			
				9	Oral cavity	1.50 (0.68–2.84)		
				7	Pharynx	2.18 (0.88–4.49)		
					10–19 years			
				3	Oral cavity	1.36 (0.28–3.98)		
				2	Pharynx	2.12 (0.26–7.66)		
					>20 years			
				0	Oral cavity	0.00		
				0	Pharynx	0.00		
					Women			
				4	Oral cavity	1.84 (0.50–4.71)		
				0	Pharynx	0.00		
					Medium exposure			
				2	Oral cavity	2.47 (0.30–8.91)		
				0	Pharynx	0.00		
					High exposure			
				2	Oral cavity	1.61 (0.19–5.81)		
				0	Pharynx	0.00		
					<10 years			
				1	Oral cavity	0.75 (0.02–4.20)		
				–	Pharynx	–		
					10–19 years			
				0	Oral cavity	0.00		
				–	Pharynx	–		
					>20 years			
				3	Oral cavity	8.10 (1.67–23.68)		
				–	Pharynx	–		
					Formaldehyde exposure (men and women)			
					No			
					Oral cavity	1.58 (0.43–4.05)		
					Pharynx	3.57 (0.97–9.14)		
					Possible			
					Oral cavity	1.25 (0.62–2.23)		
					Pharynx	1.17 (0.38–2.73)		

Boffetta et al. [95], Sweden	25,049 men butchers or meat workers from 1960 to 1970; follow-up for incidence (1971–1989)	Three categories: butchers in the meat industry, butchers employed in other industries, and non-butchers in meat industry	Oral cavity and pharynx		*SIR*		Relative risk adjusted for age, calendar period, geographical region, and urban setting	RR reference category: other workers, excluding other animal-related jobs
				73	Butcher or meat workers	1.1 (0.8–1.3)		
				14	Butcher in meat industry	1.5 (0.8–2.5)		
					RR			
				14	Butchers in meat industry	1.6 (1.0–2.7)		
				2	Butcher in other industries	1.3 (0.3–5.1)		
				5	Non-butchers in meat industry	0.7 (0.3–1.6)		
Boffetta et al. [93], Sweden	Exposed men (7,400,000 person-years) and women (240,000) to diesel engine emissions according to 1960 Census occupation and industry of employment of Swedish population; mortality follow-up (1971–1989)	Job-exposure matrix elaborated according to jobs and industry titles of cohort members (men and women with available occupational data from Census of 1960 and 1970) considering probability and intensity of exposure to diesel engine emissions	Oral cavity and pharynx		*SIR*		Relative risk adjusted for age, calendar period, geographical region, and urban/rural residence	RR reference category: unexposed to diesel engine emissions
				1,733	Men	1.05 (1.00–1.10)		
				31	Women	1.64 (1.11–2.33)		
					RR			
					Men			
					Probability			
				633	Low	1.2 (1.11–1.26)		
				559	Medium	1.11 (0.99–1.18)		
				439	High	1.1 (0.99–1.21)		
					Intensity			
				1,150	Low	1.2 (1.11–1.26)		
				280	Medium	1.2 (0.95–1.21)		
				201	High	0.98 (0.85–1.13)		
					Women			
					Probability			
				18	Low	1.4 (0.91–2.30)		
				4	Medium	1.2 (0.46–3.31)		
				6	High	1.7 (0.75–3.74)		
					Intensity			
				22	Low	1.4 (0.77–2.84)		
				6	Medium-high	1.7 (0.77–3.84)		

(continued)

Table 4.2 (continued)

Reference, location	Cohort description	Exposure assessment	Tumor site	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Marsh et al. [59], United States	7,328 workers (6,859 men, 469 women) employed at a plastic-producing plant (1941–1984); mortality follow-up until 1998	Exposure estimation was based on an examination of the available sampling data and job descriptions and verbal descriptions of jobs and tasks	Oral cavity and pharynx		*SMR*			
					Cancer			
				31	Oral cavity + pharynx	1.80 (1.22–2.55)		
				1	Lip	3.23 (0.08–18.0)		
				3	Tongue	0.76 (0.16–2.22)		
				3	Gum and other mouth sites	1.20 (0.25–3.51)		
				2	Floor of the mouth	2.07 (0.25–7.48)		
				22	Pharynx (including nasopharynx)	2.63 (1.65–3.98)		
				5	Oropharynx	2.17 (0.71–5.07)		
				3	Hypopharynx	2.25 (0.46–6.58)		
				7	Pharynx, unspecified	2.11 (0.85–4.35)		
					All pharyngeal cancers (including nasopharyngeal)			
				12	Short term (<1 year)	2.35(1.22–4.11)		
				10	Long term (1 + years)	2.10 (1.01–3.86)		
					Year of hire			
				1	1941–1946	0.46 (0.01–2.56)		
				18	1947–1956	3.24 (1.92–5.12)		
				3	1957+	1.41 (0.29–4.12)		
					DOE (year) (all workers)			
				12	<1	2.34 (1.21–4.09)		
				5	1–9	1.89 (0.61–4.42		
				5	10+	2.36 (0.76–5.50)		
					TSFE (year)			
				4	<20	1.41 (0.38–3.61)		
				7	20–29	2.32 (0.93–4.78)		
				11	30+	2.75 (1.37–4.92)		
					Formaldehyde exposure			

				2	Unexposed	1.24 (0.15–4.49)
				20	Exposed	2.42 (1.48–3.74)
					Duration of exposure	
				11	>0–<1	2.35 (1.17–4.21)
				5	1–9	1.81 (0.49–4.63)
				6	10+	3.65 (1.18–8.52)
					Cumulative exposure	
				6	>0–<0.004	3.31 (1.22–7.21)
				7	0.004–0.129	2.06 (0.83–4.24)
				7	0.22+	2.30 (0.92–4.73)
					AIE to formaldehyde (ppm)	
				6	>0–<0.03	2.02 (0.74–4.40)
				7	0.03–0.159	3.82 (1.54–7.88)
				7	0.16+	2.03 (0.82–4.19)
					Formaldehyde >0.2 ppm	
				8	Unexposed	1.72 (0.74–3.39)
				14	Exposed	2.68 (1.46–4.49)
					Duration (year)	
				6	>0–<1	2.19 (0.80–4.77)
				3	1–9	1.68 (0.34–4.90)
				5	10+	7.35 (2.39–17.16)
					Formaldehyde >0.7 ppm	
				16	Unexposed	2.12 (1.21–3.45)
				6	Exposed	2.55 (0.94–5.56)
					Duration (year)	
				4	>0–<1	2.58 (0.70–6.61)
				2	1+	2.50 (0.30–9.03)
Brown et al. [87], Sweden	Cohort of individuals identified in Census of 1960 and 1970 in Sweden. Participants were employed in painting trades and paint manufacturing cohorts: men painters (42,433), men lacquerers (12,331), men artists (6,662), men employed in paint and varnish plants (5,741), women lacquerers (974), women glazers (882), women artists (2,136), and alive and free of cancer in 1971. Follow-up (1971–1989) for cancer incidence	The jobs of individuals at either Census (1960, 1970) were classified according to Swedish Occupational Classification	Oral cavity		*SIR*	
					Men	
				122	Painters	1.0 (0.8–1.1)
				30	Any lacquerers	1.0 (0.7–1.5)
				22	Metal lacquerers	0.9 (0.6–1.4)
				10	Wood lacquerers	2.1 (1.0–3.9)
				29	Artists	1.5 (1.0–2.1)
				13	Paint/varnish workers	0.8 (0.4–1.3)
					Women	
				4	Lacquerers	3.8 (1.0–9.7)
				4	Glazers	4.6 (1.2–11.8)
				2	Artists	0.9 (0.1–3.2)

(continued)

Table 4.2 (continued)

Reference, location	Cohort description	Exposure assessment	Tumor site	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Coggon et al. [60], United Kingdom	14,014 men employed in six of formaldehyde-producing or formaldehyde-using plants; each individual was followed starting at the latest of 1 January 1941; mortality follow-up until the end of 2000	Exposure to formaldehyde was on the basis of recorded titles of jobs undertaken by each of worker occupational history. A separate job-exposure matrix was constructed for each factory. Exposure to formaldehyde was classified as follows: background (<0.1 ppm), low (0.1–0.5 ppm), moderate (0.6–2.0 ppm), high (>2.0 ppm), and unknown	All tumors	Total cohort (1941–2000)	*SMR*			This study is an update of the cohort of Gardner et al. [57]. See above in this table. Here we reported only the risks for oral cavity and pharynx cancer
				4	Tongue	0.84 (0.23–2.14)		
				6	Oral cavity	1.28 (0.47–2.78)		
				15	Pharynx	1.55 (0.87–2.56)		
					Men with high exposure (1941–2000)			
				3	Tongue	1.91 (0.39–5.58)		
				2	Oral cavity	1.32 (0.16–4.75)		
				6	Pharynx	1.91 (0.70–4.17)		
Pinkerton et al. [63], United States	11,039 workers (2,015 men, 9,024 women) exposed to formaldehyde in three garment manufactures who had been working for at least 3 months (1955–1977). Mortality follow-up until the end of 1998	Workers of the cohort were compared with the US population. Exposure assessment considered duration of employment, latency, and first-year exposure	All tumors		*SMR*			This study is an update of the cohort of Stayner et al. [129. See above in this table. Here we reported only the risks for oral cavity and pharynx cancer
					Original study period (1955–1982)			
				6	Oral cavity + pharynx	1.58 (0.58–3.45)		
				4	Oral cavity	3.53 (0.96–9.02)		
				2	Pharynx	1.15 (0.14–4.15)		
					Updated period (1983–1998)			
				2	Oral cavity + pharynx	0.31 (0.04–1.14)		
				0	Oral cavity	–		
				1	Pharynx	0.34 (0.01–1.87)		
					Total study period (1955–1998)			
				8	Oral cavity + pharynx	0.79 (0.34–1.55)		
				4	Oral cavity	1.33 (0.36–3.41)		
				3	Pharynx	0.64 (0.13–1.86)		

Hauptmann et al. [61], United States	Cohort of 25,619 workers (22,493 men, 3,126 women) employed in 10 US formaldehyde-producing or formaldehyde-using plants prior 1966; mortality from solid cancer follow-up until the end of 1994	Exposure to formaldehyde (nonexposed and exposed) was estimated from job titles, tasks, visits to the plants, discussion with workers and managers, by industrial hygienists, and defining average intensity, peak of exposure, cumulative exposure, and duration of exposure	Oral cavity		*SMR*		RR adjusted for calendar year, age, gender, race (black/white), and pay category (salary/wage)	This study is an update of the cohort of Blair et al. [56]. See above in this table. (*) 95 % confidence interval does not include 1. (NS) 95 % confidence interval include 1
				13	Nonexposed	0.99 (0.58–1.71)		
					Exposed	1.01 (0.77–1.34)		
					RR			
					Intensity (ppm)			
					0	2.42 (*)		
					>0–<0.5	1.0		
					0.5–<1.0	2.41 (*)		
					>1.0	1.89 (NS)		
					Peak (ppm)			
					0	2.08 (NS)		
					>0–<2.0	1.0		
					2.0–<4.0	1.07 (NS)		
					>4.0	1.83 (NS)		
					Cumulative (ppm-year)			
					0	1.98 (NS)		
					>0–<1.5	1.0		
					1.5–<5.5	1.59 (NS)		
					>5.5	1.74 (NS)		
					Duration (years)			
					0	1.87 (NS)		
					>0–<5	1.0		
					5–<15	1.74 (NS)		
					>15	0.95 (NS)		
Ji and Hemminki [89], Sweden	Swedish population economically active (men, 1960 Census, 1,644,958; women, 1970 Census, 1,154,091); follow-up of incidence of upper aerodigestive tract cancer until the end of 2000	Occupation was coded according to national adaptations of the Nordic Occupational Standard Classification of Occupation. We defined 53 occupational groups	Tongue, oral cavity, and pharynx		*SIR*			We reported here only occupations with SIR statistically significant
					Men (1960 Census)			
					Tongue cancer			
				7	Dentists	2.88 (1.14–5.41)		
				90	Sale	1.36 (1.09–1.65)		
				36	Shop	1.44 (1.01–1.94)		
				5	Beverage	5.95 (1.88–12.31)		
				13	Cooks	4.83 (2.56–7.82)		
				8	Waiters	5.41 (2.31–9.80)		
				9	Hairdressers	2.41 (1.09–4.25)		
					Oral cancer			
				129	Sale	1.27 (1.06–1.50)		
				43	Painter	1.40 (1.01–1.85)		
				27	Printer	1.52 (1.00–2.15)		
				9	Cooks	2.27 (1.03–4.00)		

(continued)

Table 4.2 (continued)

Reference, location	Cohort description	Exposure assessment	Tumor site	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
					Pharynx cancer			
				173	Technical	0.85 (0.73–0.98)		
				26	Artistic	1.87 (1.22–2.66)		
				160	Sale	1.19 (1.02–1.39)		
				80	Shop	1.52 (1.20–1.97)		
				16	Seamen	1.85 (1.06–2.87)		
				38	Printer	1.53 (1.08–2.06)		
				24	Launderers	1.83 (1.17–2.64)		
					Women (1970 census)			
					Pharynx cancer			
				8	Artistic	3.83 (1.63–6.94)		
				14	Mechanics	2.27 (1.24–3.62)		
				9	Hairdressers	2.49 (1.13–4.39)		
Purdue et al. [101], Sweden	Cohort of 307,799 Swedish men workers in Swedish construction industry; follow-up (1971–2001)	Exposure to diesel exhaust, asbestos, organic solvents, metal dust, asphalt, wood dust, stone dust, mineral wool, and cement dust were assessed through a semiquantitative job-exposure matrix	Oral cavity or pharynx		*RR*		Adjusted for age, smoking status, and snuff use	Included only occupational exposures with RR equal or higher than 1.5 in some level of exposure
					Oral cavity			
					Asbestos			
				161	Never	1.0		
				10	Ever	1.3 (0.7–2.6)		
				9	Moderate	1.7 (0.9–3.3)		
				1	High	0.5 (0.1–5.2)		
					Pharynx			
					Cement dust			
				92	Never	1.0		
				20	Ever	1.9 (1.2–3.1)		
				16	Moderate	1.9 (1.1–3.2)		
				4	High	1.9 (0.7–5.0)		
					Asphalt			
				1.0	Never	1.0		
				1.8	Ever	1.8 (0.7–4.9)		
Krstev et al. [85], United States	Cohort of all workers employed at the US Coast Guard shipyard workers (4,413 men; 289 women) (1950–1964); mortality follow-up until the end of 2001 (completed for 93.3 % of cohort)	Occupation groups. An exposure inventory identifying agents, such as specific metals, solvents, acids, asbestos, and others in order to classify workers as exposed or nonexposed in shipyard	Oral cavity, pharynx, and nasopharynx	18	*SMR*		Adjusted for age, sex, and race	We reported here only occupational groups with SMR >1.5 SMR was observed for a group of tumors including oral cavity, pharynx, and nasopharynx taken together. RR reference category: no occupational exposure
					Men	0.89 (0.53–1.40)		
				8	≤10 years job	0.64 (0.28–1.27)		
				10	>10 years job	1.28 (0.61–2.35)		
				18	Exposed in shipyard	0.94 (0.56–1.49)		
					Occupational groups			
				3	Carpenters	1.53 (0.31–4.48)		
				3	Machinists	2.06 (0.41–6.02)		
				6	Woodworkers	6.20 (2.27–13.50)		
				1	Professionals	2.04 (0.03–11.33)		
				0	Women	–		

Marsh et al. [107], United States	7,345 workers employed at a plastic-producing plant (1941–1984); mortality follow-up until 2003 (obtained for 98 % and cause of death for 95 % of the cohort)	Exposure assessment obtained by work histories	Tongue, gum and other oral sites unspecified, floor of the mouth, and pharynx		*SMR*			
					Tongue			
				5		1.08 (0.55–2.53)		
					Gum and other oral sites unspecified			
				4		1.36 (0.37–3.50)		
					Floor of mouth			
				2		1.91 (0.23–6.92)		
				Pharynx				
				23		2.38 (1.51–3.57)		
Tarvainen et al. [69], Finland	Cohort comprised all Finns (725,868 men and 825,528 women) born during 1906–1945; incidence follow-up (1971–1995)	Occupational branches, specific occupations, and national job-exposure matrix (FINJEM) for 43 chemical agents; cumulative exposure (annual average of exposed people X mean level of exposure in the occupation) for every 5-year birth cohort	Oral cavity and pharynx (excluding nasopharynx)		*SIR*		SIR adjusted for age, calendar period and social class. Reference total Finnish population	SIR reported here only for equal or higher than 1.2 and 95 %CI statistically significant.
					Men			
				4	Lawyers	5.70 (1.55–14.59)		
				2	Authors	9.32 (1.13–33.65)		
				10	Journalists	3.28 (1.57–6.03)		
				4	Performing artists	5.60 (1.53–14.35)		
				7	Musicians	3.03 (1.15–5.90)		
				6	Electronics, telefitters	2.92 (1.07–6.35)		
				21	Painters, building	1.63 (1.01–2.49)		
				48	Building hands	1.58 (1.16–2.09)		
				15	Dockers	2.28 (1.28–3.76)		
				7	Hotel porters	3.51 (1.41–7.23)		
					Women			
				9	Private secretaries	2.20 (1.00–4.17)		
				12	Dressmakers	2.42 (1.25–4.23)		
				2	Shoemakers and cobblers	17.42 (2.11–62.94)		
				23	Waiters	1.80 (1.14–2.70)		
				2	Pursers and stewardesses	9.56 (1.16–34.52)		
					Men and women			
					Cumulative exposure			
					Lowest			
				105	Asbestos	1.32 (1.08–1.60)		
				104	Iron	1.23 (1.00–1.49)		
				164	Lead	1.32 (1.12–1.53)		
				90	Cadmium	1.45 (1.17–1.78)		
				185	Carbon monoxide	1.26 (1.08–1.45)		
				102	Diesel engine exhaust	1.26 (1.03–1.53)		
				130	Gasoline engine exhaust	1.28 (1.07–1.52)		
				38	Fungicides	1.48 (1.05–2.04)		
					Middle			

(continued)

Table 4.2 (continued)

Reference, location	Cohort description	Exposure assessment	Tumor site	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
				37	Chlorinated hydrocarbon	1.42 (1.00–1.96)		
				87	Engine exhaust	1.34 (1.08–1.66)		
				51	Gasoline engine exhaust	1.37 (1.02–1.80)		
					Highest			
				22	Aliphatic and alicyclic hydrocarbons	1.97 (1.23–2.98)		
				23	Petroleum-based products	1.60 (1.02–2.41)		
				88	Asbestos	1.26 (1.01–1.55)		
				25	Engine exhaust	1.68 (1.09–2.48)		
				20	Diesel engine exhaust	1.62 (0.99–2.50)		
					RR		RR included age, calendar period, socioeconomic status and all three occupational exposure (high, middle, low)	RR reference category: no occupational exposure
					Men and women			
					High level of cumulative exposure			
				22	Aliphatic and alicyclic hydrocarbons	1.69 (1.06–2.71)		
				10	Pesticides	1.92 (1.00–3.68)		
				25	Engine exhaust	1.37 (0.90–2.09)		
Andersen et al. [130], Denmark	3.22 million Danish born 1925–1973 and aged >30 years in the incidence period 1994–2003				*IRR*		IRR adjusted for calendar period, age, level of education, and disposable income	
					Men			
					Affiliation to work market			
				956	Working	1.00		
				427	Unemployed early retirement	2.98 (2.63–3.37)		
				480	Retirement	4.52 (4.01–5.11)		
					Social class			
				69	Creative core	0.69 (0.52–0.90)		
				224	Creative professional	0.65 (0.56–0.76)		
				20	Bohemian	1.80 (1.15–2.82)		
				517	Service	0.92 (0.83–1.03)		
				1,022	Manual	1.00		
				47	Agricultural	0.31 (0.23–0.42)		
				182	Unknown	0.95 (0.81–1.12)		
					Women			
					Affiliation to work market			
				273	Working	1.00		
				172	Unemployment	2.46 (2.02–2.99)		
				217	Early retirement	3.90 (3.22–4.72)		
					Social class			
				11	Creative core	0.70 (0.37–1.33)		
				48	Creative professional	0.60 (0.42–0.87)		
				1	Bohemian	0.47 (0.07–3.37)		
				412	Service	0.81 (0.63–1.04)		
				74	Manual	1.00		
				2	Agricultural	0.12 (0.03–0.47)		
				227	Unknown	1.20 (0.92–1.57)		

SIR standardized incidence ratio, *SMR* standardized mortality ratio, *IRR* incidence rate ratio, *RR* relative risk

oral cancer in those employed after 1964. Andjelkovich et al. [58] found SMR 131 (95 % CI 48–286) for workers exposed to formaldehyde in an automotive iron foundry. Marsh et al. [59] in a cohort of workers in a plastic-producing plant found for oral and pharynx cancers SMR of 1.80 (95 % CI 1.22–2.55). Other results from this study, including exposure duration and cumulative exposure to formaldehyde, are difficult to interpret as analysis for pharynx cancer included nasopharyngeal carcinoma. A cohort study in the United Kingdom [60] found SMRs below 2.0 for men with high exposures (estimated as greater than 2.0 ppm). Hauptmann et al. [61] expanded the follow-up from previously cited Blair et al.'s [56] cohort study. Even though risks for oral cavity cancer above 2.0 were found for some average-intensity exposure levels, no dose-response effect was detected. Stayner et al. [62] conducted a mortality cohort study in garment manufacturers, as workers in this industry are potentially exposed to formaldehyde. They concluded that there was a possible relationship between formaldehyde and oral cavity cancer (SMR 343, 95 % CI 118–786). An extension of this cohort until 1998 [63] confirmed increased risks, particularly for oral cavity cancer SMR (3.53, 95 % CI 0.96–9.02), for the original cohort exposure period, but revealed decreased SMRs for the updated period. Several other cohorts were conducted specifically with formaldehyde-exposed professionals, such as pathologists, anatomists, medical laboratory technicians, embalmers, and funeral directors [64–68], but revealed decreased risks of oral and pharynx cancers. A Finnish cohort population [69] did not find any increased risk at the lowest, middle, or highest exposure levels to formaldehyde for oral cavity and pharynx cancer. Innos et al. [70] in a cohort of furniture workers in Estonia detected slight risks for those with possible exposure to formaldehyde. Bosetti et al. [71] conducted the most recent meta-analysis of cohort studies on formaldehyde and cancer risk; related to oral cavity and pharynx, they found RR of 1.09 (95 % CI 0.88–1.34) for industrial workers and RR of 0.96 (95 % CI 0.75–1.23) for professionals. The results of all available studies are inconsistent, and no clear association could be established between exposure to formaldehyde and oral and pharynx cancers [72, 73].

Leather Dust and Leather Industry Work

A case-control study conducted in the United States [74] showed evidence of oral and pharynx cancers in leather industry workers (RR 3.58; $p<0.01$). However, three subsequent case-control studies reporting specifically on the leather industry or exposure to leather dust showed less emphatic results: in Brazil [75] the risk was low (RR 1.3), in Italy [53] risk deficits were observed (RR 0.4 for any exposure to leather dust and RR 0.9 for probable or definitive exposure), and in Sweden [54] risks higher than 2.0 were observed, but they were not statistically significant. A cohort study in Finland [69] reported increase risk of oral and pharynx cancers from exposure to leather dust as standardized incidence ratio (SIR) 1.75 (95 % CI 0.36–5.13) for those with medium-category exposure, as no cases were observed at high exposure level. There is no specific cohort study with workers in leather industry. Even though leather dust has been classified by the International Agency for Research on Cancer (IARC) as definitively carcinogenic for humans, into Group 1 [76, 77], from results of available case-control and cohort studies which have investigated exposure to leather dust and oral and pharynx cancers, no conclusive association can be assumed.

Wood Dust and Wood Industry Work

Many case-control studies that have reported an association between wood dust exposure or jobs in wood-related work and oral and pharynx cancers have revealed decreased risks or risks around unity [53, 54, 75, 78–81]. Other studies have found risks ranging from 1.5 to 2.0 for pharyngeal cancer [55, 82, 83]. A case-control study [84] observed a high risk for oral cavity cancer in wood and wood product workers (RR 5.5, 95 % CI 1.2–25.0); and other case-control study [53] found increased risk (RR 5.5, 95 % CI 0.7–44.6) for those exposed for 16 years or more in wood furniture production. A cohort study of United States Coast Guard shipyard workmen [85] detected a high risk (RR 6.20, 95 % CI 2.27–13.50) of oral and pharynx cancers in woodworkers, but analysis included nasopharynx cancer. In Finland, two cohort studies did not reveal any risks of oral and pharynx cancers in woodworkers. In the first [86], decreased risks for oral cancer in construction carpenters and pharynx cancer in woodworkers were found. In the second [69], authors found a protection (SIR 0.79, 95 % CI 0.62–0.99) for oral and pharynx cancers in woodworkers but SIR 1.3 (95 % CI 0.7–2.1) for men and women in the highest category of exposure to hardwood dust. Innos et al. [70] conducted a cohort study in two large furniture factories; they found increased risk of pharynx cancer in men (RR 1.82, 95 % CI 0.83–3.46) and oral cavity cancer in women (RR 1.84, 95 % CI 0.50–4.71). Brown et al. [87] observed increased risk of oral cancer in male wood lacquerers (SIR 2.1, 95 % CI 1.0–3.9), but probably in the context of this cohort study, agents other than those habitually used in wood industry were involved, such as the basic components of paint, varnish, and lacquer, including pigments, resins, and solvents. In general, the risks of oral and pharynx cancers for wood dust or wood industry exposure were imprecise, and no dose-response effect could be observed considering level or time of exposure.

Gustavsson et al. [54] speculated that lowered risk to wood dust exposure could be due to residual confounding from low smoking levels in these workers because of the obvious fire hazard in this activity; however, after subdividing smoking habits into eight increasing cumulative tobacco

classes, low RR associated with exposure to wood dust persisted. IARC has classified wood dust in Group 1 [77]; however, specifically for oral and pharynx cancers, results from studies conducted until now do not allow conclusive answers on a causal relationship between wood dust exposure and oral and pharynx cancers.

Cotton Dust and Textile Work

A case-control study of women in the United States [88] found increased risk (RR 3.9, 95 % CI 1.2–12.0) of oral cancer in those with presumed exposure to dust in textile industry for 1–4 years, but no risk was observed for those exposed for 10 years or more. Increased risks were also found in France [78] for pharynx cancer (RR 2.4, 95 % CI 1.0–5.7) and in Italy [53] for oral cancer (RR 2.5, 95 % CI 0.5–9.9). However, many other case-control studies have revealed risk deficits or close to unity values for oral and pharynx cancers in textile dust exposure or textile work [54, 75, 80, 82, 83]. Tarvainen et al. [69] in a cohort study also found risk deficits in men and women exposed to any level of textile dust. This inconsistency in results does not allow the supposition of a causal relationship between cotton dust exposure or textile work and oral and pharynx cancers.

Welding Fumes and Welding as an Occupation

There are many different welding methods which involve exposure to chemicals, such as irritant gases, chromium, polycyclic aromatic hydrocarbons, and metal dust. A case-control study in Sweden [54] found risk excess of pharynx cancer (RR 2.26, 95 % CI 1.09–3.69) in workers exposed to welding fumes for more than 8 years. In another case-control study in Sweden [84], increased risk of oral cancer was detected in welders (RR 2.3, 95 % CI 0.6–9.1). There is little consistency between these findings and results from other case-control [53, 80, 82, 83] and cohort studies [85, 89]. Exposure to welding fumes clearly needs further investigation in order to arrive at a definite conclusion of carcinogenicity for the oral cavity and pharynx anatomical regions.

Diesel Engine Exhaust and Vehicle Repair Mechanics

Recently, IARC considered the evidences of causal association between diesel engine exhaust and cancer as sufficient, particularly for lung cancer [90]. This decision was taken considering a large US National Cancer Institute/National Institute for Occupational Safety and Health study conducted among underground miners [91, 92].

Boffetta et al. [93] conducted a cohort study to evaluate exposure to diesel engine emissions in a Swedish population and found a general SIR of 1.64 (95 % CI 1.11–2.33) for oral and pharynx cancers in women, but no risk was detected for men. Using a job-exposure matrix, exposure was categorized according to probability and intensity as low, medium, and high. Some tenuous positive relative risks were observed, but without a dose-response effect. A cohort study in Finland [69] detected increased risks of mouth and pharynx cancer in men and women with medium levels of exposure to engine exhaust (SIR 1.34, 95 % CI 1.08–1.66) and at the highest level of exposure to engine exhaust (SIR 1.68, 95 % CI 1.09–2.48). Vaughan [82] in a case-control study found a risk higher than 2.0 for vehicle mechanics in repair services, but they examined oral cavity, pharynx, and nasopharynx tumors all together. In a case-control study in Brazil, Andreotti et al. [80] found increased risks, greater than 2.0, for oral and pharynx cancers in every occupation of vehicle mechanic, and for every vehicle repair service job, these risks were augmented considering the restrictions of 10 or more years of exposure and induction period (equal to or greater than 20 years before diagnosis). Vehicle mechanics are potentially exposed to diesel and gasoline engine exhaust, but they are also exposed to other hazardous agents, such as solvents, mineral oils, strong acid fumes, and metal dust. They are therefore exposed to a complex mixture of potential carcinogens. Vehicle mechanics in repair and diesel and gasoline exhaust services are potentially at increased risk of contracting oral and pharynx cancers, but more studies are needed to confirm this relationship.

Other Occupations

Several other occupations, industries, and agents have been linked to oral cavity and pharynx cancer. Certainly, all these circumstances require further studies before a definitive view can be taken on their possible role in the causal chain for the disease.

Exposures in meat industry, such as viruses, nitrosamines, and polycyclic aromatic hydrocarbons, may contribute for elevated cancer risks. Two cohorts have identified increased risks for oral and pharynx cancers in butchers. Johnson et al. [94] in a mortality cohort in the United States found increased risk of oral cavity and pharynx cancer in male meat cutters working in supermarket or grocery store meat departments (SMR 1.8, 95 % CI 1.0–3.0); there was also increased risk for those working as meat cutters in other departments (SMR 1.7, 95 % CI 0.8–3.2). Boffetta et al. [95] in a cohort of butchers and meat workers in Sweden found increased risk for butchers in meat industry (RR 1.6, 95 % 1.0–2.7). Also, a case-control study in Uruguay [96] found increased risk of oral and pharynx cancers in butchers (RR 2.0, 95 % CI 0.4–9.5). In contrast, Coggon and Wield [97] in a cohort study in England and Wales found deficit risks for oral and pharynx cancers in butchers.

Moulin et al. [98] in a cohort study of workers at a man-made mineral fiber (MMMF) factory in France found SIRs of 3.0 for oral and 1.4 for pharynx cancer, both not statistically significant. A Scandinavian cohort of employees in

nine factories producing rock-slag wool and glass wool [99] found increased risk of oral cavity and pharynx cancer in those exposed to rock-slag wool (SIR 1.84, 95 % CI 1.22–2.68) but a lower risk for glass wool exposure (SIR 1.31, 95 % CI 0.65–2.34). Two case-control studies reported results for exposure to MMMF; the first [54] found risk deficits for oral or pharynx cancer, and the second [100] reported increased risk for hypopharynx cancer in those ever exposed to mineral wools (RR 1.55, 95 % CI 0.99–2.41).

Marchand et al. [100] found increased risks for those with any exposure to asbestos once (RR 1.80, 95 % CI 1.08–2.99) or cumulative low (RR 1.92, 95 % CI 1.03–3.57) or high exposure (RR 2.14, 95 % CI 1.14–4.01). However, previous case-control studies did not find increased risks of oral and pharynx cancers associated to asbestos [53, 54, 83]. A cohort of Finns born between 1906 and 1945 [69] found increased risks with cumulative asbestos exposure at the lowest (SIR 1.32, 95 % CI 1.08–1.60) and highest levels (SIR 1.26, 1.01–1.55). In a cohort study with construction industry workers [101], an RR of 1.7 was detected (95 % CI 0.9–3.3) for those with moderate exposure to asbestos, but the risk dropped for those with high exposure (RR 0.5, 95 % CI 0.1–5.2).

Several other agents such as chromium, nickel, lead, iron, cadmium, phenoxy acids, solvents, cement dust, asphalt, pesticides, and aliphatic and alicyclic hydrocarbons; occupations such as blacksmiths, bricklayers, drivers, electricians, railway workers, industrial mechanics, painters, metal workers, chemical workers, plumbers and pipe fitters, plastic transformation workers, printers, carpet installers, boiler, furnace and petroleum industry workers, dockers, shoemakers and cobblers, sugarcane farmers, glazers, cutting/sewing workers, hairdressers, dentists, and journalists; and industries such as rubber, paper, pulp, plastics, mining, and building have all been cited as presenting increased risks for oral and pharynx cancers in different cohort and case-control studies. In general, these increased risks were tenuous and imprecise and based in small number of observed cases.

Cooks, waiters, and bartenders, as well as workers at restaurants, bars, and hotels, have shown consistently increased risks of oral and pharynx cancers through some case-control and cohort studies [53, 69, 86]. However, the main hypothesis for these increased risks is the higher prevalence of heavy tobacco smoking and alcohol consumption among these workers.

Nasopharynx Cancer

Tables 4.3 and 4.4 show results of 14 case-control and 7 cohort studies, which examined the association between occupation or exposure to some agents and nasopharynx cancer. Formaldehyde and wood dust showed strong evidence of carcinogenicity to nasopharynx; however, the effect for some other agents and occupations was inconclusive because of results inconsistency among studies.

Formaldehyde

The first epidemiological evidence suggesting an association between exposure to formaldehyde and nasopharynx cancer came in 1986. A mortality cohort study of workers in ten plants producing or using formaldehyde [56] found increased SMRs for different formaldehyde exposure levels. Also a case-control study [52] found increased relative risks for longer exposures. These epidemiological studies were conducted after research with animal models had indicated nasal squamous cell carcinomas occurring in rodents submitted to formaldehyde vapor inhalation [102, 103]. A case-control study in the Philippines [104] has found increased risk for those with long induction period (25 or more years since first exposure). In a cohort study with 14,014 British chemical workers exposed to formaldehyde and followed up for almost 60 years [60], the only death from nasopharynx cancer was of a man whose exposure was classified as low. However, there was evidence of increased death rates from nasopharynx cancer in a cohort of formaldehyde-industry workers by Hauptmann et al. [61], an update of the Blair et al. cohort [56]. This cohort revealed an exposure-response effect for peak and cumulative exposure to formaldehyde, but not for average-intensity exposure or duration.

The study by Hauptmann et al. [61] was a major component in the epidemiological evidence evaluated by the IARC when making their decision on classifying formaldehyde as a definite carcinogen for humans in 2004 [105–107]. Some criticisms on the Haptmann et al.'s [61] cohort study have been addressed, such as the detected association was mainly from one cluster of deaths in a single plant, where five of nine nasopharynx deaths occurred [107]. However, as pointed out by Cogliano et al. [106], in order to classify an agent as carcinogenic, if evidence in humans is insufficient, one should consider that mechanistic evidence and sufficient evidence in experimental animals led to the agent being classified in IARC Group 1. This decision has been upheld in a recent new IARC evaluation [72, 73], and formaldehyde was listed as a known human carcinogen in the 12th Report on Carcinogens of the US National Institute of Environmental Health Sciences [108].

Wood Dust and Wood Industry Work

As well as dust, workers in wood industry may also be exposed to formaldehyde, chlorophenol, and other chemical substances, giving them increased risk of nasopharyngeal cancer. Even so, this increased risk seems to be attributable to wood dust exposure independent to other exposures in the workplace, as the other chemicals do not present relative risks of the magnitude associated to wood dust exposure [77, 109].

Table 4.3 Case-control studies on occupation and nasopharynx cancer

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Henderson et al. [121], United States	156 cases of nasopharynx squamous cell carcinoma (105 men, 51 women) diagnosed (1960–1974)	267 controls (179 men, 88 women) recruited in hospitals from the same two cities of cases	Detailed occupational history was obtained through questionnaire, and for each occupation each subject was asked if he was usually exposed to fumes, dust, smoke, chemicals, or heat	*RR* Fumes			RR adjusted for age at diagnosis, race, sex, socioeconomic class, and city of residence	Reference category: never exposed. NS = nonsignificant
				Ever		2.0 ($p = 0.006$)		
				<10 years		1.9 (NS)		
				>10 years		1.7 ($p < 0.05$)		
				Dust				
				Ever		1.5 ($p = 0.07$)		
				<10 years		1.3 (NS)		
				>10 years		1.2 (NS)		
				Smoke				
				Ever		3.0 ($p = 0.008$)		
				<10 years		1.5 (NS)		
				>10 years		7.5 ($p < 0.005$)		
				Chemicals				
				Ever		2.4 ($p = 0.006$)		
				<10 years		2.3 ($p < 0.05$)		
				>10 years		2.7 ($p < 0.05$)		
				Heat				
				Ever		1.6 (0.053)		
				<10 years		1.4 ($p < 0.05$)		
				>10 years		1.6 ($p < 0.05$)		
Armstrong [110], Malaysia	100 cases of nasopharynx squamous cell carcinoma (65 men, 35 women), Malaysian Chinese, diagnosed (1973–1980)	100 neighborhood controls matched by age and sex	Occupational history obtained through interviews using a questionnaire	*RR* Ever			RR adjusted for salted fish intake	Reference category: never exposed. NS = nonsignificant
				Smoke	13 (3)	6.0 ($p = 0.006$)		
				Wood, paper, and grass smoke	8 (2)	7.0 ($p = 0.04$)		
				Other smokes	5 (1)	5.0 ($p = 0.11$)		
				Dust	52 (25)	4.0 ($p < 0.001$)		
				Wood dust and sawdust	17 (10)	2.2 ($p = 0.08$)		
				Construction-related dust	15 (9)	1.9 ($p = 0.13$)		
				Quarry dust	10 (1)	∞ ($p = 0.002$)		
				Road dust	11 (2)	5.5 ($p = 0.01$)		
				Other dusts	17 (8)	2.3 ($p = 0.05$)		
				Smoke and/or dust	58 (26)	5.0 ($p < 0.001$)		
				Men				
				Never	26 (46)	1.0		
				1–9 years	19 (11)	3.3 (NS)		
				10 + years	22 (8)	8.4 (NS)		

				Women				
				Never	18 (28)	1.0		
				1–9 years	8 (4)	3.5 (NS)		
				10 + years	9 (3)	∞ (NS)		
				Under age 45				
				Never	19 (43)	1.0		
				1–9 years	20 (11)	4.3 (NS)		
				10 + years	17 (2)	∞ (NS)		
				Age 45+				
				Never	23 (31)	1.0		
				1–9 years	7 (4)	2.7 (NS)		
				10 + years	14 (9)	3.3 (NS)		
				Total				
				Never	42 (74)	1.0		
				1–9 years	27 (15)	3.4 (NS)		
				10 + years	31 (11)	11.4 ($p < 0.001$)		
Yu et al. [49], Hong Kong	250 cases of nasopharynx carcinoma (160 men, 90 women) of Chinese in Hong Kong, diagnosed after 1981	250 controls friend of cases, matched by sex and age	Occupational history obtained through interviews using a questionnaire	*RR*			RR adjusted for salted fish intake	Reference category: never exposed. NS = nonsignificant
				Domestic exposure				
				Wood cooking fuel	183 (161)	1.4 (NS)		
				3 years ago				
				Incense	186 (170)	1.4 (NS)		
				Antimosquito coils	61 (58)	2.4 (NS)		
				At age 10 years				
				Incense	208 (193)	0.9 (NS)		
				Antimosquito coils	78 (76)	1.8 (NS)		
				At birth (by mother)				
				Incense	108 (107)	0.6 (NS)		
				Antimosquito coils	29 (37)	0.8 (NS)		
				Carried subject while cooking				
				Occasionally	52 (63)	0.8 (NS)		
				Often	40 (41)	0.7 (NS)		
				Occupational exposure				
				Smoke	10 (3)	0.6 (NS)		
				Dust	59 (41)	1.2 (NS)		
				Chemical fumes	75 (49)	0.7 (NS)		

(continued)

Table 4.3 (continued)

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Vaughan et al. [52], United States	285 cases (186 men, 99 women) of oro- and hypopharynx cancer ($n=205$), nasopharynx cancer ($n=27$), and sinus and nasal cavity cancer ($n=53$) selected from a population-based cancer registry (1980–1983)	552 controls (327 men, 225 women) were identified via random digit dialing	Occupational formaldehyde exposure was assessed via a job-exposure matrix	*Nasopharynx* Exposure level Background Low Medium High Number of years exposed 0 1–9 10+ Exposure score (all years) 0–4 5–19 20+ Exposure score induction (excluding 15 years before diagnosis) 0–4 5–19 20+	 41 (381) 9 (121) 3 (42) 0 (8) 41 (381) 9 (127) 3 (44) 48 (464) 3 (59) 2 (29) 48 (490) 4 (40) 1 (22)	 1.0 0.8 (0.5–1.4) 0.8 (0.4–1.7) 0.6 (0.1–2.7) 1.0 0.6 (0.3–1.0) 1.3 (0.7–2.5) 1.0 0.6 (0.3–1.2) 1.5 (0.7–3.0) 1.0 0.9 (0.4–1.8) 1.3 (0.6–3.1)	Odds ratio adjusted for age, sex, cigarette smoking, and alcohol consumption	
Roush et al. [117], United States	173 men with nasopharynx cancer registered by the Connecticut Tumor Registry and dying (of any cause) in the period 1935–1975	605 controls sampled from Connecticut death certificates in the same time period as cases of deaths	An industrial hygienist classified each subject according to potential formaldehyde exposure on the basis of job title industry, specific employment, and year of employment. Analysis was conducted as yes/no exposed to each of the four potential levels of exposure to formaldehyde	*OR* *I* Probably exposed to some level for most of working life *II* Probably exposed to some level for most of working life and probably exposed to some level at 20 + years prior to death *III* Probably exposed to some level for most of working life and probably exposed to high level in some year *IV* Probably exposed to some level for most of working life and probably exposed to high level at 20 + years prior to death	 21 (79) 17 (51) 9 (27) 7 (14)	 1.0 (0.6–1.7) 1.3 (0.7–2.4) 1.4 (0.6–3.1) 2.3 (0.9–6.0)	OR adjusted for age at death, year at death, and availability of occupational information	
Kawachi et al. [112], New Zealand	19,904 cases of cancer in men of 20 years of age or older at the time of registration in the New Zealand Cancer Registry (1980–1984)	For each cancer site examined, registrants from other tumor sites formed the control group	Exposed and nonexposed in wood-related occupations and specific type of woodwork	*All woodwork* Type of woodwork Forestry and logging Sawmiller, pulp, and paper mill Cabinet makers Carpenters	2.46 (0.86–6.60) 2 (102) 0 (108) 0 (91) 5 (741)	5 (741) 6.02 (1.01–28.41) – – 2.51 (0.62–8.53)	Adjusted for age	

Yu et al. [118], China	306 cases of nasopharynx carcinoma (209 men, 97 women) in residents in Guangzhou City under the age of 50 years diagnosed in a main hospital, primary facility for treatment of this disease (1983–1985)	For each case, a control was matched for sex and date of birth (within 5 years) from neighborhood of case residence at the time of diagnosis	Subjects were asked to indicate, for each job that was held for longer than 6 months, whether exposure to dust, smoke, or chemical fumes had occurred and the name of the specific substances involved. Additionally, an industrial hygienist checked the exposure based on the job title and the industry of employment and also reviewed all specific substances named by each study participant	*RR*			RR adjusted for intake frequencies of salted fish, moldy bean curd, preserved plum, and tomatoes at age 10 years	Reference category: never exposed. NS = nonsignificant. For products of combustion and cotton dust, there are no information if assessment were done from subject response or by occupational hygienist
				Dust				
				Subject response				
				Ever	145 (134)	1.2 (NS)		
				1–9 years	74 (71)	1.2 (NS)		
				10–19 years	46 (33)	1.6 (NS)		
				20+ years	25 (30)	0.9 (NS)		
				Industrial hygienist				
				Ever	138 (146)	1.0 (NS)		
				1–9 years	67 (78)	1.0 (NS)		
				10–19 years	41 (45)	1.0 (NS)		
				20+ years	30 (23)	1.1 (NS)		
				Smoke				
				Subject response				
				Ever	62 (37)	2.4 ($p<0.05$)		
				1–9 years	31 (28)	1.6 (NS)		
				10+ years	31 (9)	7.6 ($p<0.05$)		
				Industrial hygienist				
				Ever	72 (50)	1.8 ($p<0.05$)		
				1–9 years	39 (35)	1.4 (NS)		
				10+ years	33 (15)	2.7 ($p<0.05$)		
				Chemical fumes				
				Subject response				
				Ever	111 (81)	1.7 ($p<0.05$)		
				1–9 years	54 (44)	1.5 (NS)		
				10–19 years	39 (28)	1.8 ($p<0.05$)		
				20+ years	18 (9)	2.7 (NS)		
				Industrial hygienist				
				Ever	138 (139)	1.1 (NS)		
				1–9 years	67 (85)	0.9 (NS)		
				10–19 years	53 (40)	1.5 (NS)		
				20+ years	18 (14)	1.3 (NS)		
				Combustion products				
				Ever	63 (33)	2.7 ($p<0.05$)		
				1–9 years	32 (24)	1.9 ($p<0.05$)		
				10+ years	31 (9)	10.1 ($p<0.05$)		
				Cotton dust				
				Ever	6 (19)	0.3 ($p<0.05$)		
				1–9 years	5 (12)	0.4 (NS)		
				10+ years	1 (7)	0.2 (NS)		

(continued)

Table 4.3 (continued)

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Vaughan and Davis [79], United States	21 cases of nasopharynx squamous cell carcinoma diagnosed in a single center (1983–1987)	Controls were selected by random digit dialing matched to the cases by age and sex	Lifetime occupational histories were obtained, including a description of the duties involved in each job, as well as the associated industry. Jobs considered to entail significant exposure to wood dust included carpenters, forestry and logging workers, precision woodworkers (including patternmakers, cabinetmakers, and other furniture makers and finishers), and woodworking machine operators	*OR*			OR adjusted for age, sex, cigarette smoking, and race	Reference category: never exposed
				Ever employed in wood-related occupations	3	1.2 (0.2–4.6)		
				Employed in wood-related occupations >15 years before diagnosis	3	1.5 (0.2–6.1)		
				Employment for 10 or more years taking place at least 15 years before the reference date	No information	7.3 (1.4–34.2)		
Sriamporn et al. [113], Thailand	120 cases (80 men, 40 women) diagnosed (1987–1990) in a single hospital in Thailand	120 controls were recruited in the same hospital admitted for other diseases excluding neoplasms and respiratory diseases, matched by sex and age	Several potential factors for the etiology of nasopharynx cancer were studied including occupation. Then, occupations reported were grouped into a few broad categories, but employment in sawmills and jobs such as wood cutting or rice husking were investigated specifically, since these entail high exposures to dust	Not agriculture, not wood cutting	20 (47)	1.0	Adjusted for alcohol intake, type of cigarette, salted fish consumption, education, and area of residence	
				Wood cutting, not agriculture	5 (3)	4.1 (0.8–22.1)		
				Agriculture, not wood cutting	76 (64)	2.8 (1.3–6.2)		
				Agriculture and wood cutting	19 (6)	8.0 (2.3–28.2)		

West et al. [104], Philippines	104 incident cases of nasopharynx carcinoma (76 men, 28 women) recruited in a single hospital	104 controls matched with cases for sex, age, and hospital ward type (private vs public) and 101 community controls matched to cases for sex, age, and neighborhood	Occupations reported were reviewed by an industrial hygienist using various sources of exposure information. Each occupation was classified as likely or unlikely to involve exposure to any of the following factors: formaldehyde, solvents, wood dust, dust, and pesticides. This information was combined with the complete occupational history: overall duration of exposure, duration of exposure excluding exposure in the 10 years immediately preceding diagnosis (for cases) or interview (for controls), number of years since first exposure, and age at first exposure	*RR* Formaldehyde <25 years since 1st exposure 25+ years since 1st exposure Dust/exhaust <35 years since 1st exposure 35+ years since 1st exposure Antimosquito coils <Daily Daily	 12 (12) 14 (10) 49 (59) 30 (40) 24 (36) 21 (6)	 1.2 (0.4–3.6) 4.0 (1.3–12.3) 2.5 (1.1–5.9) 4.4 (1.1–17.5) 1.4 (0.6–2.8) 5.9 (1.7–20.1)	RR adjusted for education, processed meat intake, fresh fish intake, smoking, and herbal medicines	
Armstrong et al. [111], Malaysia	282 cases (195 men aged 19–72 years, 87 females aged 24–74 years) diagnosed (1987–1992)	282 controls matched by sex and age and with no history of cancer of the head and neck and respiratory system, selected from the general Chinese population of the study area using a standard procedure of multistage area sampling	Exposure to 20 inhalants and heat from two sources were recorded by trade or profession with calendar years, frequency (days per week), and duration (hours per day) of exposure. Inhalant selection was limited to those dusts, smoke, and gases associated with deposition or absorption in the nasopharynx, with special attention to formaldehyde	*Dusts* Construction Fertilizer Metal Talc Tin Textile Wood Others *Fumes* Cooking Engine exhaust Wood Others	 22 % (14.2 %) 1.4 % (1.4 %) 16 % (9.6 %) 3.6 % (2.5 %) 3.2 % (1.8 %) 7.8 % (5 %) 24.8 % (12.1 %) 39.7 % (31.2 %) 6.7 % (4.6 %) 20.9 % (19.9 %) 9.6 % (5.3 %) 10.3 % (5.3 %)	 1.06 (0.93–1.20) 0.82 (0.51–1.32) 1.14 (0.96–1.35) 0.86 (0.61–1.21) 1.16 (0.83–1.61) 1.16 (0.94–1.42) 1.24 (1.07–1.44) 1.07 (0.96–1.19) 0.97 (0.78–1.21) 1.00 (0.88–1.14) 1.08 (0.84–1.38) 1.12 (0.91–1.39)	Adjusted for diet and cigarette smoke	The study includes cases of incidents ($n=163$), diagnosed in 1990–1992 and cases of prevalence ($n=119$) diagnosed before 1990 (initiation of data collection)

(continued)

Table 4.3 (continued)

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
				Chemicals				
				Biocides	6.7 % (6.7 %)	0.93 (0.74–1.17)		
				Dyes	2.1 % (1.8 %)	1.07 (0.73–1.58)		
				Formaldehyde	9.9 % (8.2 %)	0.88 (0.70–1.12)		
				Glues	11.0 % (6.7 %)	1.09 (0.88–1.34)		
				Other chemicals	7.1 % (3.2 %)	1.20 (0.92–1.56)		
				Motor fuel and oil	29.4 % (19.9 %)	1.05 (0.91–1.22)		
				Paints and varnishes	16.0 % (9.6 %)	1.08 (0.91–1.29)		
				Resins	2.8 % (4.6 %)	0.74 (0.54–1.01)		
				Heat				
				Solar	18.1 % (11 %)	1.02 (0.89–1.18)		
				Industrial	17 % (6.7 %)	1.21 (1.01–1.45)		
Vaughan et al. [114], United States	196 incident cases of nasopharynx cancer (133 men, 63 women), aged 18–74 years, identified at five population-based cancer registries from 1987 to 1991	244 controls were selected over the same period from the general population through random digit dialing and frequency matched to the cases by age, sex, and cancer registry	Exposure to formaldehyde and wood dust was carried with the occupational history (job-by-job basis for each subject) including industry description, job title, duties, and dates started and stopped	*OR*			OR for formaldehyde adjusted for age, sex, race, cancer registry, smoking, proxy status, and education. OR for wood dust adjusted beyond all these variables, adjusted for cumulative exposure to formaldehyde	Reference category: never exposed
				Formaldehyde				
				Ever				
				Possible, probable, or definite	61 (79)	1.6 (1.0–2.8)		
				Probable or definite	27 (30)	2.1 (1.1–4.2)		
				Definite	10 (2)	13.3 (2.5–70.0)		
				Possible, probable, or definite				
				Duration				
				1–5 years	16 (41)	0.9 (0.4–2.1)		
				6–17 years	20 (19)	1.9 (0.9–4.4)		
				18+ years	25 (19)	2.7 (1.2–6.0)		
				Cumulative exposure (ppm-year)				
				0.05–0.40	15 (40)	0.9 (0.4–2.0)		
				>0.40–1.10	22 (20)	1.8 (0.8–4.1)		
				>1.10	24 (19)	3.0 (1.3–6.6)		
				Wood dust				
				Ever				
				Maximum exposure (mg/m3)	17 (24)	1.2 (0.5–2.7)		
				>0.00–0.55	10 (15)	1.3 (0.5–3.6)		
				>0.55–1.50	6 (4)	2.0 (0.5–8.1)		
				>1.50	1 (5)	0.2 (0.0–2.1)		
				Duration				
				1–4 years	8 (12)	1.4 (0.5–4.4)		
				5–13 years	4 (6)	1.3 (0.3–5.4)		
				14+ years	5 (6)	0.8 (0.2–3.7)		
				Cumulative exposure (mg/m^3-years)				
				>0.0–2.75	5 (13)	0.7 (0.2–2.5)		
				>2.75–15.70	10 (5)	3.0 (0.9–9.8)		
				>15.70	2 (6)	0.4 (0.1–2.3)		

Hildesheim et al. [22], Taiwan	375 incident cases (260 men, 115 women) of nasopharynx cancer recruited in two hospitals in Taipei (1991–1994)	325 controls (233 men, 92 women) recruited from the lists of the National Household Registration System and matched on age, sex, and district/township of residence	Occupational history was obtained through a questionnaire and was reviewed by an industrial hygienist. Each job was classified according to industry and occupation classification. The probability and intensity of exposure to formaldehyde, wood, and organic solvents were evaluated. Years of exposure, intensity and probability of exposure, cumulative exposure, age at first exposure, and years since first exposure were considered. Duration of exposure was recalculated after exclusion of exposures occurring in the 10 years preceding diagnosis (cases) and interview (controls)	*RR* All subjects Wood exposure			RR adjusted for age, sex, education, and ethnicity	Reference category not exposed. Authors conducted an analysis only with subjects (cases and controls) who are Epstein-Barr virus positive. For wood exposure and solvent exposures, the results did not suffer important changes; however, for formaldehyde exposure, some relevant modifications were observed: ever exposed RR = 2.7 (95 % CI 1.2–6.2); years since first exposure (>20 year) RR = 2.8 (95 % CI 1.1–7.6); and age at first exposure (<25 years) RR = 2.6 (95 % CI 1.1–6.5)
				Ever exposed	52 (26)	1.7 (1.0–3.0)		
				Duration (overall)				
				<10 years	21 (15)	1.2 (0.60–2.5)		
				>10 years	31 (11)	2.4 (1.1–5.0)		
				Duration (excluding 10 years before diagnosis/interview)				
				<10 years	26 (14)	1.7 (0.85–3.5)		
				>10 years	21 (8)	2.2 (0.93–5.3)		
				Cumulative exposure (intensity X duration)				
				<25	20 (15)	1.2 (0.58–2.5)		
				>25	32 (11)	2.4 (1.2–5.1)		
				Years since first exposure				
				<20 years	21 (8)	2.4 (1.0–5.8)		
				>20 years	31 (18)	1.4 (0.75–2.7)		
				Age at first exposure				
				<25 years	37 (15)	2.3 (1.2–4.4)		
				>25 years	15 (11)	1.1(0.47–2.5)		
				Formaldehyde exposure				
				Ever exposed	74 (41)	1.4 (0.93–2.2)		
				Duration (overall)				
				<10 years	31 (21)	1.3 (0.69–2.3)		
				>10 years	43 (20)	1.6 (0.91–2.9)		

(continued)

Table 4.3 (continued)

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No cases (controls)	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
				Duration (excluding 10 years before diagnosis/interview)				
				<10 years	34 (18)	1.6 (0.89–3.0)		
				>10 years	34 (20)	1.2 (0.67–2.2)		
				Cumulative exposure (intensity X duration)				
				<25	29 (19)	1.3 (0.70–2.4)		
				>25	45 (22)	1.5 (0.88–2.7)		
				Years since first exposure				
				<20 years	19 (7)	2.3 (0.95–5.8)		
				>20 years	55 (34)	1.2 (0.76–2.0)		
				Age at first exposure				
				<25 years	62 (38)	1.3 (0.80–2.0)		
				>25 years	12 (3)	3.4 (0.94–12)		
				Solvent exposure				
				Ever exposed	178 (130)	1.2 (0.84–1.7)		
				Duration (overall)				
				<10 years	89 (54)	1.5 (0.99–2.3)		
				>10 years	89 (76)	0.93 (0.61–1.4)		
				Duration (excluding 10 years before diagnosis/interview)				
				<10 years	88 (65)	1.1 (0.74–1.6)		
				>10 years	61 (48)	0.94 (0.58–1.5)		
				Cumulative exposure (intensity X duration)				
				<40	93 (68)	1.3 (0.86–1.9)		
				>40	85 (62)	1.1 (0.70–1.6)		
				Years since first exposure				
				<20 years	74 (57)	1.2 (0.76–1.8)		
				>20 years	104 (73)	1.2 (0.79–1.8)		
				Age at first exposure				
				<25 years	133 (98)	1.1 (0.78–1.6)		
				>25 years	45 (32)	1.3 (0.78–2.2)		
Marsh et al. [107], United States	22 cases who died from pharyngeal cancer, 7 of nasopharynx cancer, from a cohort study at a plastic-producing plant between 1945 and 1998	Four controls selected randomly from the remaining living and deceased members of the cohort were matched on exact age, race, sex, and year of birth to each case	Exposure to formaldehyde (nonexposed and exposed) was estimated from job titles, tasks, visits to the plants, visits to the plant, discussion with workers and managers, by industrial hygienists, and defining average intensity, peak of exposure, cumulative exposure, and duration of exposure	*Exposure to formaldehyde*			Adjusted for smoking and the combined silversmithing and other metal work job groups	See results of a cohort study with these deaths by nasopharynx cancer in Table 4.4
				Unexposed	0 (8)	1.0		
				Exposed	7 (47	2.87 (0.21–α)		
				Duration of exposure				
				<1 year	4 (35)	1.0		
				1–9 years	1 (11)	1.81 (0.03–36.4)		
				10+ years	2 (9)	2.72 (0.16–145.6)		
				Cumulative exposure				
				<0.004	1 (16)	1.00		
				0.004–0.219	3 (21)	1.65 (0.03–173.1)		
				0.22+	3 (18)	5.91 (0.16–950.3)		
				Average intensity of exposure				
				<0.03	1 (24)	1.00		
				0.03–0.159	4 (6)	11.41 (0.80–668.5)		
				0.16+	2 (25)	2.18 (0.09–133.8)		

Table 4.4 Cohort studies on occupation and nasopharynx cancer

Reference, location	Cohort description	Exposure assessment	No of cases/ deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Blair et al. [56], United States	26,561 workers first employed in 10 formaldehyde-producing or formaldehyde-using plants before 1996. Mortality follow-up (1980)	A job-exposure matrix was prepared for industrial hygienists considering each job-work area-calendar year combination. Measures of exposure to formaldehyde used in the analysis included level or intensity, duration, average, cumulative or peak exposure, presence of particulates, and measures that excluded recent exposures from the exposure index		*SMR*			Black women were excluded from analysis because of small numbers ($n=26$). All SMRs were not statistically significant
				Cumulative formaldehyde exposure			
			1	0 ppm-year	530		
			2	<0.5 ppm-year	271		
			2	0.51–5.5 ppm-year	256		
			2	>5.5 ppm-year	433		
Malker et al. [125], Sweden	Cohort of men in occupational groups defined by employment in 1960; incidence follow-up (1961–1979)	Occupation and industries defined according to job title		*SIR*		Adjusted for age and region	Only statistically significant increases of SIR are reported for specific occupations and industries
				Occupation			
			3	Glassmaker	6.2 ($p<0.05$)		
			3	Bookbinders	6.1 ($p<0.05$)		
			5	Shoemaker	3.8 ($p<0.05$)		
				Industries			
			5	Shoe repair	4.0 ($p<0.05$)		
			4	Fiberboard plant	3.9 ($p<0.05$)		

(continued)

Table 4.4 (continued)

Reference, location	Cohort description	Exposure assessment	No of cases/deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Demers et al. [116], United Kingdom and United States	28,704 persons (26,506 men, 2,198 women) from five mortality cohort studies in wood-related industries (4 American and 1 British). These cohorts had different periods of entrance and also different follow-up periods. A total of 9 deaths by nasopharynx cancer were observed	The cohorts included in the pooled analysis differed in the amount and detail of data collected exposure. To analyze the risk of cancer associated with wood dust exposure, a special classification scheme was developed incorporating the exposure information available for each study		*SMR*			
			9	Woodworkers combined	2.4 (1.1–4.5)		
			7	Furniture workers	2.9 (1.2–5.9)		
			2	Plywood workers	4.6 (0.6–16.4)		
				Wood dust exposure for all woodworkers			
			4	Possible	2.9 (0.8–7.5)		
			0	Probable	–		
			5	Definite	5.3 (1.7–12.4)		
				Calendar period of first employment for all woodworkers			
			3	Prior to 1940	7.7 (1.6–22.5)		
			5	1940–1949	5.3 (1.7–12.3)		
			0	1950–1959	–		
			1	1960 or later	1.7 (0.0–9.3)		
				Years since first employment for all woodworkers			
			0	<10 years	–		
			2	10–19 years	1.6 (0.2–5.9)		
			0	20–29 years	–		
			7	>30 years	8.9 (3.6–18.3)		
				Wood dust exposure for furniture workers			
			2	Possible	2.2 (0.3–7.8)		
			0	Probable	–		
			5	Definite	7.3 (2.4–16.9)Z		
				Calendar period of first employment for furniture workers			

3	Prior to 1940	8.6 (1.8–25.1)
4	1940–1949	7.7 (2.1–19.7)
0	1950–1959	–
0	1960 or later	–
	Years since first employment for furniture workers	
0	<10 years	–
0	10–19 years	–
0	20–29 years	–
7	>30 years	10.8 (4.3–22.2)
	Wood dust exposure for plywood workers	
2	Possible	11.8 (1.4–42.5)
0	Probable	–
0	Definite	–
	Calendar period of first employment for plywood workers	
0	Prior to 1940	–
1	1940–1949	5.0 (0.1–27.9)
0	1950–1959	–
1	1960 or later	25.0 (0.6–99.9)
	Years since first employment for plywood workers	
0	<10 years	–
2	10–19 years	13.3 (1.6–48.2)
0	20–29 years	–
0	>30 years	–

(continued)

Table 4.4 (continued)

Reference, location	Cohort description	Exposure assessment	No of cases/deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Marsh et al. [59], United States	7,328 workers (6,859 men, 469 women) employed at a plastic-producing plant (1941–1984); mortality follow-up until 1998	Exposure estimation was based on an examination of the available sampling data and job descriptions and verbal descriptions of jobs and tasks		*SMR*			
			7	Nasopharynx	4.94 (1.99–10.19)		
			4	Short term (<1 year)	5.35 (1.46–13.71)		
			3	Long term (1 + years)	4.59 (0.95–13.42)		
				Year of hire			
			0	1941–1946	–		
			6	1947–1956	8.13 (2.98–17.69)		
			1	1957+	2.63 (0.07–14.64)		
				DOE (year) (all workers)			
			4	<1	5.33 (1.45–14.64)		
			1	1–9	2.62 (0.06–14.57)		
			2	10+	7.49 (0.91–27.06)		
				TSFE (year)			
			2	<20	5.01 (0.61–18.08)		
			3	20–29	8.72 (1.80–25.48)		
			2	30+	3.04 (0.37–11.00)		
				Formaldehyde exposure			
			0	Unexposed	–		
			7	Exposed	6.03 (2.42–12.42)		
				Duration of exposure			
			4	>0–<1	5.84 (1.59–14.94)		
			1	1–9	3.17 (0.08–17.68)		

2	10+	12.46 (1.51–45.02)
	Cumulative exposure	
1	>0–<0.004	3.97 90.10–22.10)
3	0.004–0.129	5.89 (1.22–17.22)
3	0.22+	7.51 (1.55–21.93)
	AIE to formaldehyde (ppm)	
1	>0–<0.03	2.41 (0.06–13.44)
4	0.03–0.159	15.27 (4.16–39.10)
2	0.16+	4.13 (0.50–14.91)
	Formaldehyde >0.2 ppm	
2	Unexposed	3.01 (0.36–10.87)
5	Exposed	6.79 (2.21–15.85)
	Duration (year)	
2	>0–<1	4.81 (0.58–17.37)
1	1–9	4.04 (0.10–22.51)
2	10+	27.61 (3.34–99.73)
4	Formaldehyde >0.7 ppm	3.64 (0.99–9.31)
3	Unexposed	9.98 (2.06–29.17)
	Exposed	
	Duration (year)	
2	>0–<1	9.51 (1.15–34.37)
1	1+	11.07 (0.28–61.67)

(continued)

Table 4.4 (continued)

Reference, location	Cohort description	Exposure assessment	No of cases/deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
Hauptmann et al. [61], United States	Cohort of 25,619 workers (22,493 men, 3,126 women) employed in 10 US formaldehyde-producing or formaldehyde-using plants prior 1966; mortality from solid cancer follow-up until the end of 1994	Exposure to formaldehyde (nonexposed and exposed) was estimated from job titles, tasks, visits to the plants, visits to the plant, discussion with workers and managers, by industrial hygienists, and defining average intensity, peak of exposure, cumulative exposure, and duration of exposure		*SMR*		RR adjusted for calendar year, age, gender, race (black/white), and pay category (salary/wage)	None of RR were statistically nonsignificant
			2	Nonexposed	1.56 (0.39–6.23)		
			8	Exposed	2.10 (1.05–4.21)		
				RR			
				Intensity (ppm)			
			2	0	1.0		
			0	>0–<0.5	NA		
			1	0.5–<1.0	0.38		
			6	>1.0	1.67		
				Peak (ppm)			
			2	0	1.0		
			0	>0–<2.0	NA		
			0	2.0–<4.0	NA		
			7	>4.0	1.83		
				Cumulative (ppm-year)			
			2	0	2.40		
			3	>0–<1.5	1.0		
			1	1.5 - ≤ 5.5	1.19		
			3	>5.5	4.14		
				Duration (years)			
			2	0	1.77		
			4	>0–<5	1.0		
			1	5–<15	0.83		
			2	>15	4.18		

Li et al. [119], China	Cohort of 267,400 women in 526 factories in the Shanghai Textile Industry Bureau; all currently working and retired employees, who were born in 1925–1958 were eligible to participate; incidence follow-up (1989–1998)	Job categories; a job-exposure matrix was used for estimate exposure to several potential risk factors in textile industry		*HR*	
				Job categories	
				Cotton handing, processing, and spinning	
			4	<10 years	1.9 (0.7–5.3)
			11	>10 years	1.3 (0.6–2.4)
				Mixed fiber handling, processing, and spinning process	
			2	<10 years	0.8 (0.2–3.6)
			6	>10 years	1.0 (0.4–2.3)
				Dyeing	
			1	<10 years	1.8 (0.2–14.1)
			3	>10 years	3.6 (1.0–12.1)
				Finishing	
			1	<10 years	2.6 (0.3–21.3)
			1	>10 years	1.6 (0.2–12.5)
				Weaving	
			4	<10 years	0.7 (0.3–2.1)
			12	>10 years	0.6 (0.3–1.2)
				Printing	
			2	<10 years	9.2 (1.7–48.9)
			1	>10 years	2.0 (0.3–16.3)
				Cutting/sewing	
			2	<10 years	0.9 (0.2–3.9)
			6	>10 years	1.3 (0.6–3.2)
				Warehouse, packing, and quality control	
			3	<10 years	0.7 (0.2–2.1)
			5	>10 years	0.6 (0.3–1.6)
				Occupational exposures	
				Cotton dust	
			19	<1 year	1.0
			48	>1 year	1.8 (1.1–3.2)
				Wood dust	
			61	<1 year	1.0
			6	>1 year	0.6 (0.3–1.5)
				Skill dust	
			64	<1 year	1.0
			3	>1 year	0.9 (0.3–3.0)
				Synthetic fiber dust	
			42	<1 year	1.0
			25	>1 year	0.9 (0.5–1.5)
				Non-textile dust	
			61	<1 year	1.0
			6	>1 year	0.5 (0.2–1.2)

(continued)

Table 4.4 (continued)

Reference, location	Cohort description	Exposure assessment	No of cases/deaths	Exposure categories	SIR, SMR, IRR, or RR (95 % CI)	Adjustment for potential confounders	Comments
				Solvents			
			53	<1 year	1.0		
			14	>1 year	1.3 (0.7–2.5)		
				Bleaching agents			
			64	<1 year	1.0		
			3	>1 year	2.4 (0.7–8.2)		
				Acids, bases, and caustics			
			56	<1 year	1.0		
			11	>1 year	1.8 (0.9–3.6)		
				Dyes			
			62	<1 year	1.0		
			5	>1 year	2.1 (0.8–5.5)		
				Inks			
			63	<1 year	1.0		
			4	>1 year	5.0 (1.6–15.4)		
				Pesticides			
			65	<1 year	1.0		
			2	>1 year	1.9 (0.4–8.1)		
				Endotoxin			
			42	<1 year	1.0		
			25	>1 year	1.6 (0.9–2.6)		
Marsh et al. [107], United States	7,345 workers employed at a plastic-producing plant (1941–1984); mortality follow-up until 2003; vital status was obtained for 98 % and cause of death for 95 %	Exposure assessment obtained by work histories	7	*SMR (United States)* 4.34 (1.74–8.94) SMR (local county) 4.43 (1.78–9.13)			See results of a nested case-control study with these deaths by nasopharynx cancer in Table 4.3

SIR standardized incidence ratio, *SMR* standardized mortality ratio, *IRR* incidence rate ratio, *RR* relative risk

In 1983, Armstrong et al. [110] reported increased risk of nasopharynx squamous cell carcinoma in Malaysian Chinese ever exposed to wood dust (RR of 2.2, $p=0.08$). Another case-control study in the same population [111] found RR of 2.36 (95 % CI 1.33–4.19) for those exposed once to wood dust and RR of 1.24 (95 % CI 1.07–1.44) for those exposed to a tenfold increased exposure. Almost all other case-control studies that investigated the association between wood-related occupations and nasopharyngeal cancer have found increased risks [22, 79, 112, 113]. However, Vaughan et al. [114] did not find any evidence that exposure to wood dust increased the risk of nasopharyngeal carcinoma, as the modest crude association disappeared after controlling for potential exposure to formaldehyde. Also Siew et al. [115] in a large cohort of Finnish men born from 1906 to 1945 did not find any indication that wood dust and formaldehyde would increase the risk of nasopharyngeal cancer.

In a pooled reanalysis of four American cohorts and one British cohort of wood-related industries [116], excess risks of nasopharynx cancer were found for all combined woodworkers (SMR 2.4, 95 % CI 1.1–4.5), furniture workers (SMR 2.9 95 % CI 1.2–5.9), and plywood workers (SMR 4.6, 95 % CI 0.6–16.4). Mortality risk from nasopharynx cancer was higher in those employed in wood industry prior to 1940 (RR 7.7, 95 % CI 1.6–22.5), but this was restricted to workers from the British cohort as entry into the American cohorts only began in 1946. Increased risks were identified in workers definitively exposed to wood dust from any woodwork (RR 5.3, 95 % CI 1.7–12.4), for furniture workers definitively exposed to wood dust (RR 7.3, 95 % CI 2.4–16.9), and for plywood workers possibly exposed to wood dust (RR 11.8, 95 % CI 1.4–42.5).

The IARC has considered there is sufficient evidence that human exposure to wood dust is carcinogenic to the nasopharynx [109]. This was reaffirmed in a recent revision [77].

Cotton Dust and Textile Work

Several groups of chemicals are found in the textile manufacturing industry; these include flame retardants, textile dyes, solvents, preservatives, and textile prints. Some could be carcinogenic. Also some studies have suggested that cotton dust is a possible carcinogen for the nasopharynx.

In the United States, Roush et al. [117] found a deficit risk for nasopharynx cancer in textile work. In China, Yu et al. [118] also observed decreased risks for those ever exposed to cotton dust at any exposure duration. However, in Malaysia, Armstrong et al. [111] detected RR of 1.77 (95 % CI 0.76–4.11) for those ever exposed to cotton dust and RR of 1.16 (95 % CI 0.94–1.42) for those with a tenfold exposure to cotton dust. Li et al. [119] conducted a case-cohort study in Shanghai and detected increased risks of nasopharyngeal cancer for those exposed to cotton dust: RR of 2.7 (95 % CI 1.2–5.7) for less than 10 years and RR of 1.6 (95 % CI 0.9–2.9) for 10 years or more. An RR of 3.6 (95 % CI 1.8–7.2) was found for those with the highest cumulative exposure to cotton dust category (>143.4 mg/m^3 × years). The same study has also found increased risks of nasopharynx cancer for those in the textile industry exposed to acids, bases and caustics, dyes, and inks.

The IARC classifies cotton dust and working in textile industry as possibly carcinogenic to humans (Group 2B) [120]. Results from case-control studies conducted during the last decade of the twentieth century were more incisive on the relationship between cotton dust exposure and nasopharyngeal cancer. Also workers in textile industry have a possible increased risk of nasopharyngeal cancer. Nevertheless, no definite conclusion could be taken at this point on this relationship.

Other Occupations

Evidence linking nasopharynx cancer to other occupational risk factors is less definitive, as the number of studies is limited and results are conflicting. Henderson et al. [121] in a case-control study found increased risks of nasopharynx cancer for fumes, smoke, and chemicals, but not for dusts. Yu et al. [118] found increased risks for smoke and chemical fumes, but not for dusts. Armstrong et al. [111] did not find risks for exposure to chemicals, fumes, or dusts.

Chlorophenols are classified by IARC as possibly carcinogenic to humans – Group 2B [122]. A series of case-control studies have found relationships between exposure to chlorophenols and nasopharynx cancer. Hardell et al. [123] found about a sevenfold risk of nasopharyngeal and nasal cancer analyzed together for exposure to chlorophenols in the wood industry. Mirabelli et al. [124] also found high risks for those classified as ever exposed to high levels of chlorophenols (RR 2.64, 95 % CI 1.10–5.78) and even higher risks for those exposed for less than 10 years (RR 3.52, 95 % CI 1.07–9.73) or 10 years or more (RR 9.07, 95 % CI 1.41–42.9). Zhu et al. [23] found increased risks of nasopharyngeal squamous cell carcinoma in people exposed to chlorophenol (RR 2.2, 95 % CI 1.1–4.3).

Two case-control studies have examined the effect of industrial heat on nasopharynx cancer. Henderson et al. [121] found increased risks, around 1.5, but these were not statistically significant. Armstrong et al. [111] also found increased risks of nasopharynx cancer for heat exposure of RR of 1.23 ($p=0.021$), after adjustment for wood dust, diet, and cigarette smoke. Increased risks of nasopharynx cancer were also found for exposure to combustion products in a case-control study in China [118] with RR of 2.7 ($p<0.05$) for those with occasional exposure and RR of 10.1 ($p<0.05$) for those exposed for 10 years or more. The limited number of studies does not permit definitive conclusions to be made on the effect of industrial heat on nasopharynx cancer.

A case-control study in Taiwan [22] explored the effect of organic solvents on nasopharynx cancer, but risks were low and imprecise, and no dose-response effect was detected.

Zhu et al. [23] found increased risk for all histological types of nasopharyngeal cancer in people working with or around cutting oil (RR 1.9, 95 % CI 1.1–3.1); and increased risk of squamous cell carcinoma was found for occupational exposure to chromium compounds or alloys (RR 2.6, 95 % CI 1.1–6.1). Malker et al. [125] in a cohort study in Sweden found increased SIRs for glassmakers, bookbinders, and cobblers and in shoe repair and fiberboard industries.

Further studies are needed for all these occupational factors in order to have a clearer definition of their carcinogenic role on the nasopharynx.

Conclusion

The efforts to decrease major occupational risk factors for oral, pharyngeal, and nasopharyngeal cancers depend on the knowledge of potential carcinogen agents present in a particular occupation in different industry settings and the effective surveillance and prevention of workers' exposure to these agents. Table 4.5 shows the carcinogenicity evidence strength of some agents, occupations, or industries on oral cavity, pharyngeal, and nasopharyngeal anatomical sites.

Asbestos, diesel engine exhaust, leather and wood dust, man-made mineral fibers, and welding fumes have a possible association with oral and pharyngeal cancers. Waiters, cooks, and bartenders have a high risk of oral and pharyngeal cancers; however, the prevalence of tobacco smoking and alcohol consumption is higher among these workers than those in other occupations, and this fact could be the straightest explanation for the risk observed. Butchers, vehicle repair mechanics, welders, and woodworkers have showed evidences of possible increased risk of oral and pharyngeal cancers. Regarding the type of industry, jobs in the leather industry, man-made mineral fiber manufacturing, meat industry, vehicle repair service, and wood industry have also presented a possible impact on oral and pharyngeal cancer incidence.

There are convincing documentation on the causal relationship of exposure to chlorophenols, formaldehyde, and wood dust with nasopharyngeal cancer, as well as among woodworkers and in garment manufacturing. The carcinogenicity evidences of cotton dust and heat in the workplace to the nasopharynx are limited.

Additional studies are necessary to confirm the association of many suspicious agents, occupations, and industries with oral cavity, pharyngeal, and nasopharyngeal cancers. Nevertheless, the knowledge accumulated so far enables prevention and safety at work. That can be triggered in the context of surveillance programs, particularly considering exposure to chlorophenols, formaldehyde, and wood dust. For example, a well-oriented control of exposure to dust in the wood industry would prevent not only many cases of nasopharyngeal and sinonasal cancers but also probably some cases of pharyngeal, laryngeal, and lung tumors.

Table 4.5 Strength of evidence (low, possible, high) of association of exposure to some agents, occupations or industries, and oral cavity, pharynx, and nasopharynx cancers

Agent	Evidence	Occupation	Evidence	Industry	Evidence
Oral and pharynx cancers					
Asbestos	Possible	Butcher	Possible	Garment manufacture	Low
Diesel engine exhaust	Possible	Textile worker	Low	Leather industry	Possible
Dust		Vehicle repair mechanic	Possible	Man-made mineral fiber factory	Possible
Cotton	Low	Waiters and cooks	High	Meat industry	Possible
Leather	Possible	Welder and cutter	Possible	Textile industry	Low
Wood	Possible	Woodworker	Possible	Vehicle repair service	Possible
Formaldehyde	Low			Wood industry	Possible
Man-made mineral fibers	Possible				
Welding fumes	Possible				
Nasopharynx cancer					
Chlorophenols	High	Textile worker	Possible	Garment manufacture	High
Formaldehyde	High	Woodworker	High	Textile industry	Possible
Dust				Wood industry	High
Cotton	Possible				
Wood	High				
Industrial heat	Possible				

References

1. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GOBLOCAN 2008. Int J Cancer. 2010;127:2893–917.
2. Curado MP, Hashibe M. Recent changes in the epidemiology of head and neck cancer. Curr Opin Oncol. 2009;21:194–200.
3. Curado MP, Edwards B, Shin HR, Ferlay J, Heaune M, Boyle P, Storm H. Cancer incidence in five continents, IARC Scientific Publication, No 160, vol. IX. Lyon: IARC Press; 2009.
4. Wünsch Filho V, Camargo EA. The burden of mouth cancer in Latin America and the Caribbean: epidemiological issues. Semin Oncol. 2001;28:158–68.
5. Wünsch FV. The epidemiology of oral and pharynx cancer in Brazil. Oral Oncol. 2002;38:737–46.
6. Boing AF, Peres MA, Antunes JL. Mortality from oral and pharyngeal cancer in Brazil: trends and regional patterns, 1979–2002. Rev Panam Salud Publica. 2006;20:1–8.
7. Robinson KL, Macfarlane GJ. Oropharyngeal cancer incidence and mortality in Scotland: are rates still increasing? Oral Oncol. 2003;39:31–6.
8. Conway DI, Stockton DL, Warnakulasuriya KA, Ogden G, Macpherson LM. Incidence of oral and oropharyngeal cancer in United Kingdom (1990–1999) – recent trends and regional variation. Oral Oncol. 2006;41:586–92.
9. Hammarstedt L, Dahlstrand H, Lindquist D, Onelov L, Ryott M, Luo J, Dalianis T, Ye W, Munk-Wikland E. The incidence of tonsillar cancer in Sweden is increasing. Acta Otolaryngol. 2007;127:988–92.
10. Braakhuis BJ, Visser O, Leemans CR. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: increasing incidence, but not in young adults. Oral Oncol. 2009;45:e85–9.
11. Kingsley K, O'Malley S, Ditmyer M, Chino M. Analysis of oral cancer epidemiology in the US reveals state-specific trends: implications for oral cancer prevention. BMC Public Health. 2008;8:87.
12. Schantz SP, Yu GP. Head and neck cancer incidence trends in young Americans, 1973–1997, with a special analysis for tongue cancer. Arch Otolaryngol Head Neck Surg. 2002;128:268–74.
13. Shiboski CH, Schimidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. Cancer. 2005;103:1843–9.
14. Annertz K, Anderson H, Biörklund A, Möller T, Kantola S, Mork J, Olsen JH, Wennerberg J. Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. Int J Cancer. 2002;101:95–9.
15. Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck. 2007;29:779–92.
16. Lee AWM, Foo W, Mang O, Sze WM, Chappell R, Lau WH, Ko WM. Changing epidemiology of nasopharyngeal carcinoma in Hong Kong over a 20-year period (1980–99): an encouraging reduction in both incidence and mortality. Int J Cancer. 2003;103:680–5.
17. Yang L, Parkin DM, Li L, Chen Y. Time trends in cancer mortality in China: 1987–1999. Int J Cancer. 2003;106:771–83.
18. Wei K-R, Yu Y-L, Yang Y-Y, Ji M-F, Yu B-H, Liang Z-H, Reng X. Epidemiological trends of nasopharyngeal carcinoma in China. Asian Pac J Cancer Prev. 2010;11:29–32.
19. Sun LM, Epplein M, Li CI, Vaughan TL, Weiss NS. Trends in the incidence rates of nasopharyngeal carcinoma among Chinese Americans living in Los Angeles County and the San Francisco Metropolitan Area, 1992–2002. Am J Epidemiol. 2005;162:1174–8.
20. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2006;15:1765–77.
21. Hildesheim A, Levine PH. Etiology of nasopharyngeal carcinoma: a review. Epidemiol Rev. 1993;15:466–85.
22. Hildesheim A, Dosemeci M, Chan CC, Chen CJ, Cheng YJ, Hsu MM, Chen IH, Mittl BF, Sun B, Levine PH, Chen JY, Brinton LA, Yang CS. Occupational exposure to wood, formaldehyde, and solvents end risk of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2001;10:1145–53.
23. Zhu K, Levine RS, Brann EA, Hall I, Caplan LS, Gnep DR. Case-control study evaluating the homogeneity and heterogeneity of risk factors between sinonasal and nasopharyngeal cancers. Int J Cancer. 2002;99:119–23.
24. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, La Vecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang ZF, Berthiller J, Boffetta P. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst. 2007;99:777–89.
25. Ide R, Mizoue T, Fujino Y, Hoshiyama Y, Sakata K, Tamakoshi A, Yoshimura T, JACC Study Group. Cigarette smoking, alcohol drinking, and oral and pharyngeal cancer mortality in Japan. Oral Dis. 2008;14:314–9.
26. Purdue MP, Hashibe M, Berthiller J, La Vecchia C, Dal Maso L, Herrero R, Franceschi S, Castellsague X, Wei Q, Sturgis EM, Morgenstern H, Zhang ZF, Levi F, Talamini R, Smith E, Muscat J, Lazarus P, Schwartz SM, Chen C, Neto JE, Wünsch-Filho V, Zaridze D, Koifman S, Curado MP, Benhamou S, Matos E, Szeszenia-Dabrowska N, Olshan AF, Lence J, Menezes A, Daudt AW, Mates IN, Pilarska A, Fabianova E, Rudnai P, Winn D, Ferro G, Brennan P, Boffetta P, Hayes RB. Type of alcoholic beverage and risk of head and neck cancer – a pooled analysis within the INHANCE Consortium. Am J Epidemiol. 2009;169:132–42.
27. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S, Hayes RB, Herrero R, Kelsey K, Koifman S, La Vecchia C, Lazarus P, Levi F, Lence JJ, Mates D, Matos E, Menezes A, McClean MD, Muscat J, Eluf-Neto J, Olshan AF, Purdue M, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Shangina O, Pilarska A, Zhang ZF, Ferro G, Berthiller J, Boffetta P. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18:541–50.
28. Lee YC, Boffetta P, Sturgis EM, Wei Q, Zhang ZF, Muscat J, Lazarus P, Matos E, Hayes RB, Winn DM, Zaridze D, Wünsch-Filho V, Eluf-Neto J, Koifman S, Mates D, Curado MP, Menezes A, Fernandez L, Daudt AW, Szeszenia-Dabrowska N, Fabianova E, Rudnai P, Ferro G, Berthiller J, Brennan P, Hashibe M. Involuntary smoking and head and neck cancer risk: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2008;17:1974–81.
29. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LM. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer. 2008;122:2811–9.
30. Boing AF, Ferreira Antunes JL, de Carvalho MB, de Góis Filho JF, Kowalski LP, Michaluart Jr P, Head and Neck Genome Project/GENCAPO, Eluf-Neto J, Boffetta P, Wünsch-Filho V. How much do smoking and alcohol consumption explain socioeconomic

inequalities in head and neck cancer risk? J Epidemiol Community Health. 2011;65:708–14.
31. Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. Int J Cancer. 2008;122:2330–6.
32. Peters ES, Luckett BG, Applebaum KM, Marsit CJ, McClean MD, Kelsey KY. Dairy products, leanness and head and neck squamous cell carcinoma. Head Neck. 2008;30:1193–205.
33. Gaudet MM, Olshan AF, Chuang SC, Berthiller J, Zhang ZF, Lissowska J, Zaridze D, Winn DM, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Schwartz SM, Rudnai P, Eluf-Neto J, Muscat J, Morgenstern H, Menezes A, Matos E, Bucur A, Levi F, Lazarus P, La Vecchia C, Koifman S, Kelsey K, Herrero R, Hayes RB, Franceschi S, Wunsch-Filho V, Fernandez L, Fabianova E, Daudt AW, Dal Maso L, Curado MP, Chen C, Castellsague X, Benhamou S, Boffetta P, Brennan P, Hashibe M. Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. Int J Epidemiol. 2010;39:1091–102.
34. IARC. Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 85. Lyon: IARC Press; 2004.
35. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens – part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009;10:1033–4.
36. IARC. A review of human carcinogens: personal habits and indoor combustions, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 100E. Lyon: IARC Press; 2012.
37. Guha N, Boffetta P, Wünsch Filho V, Eluf Neto J, Shangina O, Zaridze D, Curado MP, Koifman S, Matos E, Menezes A, Szeszenia-Dabrowska N, Fernandez L, Mates D, Daudt AW, Lissowska J, Dikshit R, Brennan P. Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case-control studies. Am J Epidemiol. 2007;166:1159–73.
38. Marques LA, Eluf-Neto J, Figueiredo RA, Góis-Filho JF, Kowalski LP, Carvalho MB, Abrahão M, Wünsch-Filho V. Oral health, hygiene practices and oral cancer. Rev Saude Publica. 2008;42:471–9.
39. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens – part B: biological agents. Lancet Oncol. 2009;10:321–2.
40. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and – unrelated oral squamous cell carcinoma in the United States. J Clin Oncol. 2008;26:612–9.
41. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol. 2010;11:781–9.
42. Negri E, Boffetta P, Berthiller J, Castellsague X, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, Lazarus P, Lence JJ, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Shangina O, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Lissowska J, Zhang ZF, Ferro G, Brennan P, La Vecchia C, Hashibe M. Family history of cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Int J Cancer. 2009;124:394–401.
43. IARC. A review of human carcinogens: biological agents, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 100B. Lyon: IARC Press; 2011.
44. Yuan JM, Wang XL, Xiang YB, Gao YT, Ross RK, Yu MC. Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. Int J Cancer. 2000;85:364–9.
45. Lin TM, Chen KP, Lin CC, Hsu MM, Tu SM, Chiang TC, Jung PF, Hirayama T. Retrospective study on nasopharyngeal carcinoma. J Natl Cancer Inst. 1973;51:1403–8.
46. Mabuchi K, Bross DS, Kessler II. Cigarette smoking and nasopharyngeal carcinoma. Cancer. 1985;55:2874–6.
47. Nam JM, McLaughlin JK, Blot WJ. Cigarette smoking, alcohol, and nasopharyngeal carcinoma: a case-control study among U.S. whites. J Natl Cancer Inst. 1992;84:610–22.
48. Hirayama T, Ito Y. A new view of the etiology of nasopharyngeal carcinoma. Prev Med. 1981;10:614–22.
49. Yu MC, Ho JHC, Lai SH, Henderson BE. Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: report of a case-control study in Hong Kong. Cancer Res. 1986;46:956–61.
50. Garrote LF, Herrero R, Reyes RMO, Vaccarella S, Anta JL, Ferbeye L, Muñoz N, Franceschi S. Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. Br J Cancer. 2001;85:46–54.
51. Menvielle G, Luce D, Goldberg P, Leclerc A. Smoking, alcohol drinking, occupational exposures and social inequalities in hypopharyngeal and laryngeal cancer. Int J Epidemiol. 2004;33:799–806.
52. Vaughan TL, Strader C, Davis S, Daling JR. Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I Occupations exposures. Int J Cancer. 1986;38:677–83.
53. Merletti F, Boffetta P, Ferro G, Pisani P, Terracini B. Occupation and cancer of the oral cavity or oropharynx in Turin, Italy. Scand J Work Environ Health. 1991;17:248–54.
54. Gustavsson P, Jakobsson R, Johansson H, Lewin F, Norell S, Rutkvist LE. Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden. Occup Environ Med. 1998;55:393–400.
55. Vlajinac HD, Marinkovic JM, Sipetic SB, Andrejic DM, Adanja BJ, Stosic-Divjak SL. Case-control study of oropharyngeal cancer. Cancer Detect Prev. 2006;30:152–7.
56. Blair A, Stewart P, O'Berg M, Gaffey W, Walrath J, Ward J, Bales R, Kaplan S, Cubit D. Mortality among industrial workers exposed to formaldehyde. J Natl Cancer Inst. 1986;76:1071–84.
57. Gardner MJ, Pannett B, Winter PD, Cruddas AM. A cohort study of workers exposed to formaldehyde in the British chemical industry: an update. Br J Ind Med. 1993;50:827–34.
58. Andjelkovich DA, Janszen DB, Brown MH, Richardson RB, Miller FJ. Mortality of iron foundry workers: IV. Analysis of a subcohort exposed to formaldehyde. J Occup Environ Med. 1995;37:826–37.
59. Marsh GM, Youk AO, Buchanich JM, Cassidy LD, Lucas LJ, Esmen NA, Gathuru IM. Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde. Toxicol Ind Health. 2002;18:257–68.
60. Coggon D, Harris EC, Poole J, Palmer KT. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. J Natl Cancer Inst. 2003;95:1608–15.
61. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from solid cancers among workers in formaldehyde industries. Am J Epidemiol. 2004;159:1117–30.
62. Stayner LT, Elliot L, Blade L, Keenlyside R, Halperin W. A retrospective cohort mortality study of workers exposed to formaldehyde in the garment industry. Am J Ind Med. 1988;13:667–81.
63. Pinkerton LE, Hein MJ, Stayner LT. Mortality among a cohort of garment workers exposed to formaldehyde: an update. Occup Environ Med. 2004;61:193–200.
64. Walrath J, Fraumeni Jr JF. Mortality patterns among embalmers. Int J Cancer. 1983;31:407–11.
65. Walrath J, Fraumeni Jr JF. Cancer and other causes of death among embalmers. Cancer Res. 1984;44:4638–41.
66. Stroup NE, Blair A, Erikson GE. Brain cancer and other causes of death in anatomists. J Natl Cancer Inst. 1986;77:1217–24.
67. Hayes RB, Blair A, Stewart PA, Herrick RF, Mahar H. Mortality of US embalmers and funeral directors. Am J Ind Med. 1990;18:641–52.

68. Logue JN, Barrick MK, Jessup Jr GL. Mortality of radiologists and pathologists in the Radiation Registry of Physicians. J Occup Med. 1998;28:91–9.
69. Tarvainen L, Kyyrönen P, Kauppinen T, Pukkala E. Cancer of the mouth and pharynx, occupation and exposure to chemical agents in Finland [in 1971–95]. Int J Cancer. 2008;123:653–9.
70. Innos K, Rahu M, Rahu K, Lang I, Leon DA. Wood dust exposure and cancer incidence: a retrospective cohort study of furniture workers in Estonia. Am J Ind Med. 2000;37:501–11.
71. Bosetti C, McLaughlin JK, Tarone RE, Pira E, La Vecchia C. Formaldehyde and cancer risk: a quantitative review of cohort studies through 2006. Ann Oncol. 2008;19:29–43.
72. Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens – part F: chemical agents and related occupations. Lancet Oncol. 2009;10:1143–4.
73. IARC. IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: chemical agents and related occupations, vol. 100F. Lyon: IARC Press; 2012.
74. Decoufle P. Cancer risks associated with employment in the leather and leather products industry. Arch Environ Health. 1979;34:33–7.
75. Franco EL, Kowalski LP, Oliveira BV, Curado MP, Pereira RN, Silva ME, Fava AS, Torloni H. Risk factors for oral cancer in Brazil: a case-control study. Int J Cancer. 1989;43:992–1000.
76. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens – part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 2009;10:453–4.
77. IARC. IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: arsenic, metals, fibres, and dusts, vol. 100C. Lyon: IARC Press; 2012.
78. Haguenoer JM, Cordier S, Morel C, Lefebvre JL, Hemon D. Occupational risk factors for upper respiratory tract and upper digestive tract cancers. Br J Ind Med. 1990;47:380–3.
79. Vaughan TL, Davis S. Wood dust exposure and squamous cell cancers of the upper respiratory tract. Am J Epidemiol. 1991;133:560–4.
80. Andreotti M, Rodrigues AN, Cardoso LMN, Figueiredo RAO, Eluf-Neto J, Wünsch-Filho V. Ocupação e câncer da cavidade oral e orofaringe [occupational status and cancer of the oral cavity and oropharynx]. Cad Saude Publica. 2006;22:543–52 [Portuguese].
81. Jayaprakash V, Natarajan KK, Moysich KB, Rigual NR, Ramnath N, Natarajan N, Reid ME. Wood dust exposure and the risk of upper aero-digestive and respiratory cancers in males. Occup Environ Med. 2008;65:647–54.
82. Vaughan T. Occupation and squamous cell cancers of the pharynx and sinonasal cavity. Am J Ind Med. 1989;16:493–510.
83. Huebner WW, Schoenberg JB, Kelsey JL, Wilcox HB, McLaughlin JK, Greenberg RS, Preston-Martin S, Austin DF, Stemhagen A, Blot WJ, Winn DM, Fraumeni JF. Oral and pharyngeal cancer and occupation: a case-control study. Epidemiology. 1992;3:300–9.
84. Schildt EB, Eriksson M, Hardell L, Magnuson A. Occupational exposures as risk factors for oral cancer evaluated in a Swedish case-control study. Oncol Rep. 1999;6:317–20.
85. Krstev S, Stewart P, Rusiecki J, Blair A. Mortality among shipyard coast guard workers: a retrospective cohort study. Occup Environ Med. 2007;64:651–8.
86. Pukkala E, Söderholm AL, Lindqvist C. Cancers of the lip and oropharynx in different social and occupational groups in Finland. Eur J Cancer B Oral Oncol. 1994;30B:209–15.
87. Brown LM, Moradi T, Gridley G, Plato N, Dosemeci M, Fraumeni JF. Exposures in the painting trades and paint manufacturing industry and risk of cancer among men and women in Sweden. J Occup Environ Med. 2002;44:258–64.
88. Winn DM, Blot WJ, Shy CM, Fraumeni JF. Occupation and oral cancer among women in the South. Am J Ind Med. 1982;3:161–7.
89. Ji J, Hemminki K. Occupation and upper aerodigestive tract cancers: a follow-up study in Sweden. J Occup Environ Med. 2005;47:785–95.
90. Benbrahim-Tallaa L, Baan RA, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Guha N, Loomis D, Straif K. Carcinogenicity of diesel-engine and gasoline-engine exhaust and some nitroarenes. Lancet Oncol. 2012;13:663–4.
91. Attfield MD, Schleiff PL, Lubin JH, Blair A, Stewart PA, Vermeulen R, Coble JB, Silverman DT. The diesel exhaust in miners study: a cohort mortality study with emphasis on lung cancer. J Natl Cancer Inst. 2012;104:869–83.
92. Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, Coble JB, Rothman N, Schleiff PL, Travis WD, Ziegler RG, Wacholder S, Attfield MD. The diesel exhaust in miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst. 2012;104:855–68.
93. Boffetta P, Dosemeci M, Gridley G, Bath H, Moradi T, Silverman D. Occupational exposure to diesel engine emissions and risk of cancer in Swedish men and women. Cancer Causes Control. 2001;12:365–74.
94. Johnson ES. Cancer mortality among workers in the meat department of supermarkets. Occup Environ Med. 1994;51:541–7.
95. Boffetta P, Gridley G, Gustavsson P, Brennan P, Blair A, Ekström AM, Fraumeni JF. Employment as butcher and cancer risk in a record-linkage study from Sweden. Cancer Causes Control. 2000;11:627–33.
96. Oreggia F, de Stefani E, Correa P, Rivero S, Fernàndez G, Leiva J, Zavala D. Exposición ocupacional en el cancer oral, faringeo y laringeo [occupational exposure in cancer of the mouth, pharynx and larynx]. An Otorrinolaringol Ibero Am. 1989;16:365–76 [Spanish].
97. Coggon D, Wield G. Mortality of butchers and cooks identified from the 1961 census of England and Wales. Occup Environ Med. 1995;52:157–9.
98. Moulin JJ, Mur JM, Wild P, Perreaux JP, Pham QT. Oral cavity and laryngeal cancers among man-made mineral fiber production workers. Scand J Work Environ Health. 1986;12:27–31.
99. Boffetta P, Andersen A, Hansen J, Olsen JH, Plato N, Teppo L, Westerholm P, Saracci R. Cancer incidence among European man-made vitreous fiber production workers. Scand J Work Environ Health. 1999;25:222–6.
100. Marchand JL, Luce D, Leclerc A, Goldberg P, Orlowski E, Bugel I, Brugère J. Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibers: results of a case-control study. Am J Ind Med. 2000;37:581–9.
101. Purdue MP, Järvholm B, Bergdahl IA, Hayes RB, Baris D. Occupational exposures and head and neck cancers among Swedish construction workers. Scand J Work Environ Health. 2006;32:270–5.
102. Swenberg JA, Kerns WD, Mitchell RE, Gralla EJ, Pavkov KL. Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res. 1980;40:3398–402.
103. Albert RE, Sellakumar AR, Laskin S, Kuschner M, Nelson A, Snyder CA. Nasal cancer in the rat induced by gaseous formaldehyde and hydrogen chloride. J Natl Cancer Inst. 1982;68:597–603.
104. West S, Hildesheim A, Dosemeci M. Non-viral risk factors nasopharyngeal carcinoma in the Philippines: results from a case-control study. Int J Cancer. 1993;55:722–7.
105. IARC. Formaldehyde, 2-butoxyethanol, and 1-tert-butoxy-2-propanol, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 88. Lyon: IARC Press; 2004.
106. Cogliano VJ, Grosse Y, Baan RA, Straif K, Secretan MB, El Ghissassi F, Working Group for Volume 88. Meeting report: summary of IARC monographs on formaldehyde, 2-butoxyethanol, and 1-tert-butoxy-2-propanol. Environ Health Perspect. 2005;113:1205–8.

107. Marsh GM, Youk AO, Buchanich JM, Erdal S, Esmen NA. Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers. Regul Toxicol Pharmacol. 2007; 48:308–19.
108. National Toxicology Program. National Institute of Environmental Health Science. National Institute of Health. The report on carcinogens. 12th ed. Washington: National Institute of Environmental Health Science; 2011.
109. IARC. Wood dust and formaldehyde, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 62. Lyon: IARC Press; 1995.
110. Armstrong RW, Armstrong MJ, Yu MC, Henderson BE. Salted fish and inhalants as risk factors for nasopharyngeal carcinoma in Malaysian Chinese. Cancer Res. 1983;43:2967–70.
111. Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC, Sani S. Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. Int J Epidemiol. 2000;29:991–8.
112. Kawachi I, Pearce N, Fraser J. A New Zealand cancer registry-based study of cancer in wood workers. Cancer. 1989;64:2609–13.
113. Sriamporn S, Vatanasapt V, Pisani P, Yongchaiyudha S, Rungpitarangsri V. Environmental risk factors for nasopharyngeal carcinoma: a case-control study in Northeastern Thailand. Cancer Epidemiol Biomarkers Prev. 1992;1:345–8.
114. Vaughan TL, Stewart PA, Teschke K, Lynch CF, Swanson GM, Lyon JL, Berwick M. Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. Occup Environ Med. 2000;57:376–84.
115. Siew SS, Kauppinen T, Kyyrönen P, Hiekkilä P, Pukkala E. Occupational exposure to wood dust and formaldehyde and risk of nasal, nasopharyngeal, and lung cancer among Finnish men. Cancer Manag Res. 2012;4:223–32.
116. Demers PA, Boffetta P, Kogevinas M, Blair A, Miller BA, Robinson CF, Roscoe RJ, Winter PD, Colin D, Matos E, Vainio H. Pooled reanalysis of cancer mortality among five cohorts of workers in wood-related industries. Scand J Work Environ Health. 1995;21:179–90.
117. Roush GC, Walrath J, Stayner LT, Kaplan SA, Flannery JT, Blair A. Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: a case-control study. J Natl Cancer Inst. 1987;79:1221–4.
118. Yu MC, Garabrant DH, Huang TB, Henderson BE. Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. Int J Cancer. 1990;45:1033–9.
119. Li W, Ray RM, Gao DL, Fitzgibbons ED, Seixas NS, Camp JE, Wernli KJ, Astrakianakis G, Feng Z, Thomas DB, Checkoway H. Occupational risk factors for nasopharyngeal cancer among female textile workers in Shanghai, China. Occup Environ Med. 2005;63:39–44.
120. IARC. Some flame retardants and textile chemicals, and exposures in the textile manufacturing industry, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 48. Lyon: IARC Press; 1990.
121. Henderson BE, Louie E, Jing JS, Buell P, Gardner M. Risk factors associated with nasopharyngeal carcinoma. N Engl J Med. 1976;295:1101–6.
122. IARC. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 71. Lyon: IARC Press; 1999.
123. Hardell L, Johansson B, Axelson O. Epidemiological study of nasal and nasopharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. Am J Ind Med. 1982;3: 247–57.
124. Mirabelli MC, Hoppin JA, Tolbert PE, Herrick RF, Gnepp DR, Brann EA. Occupational exposure to chlorophenol and the risk of nasal and nasopharyngeal cancers among U.S. men aged 30 to 60. Am J Ind Med. 2000;37:532–41.
125. Malker HSR, McLaughlin JK, Weiner JA, Silverman DT, Blot WJ, Ericsson JLE, Fraumeni JF. Occupational risk factors for nasopharyngeal cancer in Sweden. Br J Ind Med. 1990;47: 213–4.
126. Tisch M, Enderle G, Zöller J, Maier H. Cancer of the oral cavity in machine workers. Laryngorhinootologie. 1996;75(12): 759–63.
127. Coble JB, Brown LM, Hayes RB, Huang WY, Winn DM, Gridley G, Bravo-Otero E, Fraumeni JF Jr. Sugarcane farming, occupational solvent exposures, and the risk of oral cancer in Puerto Rico. J Occup Environ Med. 2003;45(8):869–74.
128. Lynge E, Thygesen L. Use of surveillance systems for occupational cancer: data from the Danish National system. Int J Epidemiol. 1988;17(3):493–500.
129. Stayner L, Dankovic D, Smith R, Steenland K. Predicted lung cancer risk among miners exposed to diesel exhaust particles. Am J Ind Med. 1998;34(3):207–19.
130. Andersen ZJ, Lassen CF, Clemmensen IH. Social inequality and incidence of and survival from cancers of the mouth, pharynx and larynx in a population-based study in Denmark, 1994–2003. European Journal of Cancer. 2008;44(14):1950–61.

Pancreatic Cancer

5

Yingtai Chen, Chengfeng Wang, and Yawei Zhang

Keywords
Pancreatic cancer • Occupational risk factors • Chemical production • Metal manufacturing • Solvents • Molecular markers

Introduction

Pancreatic cancer is a fatal malignancy associated with rapid progression. One-year relative survival rates are less than 30 %, and nearly all patients die from the disease within 7 years of surgery [1, 2]. It is estimated that 43,920 men and women will be diagnosed with pancreatic cancer and 37,390 will die of the disease in 2012 [2]. Although there have been improvements made in the diagnostic and prognosis of pancreatic cancer, these changes are minor [3]. Smoking is the only established nonheritable risk factor for pancreatic cancer; however, only about 30 % of the cases can be attributed to smoking [4, 5]. Although results are inconclusive, obesity, diabetes, alcohol consumption, and chronic pancreatitis have also been suggested as risk factors for pancreatic cancer [6]. Given this poorly understood etiology, prevention of this deadly disease continues to remain a challenge.

Etiological studies of pancreatic cancer have encountered tremendous methodological obstacles due to the highly aggressive nature of the disease. Disease and exposure misclassifications were major concerns as most studies had to rely upon death certificates or exposure information from next of kin. In addition, the majority of the cohort studies included very few pancreatic cancer cases (less than 50 exposed cases). Despite these challenges, many potential risk factors in occupational settings have been identified and are suspected to be associated with the pathogenesis of pancreatic cancer [7, 8].

Occupational Risk Factors of Pancreatic Cancer

Current available studies which investigated occupational factors and the risk of pancreatic cancer have suggested a connection to working in industries such as chemical production, metal manufacturing, printing and paper manufacturing, transport and communication, and textiles. Other professions associated with an increased risk of pancreatic cancer were found to occur in solvent-related occupations such as mechanics, leather tanners, and dry cleaners as well as several silica dusts and asbestos-related occupations such as glass manufacturers, potters, and construction workers.

As shown in Table 5.1 (cohort studies) [9–64] and Table 5.2 (case-control studies) [65–83], a number of studies investigated the association between specific occupations and industries and risk of pancreatic cancer. Although these studies have yielded inconsistent results, they do suggest that several occupations and industries may be associated with higher risk of pancreatic cancer.

Chemical, Petroleum, and Related Processing Industries

Previous studies have shown an increased risk of pancreatic cancer among men and women who worked in chemical industries. In a mortality study involving 3,637 deaths from

Y. Chen, MD, PhD • C. Wang, MD
Department of Abdominal Tumours Surgery,
Center of Pancreatic Tumours, Cancer Institute and Hospital,
Chinese Academy of Medical Sciences, Beijing, China

Y. Zhang, MD, PhD, MPH (✉)
Department of Environmental Health Sciences,
Yale University, School of Public Health, 60 College Street,
New Haven, CT 06520, USA
e-mail: yawei.zhang@yale.edu

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_5, © Springer-Verlag London 2014

Table 5.1 Cohort studies of occupational exposure and pancreatic cancer

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95 % CI)*
Li et al. [12]	A mortality study involving 3,637 deaths from the American Chemical Society between 1948 and 1967	Occupational history from plant records	56	Significant higher proportion of deaths from pancreatic cancer among male chemists aged 20–64 years compared with professional men in general
Milham [13], Washington State, USA	A PMR study involving male death in Washington State between 1951 and 1970	Death certificates	152	Sheet-metal workers PMR = 132; aluminum mill workers PMR = 204
Williams et al. [14], USA	From the Third National Cancer Survey Interview Study of 7,518 incident cases, lifetime histories of occupations and industries were studied controlling for age, sex, race, education, use of cigarettes or alcohol, and geographic location	Interview of part of the study subjects	Unknown	Increased risk for farmers, painters, trucking services, and public administration
Decoufle [10], USA	2,485 white males employed between 1938 and 1967 and had 5 or more years of employment in jobs exposed to cutting oil mists	Company records	8	Expected death = 7.6 for white male workers exposed to cutting oil mists
Chiazze and Ference [9], USA	A cross-sectional mortality study of 3,847 deaths occurring among current and former (white) employees of 17 PVC fabricators during 1964–1973 is presented. Sex-race cause-specific PMRs were computed	Industry records	Male = 37; female = 7	PMR = 113 for male and 116 for female employees of PVC fabricators
Hanis et al. [11], USA	A dynamic retrospective cohort including 8,666 employees worked at least 1 month between January 1, 1970, and December 31, 1977, at refinery and chemical plant	Occupational history from plant records	23	SMR = 152(96–228) for workers employed in refinery and chemical plant
Rockette and Arena [16], USA	A cohort of 21,829 workers with five or more years of employment in 14 aluminum reduction plants	Plant records	63	SMR = 125 for workers employed in aluminum reduction plants
Howe et al. [15], Canada	A mortality study of a cohort of 43,826 male pensioners of the Canadian National Railway Company. The cause of death of 17,838 pensioners who died between 1965 and 1977 was ascertained by computerized record linkage to the Canadian national mortality database	Occupation at the time of retirement	197	SMR = 93 for workers employed in railway company
Decoufle et al. [19], USA	A historical cohort mortality study of 259 male employees of a chemical plant where benzene has been used in large quantities who were employed by the company any time between January 1, 1947, and December 31, 1960, and were followed through December 31, 1977	Industry records	1	SMR = 164 for workers exposed to benzene
Acheson et al. [17], UK	The mortality experience of 5,969 men employed in a factory where insulation board was manufactured using amosite asbestos from 1947 to 1979	An industrial hygienist assigned exposure based on job titles	3	SMR = 96 for workers exposed to asbestos
Elinder et al. [20], Sweden	545 men who had been exposed to cadmium for at least 1 year between 1940 and 1980 in a Swedish cadmium-nickel battery factory and who had not died before 1951 were followed through 1983	Industry records	3	SMR = 130 for workers employed in cadmium and/or nickel battery factory

Table 5.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95 % CI)*
Lynge [21], Denmark	Registration of the cohort was based on company records, supplemented with data from a public pension scheme from 1964 onward till 1982. Cancer cases were identified by linkage with the National Cancer Register. Totals of 3,390 males and 1,069 females were included in the study	Records	3	RR = 0.59 for workers employed in manufacture of phenoxy herbicides
Bond et al. [18], Texas, USA	A general mortality survey was done on a 5 % random-start systematic sample (N = 1,666) of present and former white male employees of a Texas chemical plant	Occupational history from the plant records	7	SMR = 233 for workers employed in chemical plant
Wen et al. [25], Texas, USA	A retrospective cohort mortality study of 1,008 male oil refinery workers who ever worked on the lubricating-dewaxing process of the lube oil department and who have been followed for a period of 43 years (January 15, 1935–January 1, 1978)	Occupational history from the plant records	5	SMR = 1.67(0.54–3.89) for workers on the lubricating-dewaxing process
Vena et al. [24], USA	A PMR study including death certificates for workers from three unions representing an integrated automobile factory composed of forge, foundry, and engine (machine and assembly) plants, who died during the period January 1, 1970–December 31, 1979	Occupational history from the plant records	11	PMR = 297* for worker in the engine plant who were employed for more than 20 years
Ott et al. [23], California, USA	A retrospective cohort mortality study (n = 1,919) was conducted among men employed for 1 or more years, between 1940 and 1969, at an operating division of a large chemical company, followed through 1979	Occupational history from the plant records	6	SMR = 117(43–254) for workers employed in chemical plant
Milham [22], Washington State, USA	In an occupational mortality analysis of 486,000 adult male death records filed in Washington State in the years 1950–1982	Occupational records	174	PMR = 117* for workers occupationally exposed to electromagnetic fields
Zoloth et al. [26], USA	A PMR study in 1,401 commercial pressmen	Occupational records	18	PMR = 162 for those employed as commercial pressmen for more than 20 years
Coggon et al. [27], Finland	A mortality study of 5,784 employees at a company which has manufactured, formulated, and sprayed 2 methyl-4 chlorophenoxyacetic acid (MCPA) and other phenoxy acid herbicides who were employed by the company during 1947–1975 was traced to the end of 1983	Records	9	SMR = 68 for workers exposed to MCPA and other phenoxy acid herbicides
Brown [29], USA	A retrospective cohort mortality study of workers exposed to polychlorinated biphenyls (PCBs) in two plants manufacturing electrical capacitors was reported in 1981	Records	2	SMR = 54 for workers exposed to PCBs

(continued)

Table 5.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95 % CI)*
Wong [34], USA	A cohort of 7,676 chemical workers from seven plants who had been occupationally exposed (continuously or intermittently) to benzene for at least 6 months and a comparison group of male chemical workers from the same plants who had been employed for at least 6 months during the same period but were never occupationally exposed to benzene	Occupational records	14	SMR = 92.1 for workers exposed to benzene; SMR = 133 for workers unexposed to benzene
Enterline et al. [30], USA	A mortality study of 1,074 white men who retired from a US asbestos company during the period 1941–1967 and who were exposed to asbestos working as production and maintenance employees for the company is reported to the end of 1980	Industry records	8	SMR = 108 for workers exposed to asbestos
Silverstein et al. [32], Detroit, USA	1,766 bearing plant workers died between January 1, 1950, and June 30, 1982	Occupational history from plant records	24	Machining (SMOR = 9.9) and grinding (SMOR = 3.2) jobs in straight oil
Smulevich et al. [33], Soviet Union	The results of a cancer mortality study among workers employed in the production of vinyl chloride and polyvinyl chloride between 1939 and 1977	Industry records	3	SMR = 172 for males
Boffetta et al. [28], USA	In 1982, the American Cancer Society enrolled over 1.2 million American men and women in a prospective mortality study of cancer and other causes in relation to different risk factors. The 2-year mortality of 461,981 males aged 40–79 years with known smoking habit has been analyzed in relation to exposure to diesel exhaust (DE) and to employment in selected occupations related to DE exposure	Questionnaire	27	RR = 1.39 workers exposed to diesel exhaust
Hansen et al. (1989), Denmark	A cohort of auto mechanics has been followed through 10 years with regard to cause-specific mortality	Occupational history from plant records	17	SMR = 219* for workers exposed to auto mechanics
Costantini et al. [37], Italy	The mortality of 2,926 male workers at the tanneries in the "leather area" of Tuscany was examined from 1950 to 1983	Occupational history from the tanning industry	4	SMR = 146(39–373) for workers at the tanneries
Hearne et al. [40], New York, USA	Mortality study in a 1964–1970 cohort of 1,013 hourly wage men exposed to methylene chloride were followed through 1988	Measurement in plant area	8	SMR = 1.9 for workers exposed to methylene chloride
Langard et al. [42], Norway	A cohort study on the incidence of cancers and crude death rates in ferrochromium and ferrosilicon workers was conducted from January 1, 1953, to December 31, 1985	Measurement in plant area	7	Expected death = 6.2 for ferrochromium and ferrosilicon workers
Gustavsson and Reuterwall [39], Sweden	The mortality and incidence study of cancer of 295 workers at a Swedish gas production company. All men employed for at least 1 year in 1965–1972. The follow-up period for mortality was 1966–1986 and the incidence of cancer from 1966 to 1983	Measurement in plant area	Death = 1; incidence = 1	SMR = 67; SIR = 106 for workers at gas production company

Table 5.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95 % CI)*
Lanes et al. [41], South Carolina, USA	Mortality study of a cohort of 1,271 workers involved in the production of cellulose triacetate fiber at a plant in Rock Hill, South Carolina. Each subject was employed for at least 3 months between 1954 and 1977 in jobs that entailed exposure to the highest concentrations of methylene chloride and were followed through 1990	Industry records	2	SMR = 83 for workers exposed to methylene chloride
Gardner et al. [38], UK	A cohort study of 7,660 workers exposed to formaldehyde in the British chemical industries was followed through the end of 1989. Those worker first employed before 1965	Measurement records	27	SMR = 90 for workers exposed to formaldehyde
McDonald et al. [43], Canada	A cohort of some 11,000 men born in 1891–1920 and employed for at least 1 month in the chrysotile mines and mills of Quebec was established in 1966 and has been followed between 1976 and 1988	Industry records	37	SMR = 102 for workers employed in the chrysotile mines and mills
Benson et al. [36], West Virginia, USA	278 men assigned to the chlorohydrin unit, which produced ethylene chlorohydrin (ethylene dichloride and bischloroethyl ether as by-products), were followed up for mortality from 1940 to the end of 1988. Mean duration of assignment was 5.9 years, and mean duration of follow-up was 36.5 years	Occupational records	8	SMR* = 492(158–1,140) for workers exposed to ethylene chlorohydrin
Asp et al. [45], USA	An 18-year follow-up for mortality and cancer morbidity in a cohort of 1,909 men who had started spraying chlorophenoxy herbicides (mixture of 2,4-dichlorophenoxyacetic acid [2,4-D] and 2,4,5-trichlorophenoxyacetic acid [2,4,5-T]) in 1955 through 1971	Questionnaire to subjects or next of kin	12	SMR = 73–12 for workers exposed to chlorophenoxy herbicides
Yassi et al. [54], Canada	A mortality study to December 1989 of a cohort of 2,222 males employed between 1947 and 1975 at a transformer manufacturing plant in Canada where there had been extensive use of transformer fluid, some containing polychlorinated biphenyls (PCBs)	Industry records	11	SMR = 292–764* for workers exposed to PCBs
Wong et al. [53], USA	A mortality study of 15,826 workers employed in the reinforced plastics and composites industry with exposures to styrene monomer and other chemicals for at least 6 months in 1948–1989	Occupational records	19	SMR = 113 for workers exposed to styrene monomer and other chemicals
Brown et al. [49], South Carolina, USA	A retrospective cohort mortality analysis of 3,022 workers from a South Carolina textile plant where chrysotile asbestos was the primary exposure	Records	15	SMR = 146 for workers exposed to chrysotile asbestos
Anttila et al. [44], Finland	A cohort of 2,050 male and 1,924 female workers monitored for occupational exposure to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane was followed up for cancer incidence in 1967–1992	Personal measurement, monitoring	12	SIR = 204* for after 10 years of exposure to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane

(continued)

Table 5.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95 % CI)*
Enterline et al. [50], England	A mortality study of 2,802 men who worked at a copper smelter for a year or more during the period 1940–1964 and who were followed up for deaths during the period 1941–1986. Estimates of exposure for the period 1977–1984 were added	Measurement from air and urine	14	SMR = 86 for workers worked at a copper smelter
Hansen and Olsen [52], Denmark	The risk for cancer morbidity in Denmark during 1970–1984 was estimated among men whose longest employment had been held since 1964, at least 10 years before diagnosis, in 265 companies in which exposure to formaldehyde was identified	Registry data	69	Standardized proportionate incidence ratio (SPIR) = 1.0 for workers exposed to formaldehyde
Baris et al. [47], Canada	A historical cohort mortality study was carried out on 21,744 workers who were employed in an electrical company in the province of Quebec between 1970 and 1988	The last job held by each study subject was coded. A job-exposure matrix (JEM) was used to estimate the exposure to 60 Hz electromagnetic fields (EMFs) and pulsed EMFs in this job	23	SMR = 76 exposed to EMFs
Gibbs et al. [51],	A mortality study of 3,211 cellulose fiber production workers who were on the payroll on or after January 1, 1970, and who had worked at a plant for 3 or more months were followed through December 31, 1989	Measurement records	3	SMR = 35–89 for cellulose fiber production workers
Boffetta et al. [48], Europe	A follow-up of cancer mortality for a cohort study of 22,002 workers employed in man-made vitreous fiber production industries from Denmark, Finland, Norway, Sweden, the United Kingdom, Germany, and Italy, from 1982 to 1990	Factory records	60	SMR = 120 for workers employed in man-made vitreous fiber production industries
Cocco et al. [57], Italy	A mortality study of 1,388 workers and laborers in production and maintenance departments was conducted in an Italian lead-smelting plant. The vital status of cohort members was determined from 1950 to 1992	Measurement from industrial hygiene survey	7	SMR = 99 for workers employed in lead-smelting plant
Cocco et al. [57], Italy	A PMR of 1,043 deaths among men who took part in an antimalarial campaign in Sardinia, Italy, from 1946 to 1950	Records	3	PMR = 55 for workers exposed to DDT
Kogevinas et al. [61], International	Cancer mortality in a historical cohort study of 21,863 male and female workers in 36 cohorts exposed to phenoxy herbicides, chlorophenols, and dioxins in 12 countries. Subjects were followed from 1939 to 1992	Job records, company exposure questionnaire	47	SMR = 94 for workers exposed to phenoxy herbicides, chlorophenols, and dioxins
Anttila et al. [56], Finland	Cancer incidence among 3,922 male and 1,379 female workers monitored for exposure to styrene, toluene, or xylene was followed after the first personal measurement comprised 66,500 person-years at risk over the period 1973–1992	Personal measurement, monitoring	5	SIR = 277 for those exposed to aromatic hydrocarbons for more than 10 years

Table 5.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95 % CI)*
Hooiveld et al. [59], Netherlands	A mortality study of 1,167 workers exposed to phenoxy herbicides, chlorophenols, and contaminants (2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and other polychlorinated dioxins and furans) between 1955 and 1985 were followed through 1991 in a chemical industry in the Netherlands	Industry records and questionnaire	4	SMR = 250 for workers exposed to phenoxy herbicides, chlorophenols, and contaminants
Sathiakumar et al. [63], USA	A retrospective follow-up study (1943–1991) was conducted of 15,649 men employed for at least 1 year at any of eight North American styrene-butadiene rubber plant	Occupational records	43	SMR = 82 for workers employed in styrene-butadiene rubber plant
Jarup et al. [60], Sweden	869 battery workers exposed to nickel hydroxide and cadmium oxide, employed at least 1 year between the years 1940 and 1980, were followed up until 1992. Incidence obtained from the Swedish Cancer Registry, vital status and cause of death obtained from the Swedish cause of death registry	Employment records, workplace measurement reports, and interviews with key informants in the factory	Death (male = 6; female = 1); incidence (male = 7)	SMR = 148 for males; SMR = 220 for females; SIR = 194 for male workers exposed to nickel hydroxide and cadmium oxide
Wiebelt et al. [64], Germany	A historical cohort included 6,830 German men from 11 plants who were exposed to toluene from 1960 to 1992 in three work areas with different exposure levels	Industry records	5	SMR = 94.3 for workers exposed to toluene
Rafnsson, et al. [62], Iceland	A cohort comprised 1,332 men and 426 women employed in the printing industry in Iceland according to a published union registry, then linked to the Cancer Registry	Industry records	Death (male = 3, female = 1)	SIR = 83 for male workers; SIR = 124 for female workers employed in printing industry
Alguacil et al. [55], Sweden	Historical cohort of 1,779,646 men and 1,101,669 women gainfully employed at the time on January 1, 1970, census and were still alive and over age 24 on January 1, 1971, followed up for 19 years until 1989	Occupational records from Swedish cancer environment register and census	4,420 men and 2,143 women	Women: educational methods advisors (RR = 2.6*); librarian, archivist, and curator (RR = 1.7*); motor vehicle or train driver (RR = 2.5*); typographer and lithographer (RR = 2.3*); purser, steward, and stewardess (RR = 5.2*); other housekeeping and related workers (RR = 2.9*); electrical, electronic, and related workers (RR = 1.7*); and glass, pottery, and tile workers (RR = 2.4*). Men: technical assistants (RR = 2.8*), traveling agents (RR = 1.6*), other metal processing workers (RR = 1.9*), baker and pastry cook (RR = 1.4*), docker and freight handler (RR = 1.6*), and waiters (RR = 2.1)

Cohort studies reported results on pancreatic cancer somewhere in the tables but not in the abstract or the title were not included in this table
*$P < 0.05$

the American Chemical Society between 1948 and 1967, Li et al. [12] reported a significantly higher proportion of deaths from pancreatic cancer among male chemists aged 20–64 years compared to professional men in general. In standardized mortality ratio (SMR) studies, Hanis et al. [11] reported an increased risk of pancreatic cancer (SMR = 152) among refinery and chemical plant workers. Bond et al. [18] reported an increased risk of pancreatic cancer (SMR = 233) among chemical workers. Wen et al. [25] reported an elevated risk among oil refinery workers (SMR = 167). Ott et al. [23] found an increased risk of pancreatic cancer associated with chemical manufacturing job. However, none of the results from the above studies were statistically significant. In a mortality study of chlorohydrin production workers, Benson and Teta [36]

Table 5.2 Case-control studies of occupational exposure and pancreatic cancer

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Results	Comments
Pickle et al. [70], Louisiana, USA, 1960–1975	876 death of pancreatic cancer	Death controls matched by age, race, sex, year of death, and parish of residence	Death certificate	Oil refining (OR = 2.1); paper processing (OR = 1.8)	
Lin and Kessler [67], USA	109 incident cases	109 cancer-free hospital controls	Personal interview	OR = 5.1* for men exposed to dry cleaning and gasoline for more than 10 years	Adjusted for smoking
Mack et al. [68], Los Angeles, USA, 1975–1981	490 cases representing working-age population	Equal number of neighborhood controls	Questionnaire directly from 124 pairs	No association	
Magnani et al. [69], UK	343 aged 18–54 male pancreatic cancer identified from 1959–1963 to 1965–1979 death certificates	Each case was assigned two controls who had died in the same year from other causes	Death certificate, JEM	Paper, printing, and publishing (OR = 2.2*); chemicals and allied industries (OR = 1.4); coal and petroleum products (OR = 1.8); food, drink, and tobacco (OR = 1.5);public administration and defense (OR = 1.6)	No confounding information available
Mallin et al. [72], Illinois, USA	2,444 pancreatic cancer deaths	3,198 noncancer death	Death certificates	OR = 3.7* for metal workers; OR = 4.2* for photoengravers and lithographers; OR = 5.3* for sales occupation; and OR = 3.8* for brickmasons and stonemasons	No confounding information available
Pietri et al. [71], France, 1982–1985	171 (105 men and 66 women) from 7 hospitals in Paris	317 controls matched for age at interview, sex, hospital, and interviewer	In-person interview	Workers in the textile industry (OR = 1.87), food industry (OR = 1.86)	Adjusted for smoking
Falk et al. [65], Louisiana, USA, 1979–1983	198 cases	209 hospital-based controls	Questionnaire	White-collar occupations showed consistent elevations in risk; risks for truck drivers (OR = 1.7) and those with long-term employment in machine repair or as mechanics were suggestive (OR = 2.5); risks were slightly elevated for long-term workers in the chemical processing industry (OR = 1.2)	Adjusted for smoking
Garabrant et al. [66], Philadelphia, USA, 1953–1988	28 cases from a mortality cohort in chemical plant	112 matched controls	Questionnaire from next of kin	Exposure to DDT associated with increased risk RR = 4.8*	Adjusted for smoking
Partanen et al. [80], Finland, 1984–1987	625 incident cases aged 40–74	1,700 cancer referents (stomach, colon, and rectum) matched on age	Job history obtained from next of kin	Elevated risk for stone mining (OR = 3.7), cement and building materials (OR = 11.1), pharmacists and sales associates in pharmacies (OR = 12.9), male wood machinists (OR = 4.1), male gardeners (OR6.7), female textile workers (OR = 5.4), and male transport inspectors and supervisors (OR = 9.4)	No confounding information available
Selenskas et al. [81], New Jersey, 1946–1988	28 male cases from a mortality cohort with potential exposure at plastics manufacturing and research and development facility	140 randomly selected controls	Job history obtained from work plant records	OR = 7.15* for male worker assigned to a work area that processed vinyl resins and polyethylene more than 16 years	Nested case-control study, no confounding information available

Table 5.2 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Results	Comments
Kauppinen et al. [77], Finland, 1984–1987	595 incident cases with a response rate of 47 %	1,622 community controls with a response rate of 50 %	Mailed questionnaire to next of kin, job-exposure matrix	Ionizing radiation (OR = 4.3*), nonchlorinated solvents (OR = 1.6–1.8), pesticides (OR = 1.7), inorganic dust containing crystalline silica (OR = 2.0*), heat stress (OR = 2.2), rubber chemicals including acrylonitrile (OR = 2.1)	Adjusted for smoking, all proxies
Mikoczy et al. [79], Sweden, 1900–1989	Nested case-control study, cases = 68 with 10 pancreatic cancer cases	178 matched controls from the cohort of 2,487 workers employed for at least 6 months during the period 1900–1989 in three Swedish leather tanneries	Industry records	OR = 7.2* for leather dust exposure	Adjusted for tobacco smoking
Bardin et al. [75], Michigan, USA	97 deceased cases from a cohort of 46,384 hourly employees who had worked at least 3 years prior to January 1, 1985, at three auto part manufacturing facilities	1,825 controls selected from the same cohort matched on race, sex, plant, and date of birth (±5 years)	Exposures were estimated for each unique plant, department, job, and calendar period in an exposure matrix	OR = 3.0* for those exposure to synthetic fluids in grinding operations with more than 1.4 mg/m^3 years of exposure	No confounding information available
Ji et al. [76], Shanghai, China, 1990–1993	451 incident cases with a response rate of 78.2 %, 37 % histologically confirmed	1,552 population controls with a response rate of 84.5 %	In-person interview, JEM	Men: electrician (OR = 7.5*); metal workers (OR = 2.1); toolmakers (OR = 3.4*); plumbers and welders (OR = 3.0*); glass manufactures, potters, painters, and construction workers (OR = 2.6*); exposure to electromagnetic fields (EMFs). Women: textile workers (OR = 1.4)	Adjusted for confounding factors
Kernan, et al. [78], 24 US states, 1984–1993	63,097 persons who died from pancreatic cancer in 24 US states	252,386 persons who died from causes other than cancer in the same period	Death certificate, JEM	Industries (i.e., printing and paper manufacturing; chemical, petroleum, and related processing; transport, communication and public service; medical and other health-related services) and occupations (i.e., managerial, administrative, and other professional occupations; technical occupations; and sales, clerical, and other administrative support occupations) associated with increased risk with OR = 1.1–1.2. Based on JEM, formaldehyde OR = 1.4 for high probabilities of exposure	No confounding information available

(continued)

Table 5.2 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Results	Comments
Alguacil et al. [73, 74], Spain, 1992–1995	185 incident cases with 164 included	264 hospital-based controls with 238 included	In-person interview	Men: significant increased risks for physical, chemistry, and engineering science technicians; nonsignificant risks for metal molders, sheet-metal workers, structural metal workers, welders, and related workers; painters and varnishers; machinery mechanics and fitters. Women: elevated risks for agricultural workers; textile and garment workers. Mutations in K-ras gene modified association with hydrocarbon solvents	Adjusted for smoking
Zhang et al. [82], Iowa, USA, 1985–1987	376 incident cases (202 males and 174 females) with a response rate of 88 %	2,434 population-based controls (1,601 males and 833 females) with response rates of 82 % (<65 years) and 79 % (≥65 years)	Self-administered questionnaire, 90.2 % of cases and 10 % of controls from proxies	Men: industries of chemicals and allied products (OR = 3.5*) and railroad transportation (OR = 4.1*); insurance sales occupations (OR = 5.5*) and railroad brake, signal, and switch operators (OR = 5.9*). Women: industries of furniture and home furnishing stores (OR = 5.5*); textile sewing machine operators and tenders(OR = 3.9*)	Adjusted for smoking, but too many proxies in cases
Santibanez et al. [83], Spain, 1995–1999	161 incident cases (95 cases histologically confirmed) with a response rate of 80.9 %	455 hospital-based controls with a response rate of 99.6 %	In-person interviews; 12 % of cases and 4 % of controls are proxies, JEM	Men: worked as miners, shot-firers, stone cutters, and carvers; machinery mechanics and fitters; building trades workers; motor vehicle drivers; and waiters. Women: office clerks and waiters. Occupational exposure to chlorinated hydrocarbon solvents (OR = 4.1*), synthetic polymer dust, ionizing radiation, suggestion risk for pesticides, diesel and gasoline engine exhaust, and hydrocarbon solvents	Adjusted for smoking

*$P < 0.05$

observed a statistically significantly elevated death due to pancreatic cancer (SMR = 492) in these workers who produced dichloromethane. An occupational mortality study in Washington State also indicated that chemists, chemical engineers, and chemical company workers experienced elevated proportional mortality rate (PMR) for pancreatic cancer [84].

A case-control study using the death certificates of 343 pancreatic cancer cases and 1,315 other-cause-of-death cases as controls observed an odds ratio (OR) of 1.4 for people working in the chemical and allied industries [69]. A hospital-based case-control study of 198 pancreatic cancer cases and 209 controls reported a slightly elevated risk (OR = 1.2) among long-term workers in a chemical processing industry [65]. One case-control study of 625 pancreatic cancer cases and 1,700 other cancer controls by Partanen et al. [80] reported a slightly reduced risk of pancreatic cancer associated with employment in the chemical and allied industries. In a high pancreatic cancer mortality region of Louisiana, 876 pancreatic cancer death records were matched to controls by age, race, sex, year of death, and parish of residence.

The study found a twofold OR for workers in the oil refining industries [70]. A population-based case-control study in Iowa by Zhang et al. [82] observed a statistically significantly increased risk of pancreatic cancer associated with industries of chemical and allied products (OR = 3.5).

It is biologically plausible that an increased risk of pancreatic cancer can be associated with working in chemical industries, since many chemical agents have been suggested as carcinogens, and some have been shown to increase the risk of pancreatic cancer. For example, a cohort study in Finland including 2,050 male and 1,924 female workers exposed to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane between 1967 and 1992 reported an increased risk of pancreatic cancer [44]. In a nested case-control study involving 28 pancreatic cancer deaths and 140 randomly selected controls, Selenskas et al. [81] observed an increased risk of pancreatic cancer associated with processing vinyl and polyethylene. Another nested case-control study by Garabrant et al. [66] involving 28 pancreatic cancer deaths and 112 matched controls reported that exposure to DDT was associated with an increased risk of pancreatic cancer. A population-based case-control study from Finland including 595 cases and 1,622 controls reported an elevated risk associated with occupational exposure to solvents (including aliphatic and aromatic hydrocarbons) [77]. A meta-analysis based on 20 populations reported an elevated risk of pancreatic cancer associated with occupational exposure to chlorinated hydrocarbon solvents (OR = 1.4; 95 % CI, 1.0, 1.8) [85].

Metal Manufacturing Industries

Elevated risks of pancreatic cancer have been reported to be associated with metal manufacturing industries by a number of studies. Milham [13] reported an increased mortality of pancreatic cancer in aluminum mill workers and in sheet-metal workers. Maruchi et al. [86] reviewed all cases diagnosed in bona fide residents of Olmsted County, Minnesota, from 1935 to 1974 and found an overrepresentation of metal workers among patients with pancreatic cancer. A PMR study in workers from an automobile factory composed of forge, foundry, and engine (machine and assembly) plants reported a statistically significant PMR of pancreatic cancer in the engine plant (PMR = 1.9) [24]. Another PMR study in a bearing plant also reported an increased risk of pancreatic cancer [32]. A death certificate mortality study in Illinois reported an elevated risk of pancreatic cancer among metal workers [72]. Acquavella et al. [35] examined a metal work cohort (n = 3,630) and found an excess in the mortality rate of pancreatic cancer. Ji et al. [76] reported an increased risk of pancreatic cancer among Chinese metal workers.

Studies have also investigated specific metals and metallic compounds in relation to pancreatic cancer. A study followed a group of Swedish battery workers exposed to nickel hydroxide and cadmium oxide and found an increased SIR and SMR for pancreatic cancer [60]. Rockette and Arena [16] followed a cohort of 21,829 workers with 5 or more years of employment in 14 aluminum reduction plants and found an elevated mortality for pancreatic cancer. A meta-analysis reported an excess in pancreatic cancer risk for nickel and nickel compounds and chromium and chromium compounds, but not for cadmium and cadmium compounds [85]. Individuals who work in metal manufacturing industries are exposed not only to different metals and metallic compounds but also to silica, lubricants, and chemical fumes [13]. It is possible that the elevated risk of pancreatic cancer associated with metal manufacturing industries could be the joint effect of multiple exposures.

Printing and Paper Manufacturing Industries

A PMR study of 1,401 commercial pressmen showed a significant PMR of pancreatic cancer among those employed 20 years or more [26]. Similar results were found in another study of printing pressmen [87]. The Third National Cancer Survey of 7,518 incident cancer cases found an elevated risk of pancreatic cancer associated with printing workers [14]. Wingren et al. [88] investigated mortality patterns among Swedish pulp and paper mill workers and reported excess risk of pancreatic cancer. The Louisiana study found twofold odds ratios for workers in the paper manufacturing industries [70]. Kernan et al. [78] reported a statistically significant increase in risk of pancreatic cancer associated with printing and paper manufacturing. In the Swedish population, Alguacil et al. [55] reported an elevated risk of pancreatic cancer among printing workers in women. While most studies reported an elevated risk, some studies did not observe an association with pancreatic cancer among those workers [62, 64]. It was suggested that exposures to solvents may be the most likely explanation for the association even though specific solvents were not identified [78].

Transport and Communication Industries

A prospective mortality study of cancer by the American Cancer Society involving 461,981 males, aged 40–79 years, with known smoking habits, reported an elevated risk of pancreatic cancer among truck drivers [28]. The Finland study, using other cancer patients as controls, reported an elevated risk of pancreatic cancer for male transport inspectors and

supervisors [80]. A hospital-based case-control study of 198 cases and 209 controls indicated an increased risk of pancreatic cancer for truck drivers [65]. A population-based study in Iowa reported that men who worked as heavy truck drivers, or as railroad brake, signal, and switch operators, had an increased risk of pancreatic cancer [82]. Workers in these occupations may be heavily exposed to motor exhaust, which contains polycyclic aromatic hydrocarbons (PAHs) that have been classified as human carcinogens [89]. An increased risk of pancreatic cancer associated with occupational exposure to PAHs has been suggested by a meta-analysis [85]. In addition to PAHs, individuals who worked in such industries may also be exposed to a variety of hazardous materials such as cutting oils, solvents, and metal dust, which have been suggested as risk factors [32, 85, 90].

Textile Industries

An occupational mortality study in Washington State reported a threefold increase in pancreatic cancer mortality in both men and women fabric workers under the age of 65 years [91]. A case-control study involving 625 pancreatic cancer cases and 1,700 other cancer controls in Finland found an increased risk among female textile workers [80]. A hospital-based case-control study in Spain observed an elevated risk among female textile and garment workers [73]. A hospital-based case-control study in France reported an increased risk of pancreatic cancer associated with textile industry [71]. A population-based case-control study in Iowa observed an increased risk of pancreatic cancer for female textile sewing machine operators and tenders, and the risk was greater with longer duration of employment in this occupation [82]. A population-based case-control study in Shanghai China also found an elevated risk among female textile workers [76]. It has been speculated that the excessive risk associated with textiles workers may be related to exposure to spinning oils or textile dusts [65].

Other Occupations and Industries

In addition to the abovementioned industries and occupations, which have been relatively well studied, an increased risk of pancreatic cancer has been linked to several other occupational settings. Results from these epidemiological studies, however, have been inconsistent. For example, an elevated risk in glass manufacturers, potters, and construction workers was suggested by some studies [71, 76]. It was unclear whether the association was due to exposures to silica dusts, asbestos, or other industrial dusts [65, 91]. Several solvent-related occupations or industries such as mechanics [31, 65, 73, 80], leather tanners or other leather industries [26, 37, 69, 71], and dry cleaners [67] have been associated with an increased risk of pancreatic cancer. Although farmers are typically exposed to pesticides which have been linked to an increased risk of pancreatic cancer [66, 92, 93], studies have not observed an increased risk of pancreatic cancer among farmers [78, 82]. Employment in furniture and home furnishing stores, medical and other health-related services, educational services, purchasing agents and buyers, supervisors of sales occupations, and insurance sales people have also been suggested to be associated with pancreatic cancer risk [78, 82]. In the absence of exposure to environmental hazards, lifestyle risk factors, such as lack of physical activity [94, 95], may play a role in the development of pancreatic cancer among these workers. It is also possible that exposure to infectious agents may play a role in the development of pancreatic cancer in these professions, since they require extensive personal contacts [82].

General Considerations

When interpreting results from occupational studies, it is important to take the "healthy worker effect" into consideration. Individuals able to sustain employment require at least a minimum level of health. As such, employed individuals tend to be healthier than the general population which includes both healthy and sick people. In studies comparing the incidence or mortality of occupational settings to those of the general population, true associations are likely to be underestimated.

Several other issues needed to be considered as well, when interpreting the occupational risk factors.

First, studies using occupation/industry titles to evaluate occupational exposures are likely to introduce exposure misclassification. Occupation/industry titles lack information on specific environmental hazardous agents. Workers classified under a specific occupational title or employed in a specific industry can be exposed to more than one agent. On the other hand, exposure to one agent can occur at multiple occupations or industries. The same occupational title may vary between different industries and may have very different exposure levels with regard to agents. A job-exposure matrix, linking information from both occupation and industry titles with specific exposure, would therefore minimize exposure misclassification.

Second, many occupational studies were based on deceased cases due to the clinically aggressive nature of the disease. This limits the quality and quantity of information available. As such, many previous studies have failed to control for potentially confounding factors such as smoking.

Third, given the rarity of pancreatic cancer, most available studies had limited power to detect small to moderate associations between certain occupational exposures and risk of pancreatic cancer; many studies were likely

unpublished as a result of not finding associations. For this reason, pooling of data from projects and replication of studies is very important.

Fourth, non-occupational risk factors may play a synergistic role with occupational factors in the risk of pancreatic cancer. Integration of both occupational and non-occupational risk factors would provide a more precise profile for prediction of an individual's risk. Finally, genetic susceptibility should also be considered when investigating occupational risk factors.

Non-occupational Risk Factors of Pancreatic Cancer

Smoking

A positive association between cigarette smoking and pancreatic cancer has been demonstrated by nearly all studies published since the 1960s. In a large meta-analysis, current smokers experienced a 70 % increased risk of pancreatic cancer compared to nonsmokers, and the risk showed clear dose-responses [96]. After cessation of cigarette smoking, the risk remains elevated for a minimum of 10 years [96]. A recent pooled analysis from the International Pancreatic Cancer Cohort Consortium further demonstrated that current smokers had significantly elevated risk of pancreatic cancer (OR = 1.77) compared to nonsmokers and the risk increased significantly with greater intensity, duration, and cumulative smoking dose [97]. This pooled analysis also indicated that risks after more than 15 years after smoking cessation were similar to that for never smokers [97], which highlights the importance of smoking cessation in disease prevention. Environmental tobacco smoke or passive smoke contains many of the same carcinogenetic chemicals as active smoke [98]. However, very few studies have investigated the association between passive smoke and pancreatic cancer risk. Results from the limited studies have failed to establish a positive association between passive smoke and pancreatic cancer [99–101].

Alcohol Consumption

An International Agency for Research on Cancer (IARC) Monograph working group in 2007 concluded that there was an inadequate evidence of the role of alcohol in pancreatic cancer in humans based on the results from most case-control studies and cohort studies [102]. However, a positive association between heavy alcohol consumption and pancreatic cancer has been suggested by studies which collected detailed information on alcohol consumption [103–114]. A recent pooled analysis using data from the International Pancreatic Cancer Case-Control Consortium further demonstrated that heavy drinkers experienced an increased risk of pancreatic cancer, whereas light to moderate alcohol consumption was not associated with an increased risk of pancreatic cancer [115].

Coffee Consumption

Since McMahon et al. [116] in 1981 reported a strong positive association between coffee consumption and risk of pancreatic cancer, numerous studies have subsequently investigated the relationship. However, most of the studies provided no evidence of an association between coffee consumption and pancreatic cancer risk [117]. A recent meta-analysis of cohort studies suggested an inverse association between coffee consumption and risk of pancreatic cancer [118].

Obesity

World Cancer Research Fund (WCRF) and American Institute of Cancer Research (AICR) panel concluded that there was a dose-response relationship between BMI and pancreatic cancer risk based on 23 cohort studies (RR = 1.14; 95 % CI, 1.07, 1.22 per 5 kg/m^2 increase in BMI) and 15 case-control studies (OR = 1.00; 95 % CI, 0.87, 1.15 per 5 kg/m^2 increase in BMI) [119]. A recent pooled analysis including 14 cohort studies reported that the risk of pancreatic cancer was 47 % greater among obese (BMI ≥30 kg/m^2) individuals compared to individuals with BMIs between 21 and 22.9 kg/m^2.

Nutrition

Although studies linking dietary intake and risk of pancreatic cancer have provided inconclusive results, a majority of the studies have suggested a reduced risk of pancreatic cancer associated with high fruit and vegetable intake [120–125]. Studies also suggested that certain nutrients found in fruits and vegetables (i.e., vitamin C, vitamin E, carotenoids, and other antioxidants) were associated with a reduced risk of pancreatic cancer [126–131]. High fat and red meat intake was associated with an increased risk of pancreatic cancer in some studies [122, 132–134] but not in others [123, 129, 135, 136].

Diabetes

Diabetes has been considered to be associated with the risk of pancreatic cancer. However, the causal relationship between diabetes and pancreatic cancer remains controversial. A recent meta-analysis including 35 cohort studies reported that diabetes was associated with 90 % increased risk of

pancreatic cancer and the risk was inversely correlated with the duration of diabetes with the highest risk found among patients diagnosed within less than 1 year [137].

Pancreatitis

Chronic pancreatitis is another established risk factor for pancreatic cancer. A six-country historical cohort study of 2,015 subjects with chronic pancreatitis reported 10-year and 20-year cumulative risks of pancreatic cancer were 1.8 and 4.0 %, respectively [138].

Clinical and Pathological Features of Pancreatic Cancer

Clinical Features

Pancreatic cancer is rare before the age of 40, and the median age at diagnosis is approximately age 70. Pancreatic cancer is difficult to detect and diagnose because of unnoticeable signs and symptoms at early stages as well as the insidious anatomic location of the pancreas. The presenting symptoms of pancreatic cancer depend on the location of the tumor within the gland. For tumors located in the head and body of the pancreas, symptoms are generally precipitated by compression of surrounding structures: the bile duct, the mesenteric and celiac nerves, the pancreatic duct, and the duodenum [139]. As a result, classic symptoms include unexplained weight loss, jaundice, and pain in the upper or middle abdomen and back. Other symptoms may include dyspepsia, nausea, vomiting, and fatigue. Pain is the most common presenting symptom in patients with pancreatic cancer. The pain may become gnawing as a result of tumor invasion of the celiac and mesenteric plexus. Besides abdominal pain, patients with pancreatic head cancer usually suffer from jaundice caused by biliary tract obstruction. Biliary obstruction can increase levels of conjugated bilirubin and alkaline phosphatase, and, as a result, the patient's urine darkens. In addition, the stool may be pale from decreased stercobilinogen in the bowel. More rarely, a pancreatic tumor may also cause duodenal obstruction or gastrointestinal bleeding. Obstruction of the pancreatic duct may lead to pancreatitis. Patients with pancreatic cancer often have dysglycemia. As such, pancreatic cancer should be considered in the differential diagnoses of acute pancreatitis and newly diagnosed diabetes.

Pathological Features

Pancreatic cancer tumors can arise anywhere in the pancreas with the most frequent focus being in the head, followed by the body and tail. Pancreatic cancer grossly produces a firm, poorly demarcated, multinodular mass with an intense desmoplastic reaction [140]. In addition to ductal adenocarcinomas, a number of histological types of pancreatic cancer have been recognized, such as adenosquamous carcinoma, colloid carcinoma, hepatoid carcinoma, medullary carcinoma, signet-ring cell carcinoma, undifferentiated carcinoma, and undifferentiated carcinoma with osteoclast-like giant cells. Pancreatic cancers are extremely infiltrative neoplasms. Vascular and perineural invasion are present in the majority of surgically resected cancers. Pancreatic cancer metastasizes most commonly to regional lymph nodes and the liver. Other frequent metastatic sites include the peritoneum, lungs, adrenals, and bones [140].

Molecular Markers

The most widely utilized tumor marker for pancreatic cancer in the clinic is cancer antigen (CA) 19-9. The serum marker CA 19-9 is useful in confirming the diagnosis in symptomatic patients and in predicting prognosis and recurrence after resection [141, 142]. However, it is not useful in screening asymptomatic patients because of the lack of sufficient sensitivity and specificity [139].

Global gene expression studies of pancreatic cancers have suggested several potential new serum markers for pancreatic cancer such as macrophage inhibitory cytokine 1 (MIC1) [143]. Elevated serum MIC1 antigen levels significantly outperformed CA 19-9 and other tumor markers in distinguishing patients with resectable pancreatic cancers from healthy controls [144]. In addition to MIC1, gene products of *osteopontin* [145], *tissue inhibitor of metalloproteinase-1* [146], and *mesothelin* genes [147] have also been suggested as potential novel tumor markers of pancreatic cancer.

Pancreatic juice, as a potential source of biomarkers of early-stage pancreatic cancer, has attracted significant interest [148, 149]. Because of its direct relationship to the ductal system of the pancreas, it would undoubtedly contain enriched fractions of tumor markers unadulterated by serum components [150]. However, pancreatic juice can only be obtained during an invasive endoscopic procedure, and as such, pancreatic juice-based biomarkers are not feasible for screening.

Carcinogenic Mechanisms

During the past two decades, the rapid accumulation of knowledge of the molecular biology of this disease has significantly advanced our understanding of pancreatic carcinogenesis. Like many other malignancies, pancreatic carcinogenesis involves multiple subsets of genes undergoing

genetic changes [151]. Pancreatic cancer develops from normal ductular epithelium through a sequential worsening of precursor lesions which can be identified through histology and genetic testing [152, 153]. Overexpression of *HER2/neu* and point mutations in the *K-ras* gene present in more than 90 % of pancreatic cancer cases at early stages of the disease [153–155]. The p16 tumor suppressor gene is inactivated in more than 80–90 % of pancreatic cancer cases at an intermediate stage [156]. The *P53* and *DPC4* genes are inactivated in about 50 % of pancreatic cancer cases and *BRCA2* in about 7–10 % at a relatively later stage [151, 157, 158].

Several genetic syndromes (i.e., hereditary pancreatitis, hereditary nonpolyposis colorectal cancer, ataxia-telangiectasia, Peutz-Jehers syndrome, familial breast cancer, and familial atypical multiple-mole melanoma) have been associated with pancreatic cancer risk [159]. However, the carriers of these genetic disorders in general populations are rare. It has been recognized that single-nucleotide polymorphisms (SNPs) in common and low-penetrance genes influence both the response and susceptibility to carcinogens and may play important roles in pancreatic carcinogenesis. Exogenous and endogenous carcinogens can alter gene expression, proliferation, or differentiation through the mechanisms including aberrant DNA methylation, the oxidative effect, impaired DNA repair pathways and activation of receptors, transcription factors, and cell cycle proteins [160]. While major advances have been made regarding understanding the interaction between environmental factors and genetic susceptibility to human cancers, the gene-environment interaction to pancreatic cancer has not yet been fully evaluated. There are currently several studies investigating genetic polymorphisms and risk of pancreatic cancer.

Genetic Susceptibility

Studies using candidate gene approaches have focused on the genes mainly in the following pathways: carcinogen metabolism [161–170], DNA repair [171–177], inflammatory response [178, 179], alcohol-metabolizing enzymes [180, 181], methylation [107, 182–184], and protease inhibitors [167, 185–187]. The associations between polymorphisms in metabolic genes (i.e., *GSTM1*, *GSTT1*, *CYP1A1*, *CYP1A2*, *NAT1 NAT2*, and *UGT1A7*) and risk of pancreatic cancer were generally null from a meta-analysis [153]. However, studies suggested that the combination of *GSTT1-null* and *GSTP1*-codon 105 Val variants significantly increased the risk for pancreatic cancer [170]. Individuals who were heavy smokers and carried *GSTT1*-null genotype significantly increased their risk of pancreatic cancer compared to nonsmokers with *GSTT1*-present genotype [165]. Heavy smokers with the *CYP1A2**1F(A-163C) C allele or *NAT1* rapid alleles experienced a significantly elevated risk of pancreatic cancer as compared with never smokers carrying non-at-risk alleles [168].

A case-control study conducted at the MD Anderson Cancer Center investigated genetic variants in glucose metabolism genes and risk of pancreatic cancer in 1,654 cases and 1,182 controls [188]. The study genotyped 26 SNPs of five glucose metabolism genes, *GCK*, *GFPT1*, *GPI*, *HK2*, and *OGT*, and found a significant association of *HK2* R844K GA/AA genotype with reduced pancreatic cancer risk (OR = 0.78). A significant interaction with diabetes was observed. The *HK2* R844K GA/AA genotype was associated with a reduced risk of pancreatic cancer among nondiabetic individuals (OR = 0.68) but with increased risk among diabetic patients (OR = 3.69). These risk associations remained statistically significant when the analysis was restricted to whites or after exclusion of recent-onset diabetes. No significant effect of other genes or significant interaction of genotype with other risk factors was observed.

Two studies from Japan examined polymorphisms in alcohol-metabolizing enzyme genes and risk of pancreatic cancer [180, 181]. Miyasaka et al. [180] reported that the risk of pancreatic cancer associated with smoking was enhanced in subjects with an inactive form of *ALDH2* in a male population. Kanda et al. [181] found that drinkers carrying both *ADH1B* His/His and *ALDH2* Lys + had significantly increased risk of pancreatic cancer as compared to nondrinkers with both *ADH1B* His/His and *ALDH2* Glu/Glu.

Li et al. [177] investigated nine SNPs of seven DNA repair genes (*LIG3*, *LIG4*, *OGG1*, *ATM*, *POLB*, *RAD54L*, and *RECQL*) and found SNPs in *ATM* and *LIG3* genes significantly associated with the risk of pancreatic cancer and suggested significant interactions between SNPs in *ATM* or *LIG4* genes and diabetes to pancreatic cancer. Several studies suggested that polymorphisms of *XRCC2* and *XPD* genes modified smoking-related pancreatic cancer [172, 173, 175]. Some studies also suggested potential gene-gene interactions within the same pathway (i.e., XRCC1 with APE1, XRCC1 with MGMT, OGG1 with XPC, XPA with ERCC2) [171] or cross different pathways (i.e., XRCC1 with GSTT1/GSTM1) [174] in relation to pancreatic cancer risk.

A case-control study from Mayo Clinic of 1,354 Caucasian pancreatic cancer patients and 1,189 healthy Caucasian controls investigated 1,538 SNPs in 102 inflammatory pathway genes [178]. After adjusting for known risk factors for pancreatic cancer, single SNP analysis revealed an association between four SNPs in *NOS1* and one in the *CD101* gene with pancreatic cancer risk. These results, however, were not replicated in other pancreatic cancer case-control and cohort populations. A population-based case-control study with 308 cases and 964 controls from San Francisco Bay Area suggested that proinflammatory gene polymorphisms in combination with proinflammatory conditions may influence the development of pancreatic cancer [179].

Suzuki et al. [107] investigated polymorphisms in *MTHFR*, *MTR*, *MTRR*, and *TS* genes and found that heavy drinkers carrying *MTHFR* 667 CC, *MTR* 2756 AA, or *MTRR* 66G allele had significantly increased risk of pancreatic cancer compared to nondrinkers, suggesting that folate-related enzyme polymorphisms modify the association between alcohol consumption and pancreatic cancer risk. Wang et al. [184] reported an increased risk of pancreatic cancer associated with *MTHFR* 677CT or TT genotypes compared to *MTHFR* CC genotype and with *TS* 3Rc/3RC genotype compared to *TS* 3Rg/3Rg genotype. This study also suggested an interaction between *MTHFR* C677T polymorphism and smoking and drinking. Similar interactions were also reported in another study [182].

Recently, genome-wide association (GWA) studies have identified common SNPs in four genomic regions (i.e., 9q34, 13q22.1, 1q32.1, and 5p15.33) that are associated with pancreatic cancer risk [189, 190]. Future studies are needed to investigate gene-environmental interactions with a broad spectrum of occupational and environmental factors in addition to smoking and alcohol consumption.

Conclusion

Although the overall incidence of pancreatic cancer is low in comparison to other cancers, this devastating disease is associated with a low rate of survival, often claiming the life of its victims within the first year. As a result of previous studies, a wide array of risk factors, from occupational to non-occupational, have been suggested as contributing factors. Some of these include smoking, excessive alcohol consumption, obesity, diabetes, chronic pancreatitis, and nutritional considerations, as well as complex genetic predispositions and interactions. Further studies and data pooling may help pinpoint these and other risks and ultimately lead to awareness and prevention programs.

In addition, delays in early diagnosis may contribute to poor prognosis. Misclassification of initial symptoms may be prevented and earlier diagnosis accomplished by the use of specific molecular markers. The identification and implementation of pancreatic tumors markers could ultimately prove to be an important diagnostic tool.

References

1. Garcea G, Dennison AR, Pattenden CJ, Neal CP, Sutton CD, Berry DP. Survival following curative resection for pancreatic ductal adenocarcinoma. A systematic review of the literature. JOP. 2008;9(2):99–132.
2. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975–2009 (Vintage 2009 Populations). Bethesda: National Cancer Institute. http://seer.cancer.gov/csr/1975_2009_pops09/. Based on Nov 2011 SEER data submission, posted to the SEER web site, Apr 2012.
3. David M, Lepage C, Jouve JL, et al. Management and prognosis of pancreatic cancer over a 30-year period. Br J Cancer. 2009;101(2):215–8.
4. Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. J Natl Cancer Inst. 2003;95(13):948–60.
5. Lowenfels AB, Maisonneuve P. Epidemiologic and etiologic factors of pancreatic cancer. Hematol Oncol Clin North Am. 2002;16(1):1–16.
6. Dunphy EP. Pancreatic cancer: a review and update. Clin J Oncol Nurs. 2008;12(5):735–41.
7. Pietri F, Clavel F. Occupational exposure and cancer of the pancreas: a review. Br J Ind Med. 1991;48(9):583–7.
8. Seilkop SK. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med. 2001;58(1):63–4.
9. Chiazze Jr L, Ference LD. Mortality among PVC-fabricating employees. Environ Health Perspect. 1981;41:137–43.
10. Decoufle P. Further analysis of cancer mortality patterns among workers exposed to cutting oil mists. J Natl Cancer Inst. 1978;61(4):1025–30.
11. Hanis NM, Holmes TM, Shallenberger G, Jones KE. Epidemiologic study of refinery and chemical plant workers. J Occup Med. 1982;24(3):203–12.
12. Li FP, Fraumeni Jr JF, Mantel N, Miller RW. Cancer mortality among chemists. J Natl Cancer Inst. 1969;43(5):1159–64.
13. Milham Jr S. Cancer mortality pattern associated with exposure to metals. Ann N Y Acad Sci. 1976;271:243–9.
14. Williams RR, Stegens NL, Goldsmith JR. Associations of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. J Natl Cancer Inst. 1977;59(4):1147–85.
15. Howe GR, Fraser D, Lindsay J, Presnal B, Yu SZ. Cancer mortality (1965-77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. J Natl Cancer Inst. 1983;70(6):1015–9.
16. Rockette HE, Arena VC. Mortality studies of aluminum reduction plant workers: potroom and carbon department. J Occup Med. 1983;25(7):549–57.
17. Acheson ED, Gardner MJ, Winter PD, Bennett C. Cancer in a factory using amosite asbestos. Int J Epidemiol. 1984;13(1):3–10.
18. Bond GG, Reeve GR, Ott MG, Waxweiler RJ. Mortality among a sample of chemical company employees. Am J Ind Med. 1985;7(2):109–21.
19. Decoufle P, Blattner WA, Blair A. Mortality among chemical workers exposed to benzene and other agents. Environ Res. 1983;30(1):16–25.
20. Elinder CG, Kjellstrom T, Hogstedt C, Andersson K, Spang G. Cancer mortality of cadmium workers. Br J Ind Med. 1985;42(10):651–5.
21. Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br J Cancer. 1985;52(2):259–70.
22. Milham Jr S. Mortality in workers exposed to electromagnetic fields. Environ Health Perspect. 1985;62:297–300.
23. Ott MG, Carlo GL, Steinberg S, Bond GG. Mortality among employees engaged in chemical manufacturing and related activities. Am J Epidemiol. 1985;122(2):311–22.
24. Vena JE, Sultz HA, Fiedler RC, Barnes RE. Mortality of workers in an automobile engine and parts manufacturing complex. Br J Ind Med. 1985;42(2):85–93.
25. Wen CP, Tsai SP, Weiss NS, Gibson RL, Wong O, McClellan WA. Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. J Natl Cancer Inst. 1985;74(1):11–8.
26. Zoloth SR, Michaels DM, Villalbi JR, Lacher M. Patterns of mortality among commercial pressmen. J Natl Cancer Inst. 1986;76(6):1047–51.
27. Coggon D, Pannett B, Winter PD, Acheson ED, Bonsall J. Mortality of workers exposed to 2 methyl-4 chlorophenoxyacetic acid. Scand J Work Environ Health. 1986;12(5):448–54.
28. Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. Am J Ind Med. 1988;14(4):403–15.

29. Brown DP. Mortality of workers exposed to polychlorinated biphenyls–an update. Arch Environ Health. 1987;42(6):333–9.
30. Enterline PE, Hartley J, Henderson V. Asbestos and cancer: a cohort followed up to death. Br J Ind Med. 1987;44(6):396–401.
31. Hansen ES. Mortality of auto mechanics. A ten-year follow-up. Scand J Work Environ Health. 1989;15(1):43–6.
32. Silverstein M, Park R, Marmor M, Maizlish N, Mirer F. Mortality among bearing plant workers exposed to metalworking fluids and abrasives. J Occup Med. 1988;30(9):706–14.
33. Smulevich VB, Fedotova IV, Filatova VS. Increasing evidence of the rise of cancer in workers exposed to vinylchloride. Br J Ind Med. 1988;45(2):93–7.
34. Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results. Br J Ind Med. 1987;44(6):365–81.
35. Acquavella J, Leet T, Johnson G. Occupational experience and mortality among a cohort of metal components manufacturing workers. Epidemiology. 1993;4(5):428–34.
36. Benson LO, Teta MJ. Mortality due to pancreatic and lymphopoietic cancers in chlorohydrin production workers. Br J Ind Med. 1993;50(8):710–6.
37. Costantini AS, Paci E, Miligi L, Buiatti E, Martelli C, Lenzi S. Cancer mortality among workers in the Tuscan tanning industry. Br J Ind Med. 1989;46(6):384–8.
38. Gardner MJ, Pannett B, Winter PD, Cruddas AM. A cohort study of workers exposed to formaldehyde in the British chemical industry: an update. Br J Ind Med. 1993;50(9):827–34.
39. Gustavsson P, Reuterwall C. Mortality and incidence of cancer among Swedish gas workers. Br J Ind Med. 1990;47(3):169–74.
40. Hearne FT, Pifer JW, Grose F. Absence of adverse mortality effects in workers exposed to methylene chloride: an update. J Occup Med. 1990;32(3):234–40.
41. Lanes SF, Rothman KJ, Dreyer NA, Soden KJ. Mortality update of cellulose fiber production workers. Scand J Work Environ Health. 1993;19(6):426–8.
42. Langard S, Andersen A, Ravnestad J. Incidence of cancer among ferrochromium and ferrosilicon workers: an extended observation period. Br J Ind Med. 1990;47(1):14–9.
43. McDonald JC, Liddell FD, Dufresne A, McDonald AD. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-88. Br J Ind Med. 1993;50(12):1073–81.
44. Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med. 1995;37(7):797–806.
45. Asp S, Riihimaki V, Hernberg S, Pukkala E. Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators: an 18-year prospective follow-up. Am J Ind Med. 1994;26(2):243–53.
46. Axelson O, Selden A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. J Occup Med. 1994;36(5):556–62.
47. Baris D, Armstrong BG, Deadman J, Theriault G. A mortality study of electrical utility workers in Quebec. Occup Environ Med. 1996;53(1):25–31.
48. Boffetta P, Saracci R, Andersen A, et al. Cancer mortality among man-made vitreous fiber production workers. Epidemiology. 1997;8(3):259–68.
49. Brown DP, Dement JM, Okun A. Mortality patterns among female and male chrysotile asbestos textile workers. J Occup Med. 1994;36(8):882–8.
50. Enterline PE, Day R, Marsh GM. Cancers related to exposure to arsenic at a copper smelter. Occup Environ Med. 1995;52(1):28–32.
51. Gibbs GW, Amsel J, Soden K. A cohort mortality study of cellulose triacetate-fiber workers exposed to methylene chloride. J Occup Environ Med. 1996;38(7):693–7.
52. Hansen J, Olsen JH. Formaldehyde and cancer morbidity among male employees in Denmark. Cancer Causes Control. 1995;6(4):354–60.
53. Wong O, Trent LS, Whorton MD. An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. Occup Environ Med. 1994;51(6):386–96.
54. Yassi A, Tate R, Fish D. Cancer mortality in workers employed at a transformer manufacturing plant. Am J Ind Med. 1994;25(3):425–37.
55. Alguacil J, Pollan M, Gustavsson P. Occupations with increased risk of pancreatic cancer in the Swedish population. Occup Environ Med. 2003;60(8):570–6.
56. Anttila A, Pukkala E, Riala R, Sallmen M, Hemminki K. Cancer incidence among Finnish workers exposed to aromatic hydrocarbons. Int Arch Occup Environ Health. 1998;71(3):187–93.
57. Cocco P, Blair A, Congia P, Saba G, Ecca AR, Palmas C. Long-term health effects of the occupational exposure to DDT. A preliminary report. Ann N Y Acad Sci. 1997;837:246–56.
58. Cocco P, Hua F, Boffetta P, et al. Mortality of Italian lead smelter workers. Scand J Work Environ Health. 1997;23(1):15–23.
59. Hooiveld M, Heederik DJ, Kogevinas M, et al. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. Am J Epidemiol. 1998;147(9):891–901.
60. Jarup L, Bellander T, Hogstedt C, Spang G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occup Environ Med. 1998;55(11):755–9.
61. Kogevinas M, Becher H, Benn T, et al. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epidemiol. 1997;145(12):1061–75.
62. Rafnsson V. Incidence of cancer among bookbinders, printers, photoengravers, and typesetters. Occup Environ Med. 2001;58(8):523–7.
63. Sathiakumar N, Delzell E, Hovinga M, et al. Mortality from cancer and other causes of death among synthetic rubber workers. Occup Environ Med. 1998;55(4):230–5.
64. Wiebelt H, Becker N. Mortality in a cohort of toluene exposed employees (rotogravure printing plant workers). J Occup Environ Med. 1999;41(12):1134–9.
65. Falk RT, Pickle LW, Fontham ET, et al. Occupation and pancreatic cancer risk in Louisiana. Am J Ind Med. 1990;18(5):565–76.
66. Garabrant DH, Held J, Langholz B, Peters JM, Mack TM. DDT and related compounds and risk of pancreatic cancer. J Natl Cancer Inst. 1992;84(10):764–71.
67. Lin RS, Kessler II. A multifactorial model for pancreatic cancer in man. Epidemiologic evidence. JAMA. 1981;245(2):147–52.
68. Mack TM, Peters JM, Yu MC, Hanisch R, Wright WE, Henderson BE. Pancreas cancer is unrelated to the workplace in Los Angeles. Am J Ind Med. 1985;7(3):253–66.
69. Magnani C, Coggon D, Osmond C, Acheson ED. Occupation and five cancers: a case-control study using death certificates. Br J Ind Med. 1987;44(11):769–76.
70. Pickle LW, Gottlieb MS. Pancreatic cancer mortality in Louisiana. Am J Public Health. 1980;70(3):256–9.
71. Pietri F, Clavel F, Auquier A, Flamant R. Occupational risk factors for cancer of the pancreas: a case-control study. Br J Ind Med. 1990;47(6):425–8.
72. Mallin K, Rubin M, Joo E. Occupational cancer mortality in Illinois white and black males, 1979–1984, for seven cancer sites. Am J Ind Med. 1989;15(6):699–717.
73. Alguacil J, Porta M, Benavides FG, et al. Occupation and pancreatic cancer in Spain: a case-control study based on job titles. PANKRAS II Study Group. Int J Epidemiol. 2000;29(6):1004–13.
74. Alguacil J, Porta M, Malats N, et al. Occupational exposure to organic solvents and K-ras mutations in exocrine pancreatic cancer. Carcinogenesis. 2002;23(1):101–6.
75. Bardin JA, Eisen EA, Tolbert PE, et al. Mortality studies of machining fluid exposure in the automobile industry. V: a case-control study of pancreatic cancer. Am J Ind Med. 1997;32(3):240–7.

76. Ji BT, Silverman DT, Dosemeci M, Dai Q, Gao YT, Blair A. Occupation and pancreatic cancer risk in Shanghai, China. Am J Ind Med. 1999;35(1):76–81.
77. Kauppinen T, Partanen T, Degerth R, Ojajarvi A. Pancreatic cancer and occupational exposures. Epidemiology. 1995;6(5):498–502.
78. Kernan GJ, Ji BT, Dosemeci M, Silverman DT, Balbus J, Zahm SH. Occupational risk factors for pancreatic cancer: a case-control study based on death certificates from 24 U.S. states. Am J Ind Med. 1999;36(2):260–70.
79. Mikoczy Z, Schutz A, Stromberg U, Hagmar L. Cancer incidence and specific occupational exposures in the Swedish leather tanning industry: a cohort based case-control study. Occup Environ Med. 1996;53(7):463–7.
80. Partanen T, Kauppinen T, Degerth R, et al. Pancreatic cancer in industrial branches and occupations in Finland. Am J Ind Med. 1994;25(6):851–66.
81. Selenskas S, Teta MJ, Vitale JN. Pancreatic cancer among workers processing synthetic resins. Am J Ind Med. 1995;28(3):385–98.
82. Zhang Y, Cantor KP, Lynch CF, Zhu Y, Zheng T. Occupation and risk of pancreatic cancer: a population-based case-control study in Iowa. J Occup Environ Med. 2005;47(4):392–8.
83. Santibanez M, Vioque J, Alguacil J, et al. Occupational exposures and risk of pancreatic cancer. Eur J Epidemiol. 2010;25(10):721–30.
84. Milham S. Occupational mortality in Washington State, 1950–1989. Cincinnati, DHHS (NIOSH) publication No. 96–133, 1997, p. 56.
85. Ojajarvi IA, Partanen TJ, Ahlbom A, et al. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med. 2000;57(5):316–24.
86. Maruchi N, Brian D, Ludwig J, Elveback LR, Kurland LT. Cancer of the pancreas in Olmsted County, Minnesota, 1935–1974. Mayo Clin Proc. 1979;54(4):245–9.
87. Lloyd JW, Decoufle P, Salvin LG. Unusual mortality experience of printing pressmen. J Occup Med. 1977;19(8):543–50.
88. Wingren G, Persson B, Thoren K, Axelson O. Mortality pattern among pulp and paper mill workers in Sweden: a case-referent study. Am J Ind Med. 1991;20(6):769–74.
89. Mastrangelo G, Fadda E, Marzia V. Polycyclic aromatic hydrocarbons and cancer in man. Environ Health Perspect. 1996;104(11):1166–70.
90. Calvert GM, Ward E, Schnorr TM, Fine LJ. Cancer risks among workers exposed to metalworking fluids: a systematic review. Am J Ind Med. 1998;33(3):282–92.
91. Milham S. Occupational mortality in Washington State, 1950–1979. Washington, DC: US NIOSH publication No 83–116; 1983.
92. Cantor KP, Silberman W. Mortality among aerial pesticide applicators and flight instructors: follow-up from 1965–1988. Am J Ind Med. 1999;36(2):239–47.
93. Porta M, Malats N, Jariod M, et al. Serum concentrations of organochlorine compounds and K-ras mutations in exocrine pancreatic cancer. PANKRAS II Study Group. Lancet. 1999;354(9196): 2125–9.
94. Hanley AJ, Johnson KC, Villeneuve PJ, Mao Y. Physical activity, anthropometric factors and risk of pancreatic cancer: results from the Canadian enhanced cancer surveillance system. Int J Cancer. 2001;94(1):140–7.
95. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). Cancer Causes Control. 2002;13(5):417–26.
96. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg. 2008;393(4):535–45.
97. Lynch SM, Vrieling A, Lubin JH, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol. 2009;170(4):403–13.
98. Brownson RC, Figgs LW, Caisley LE. Epidemiology of environmental tobacco smoke exposure. Oncogene. 2002;21(48):7341–8.
99. Gallicchio L, Kouzis A, Genkinger JM, et al. Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. Prev Med. 2006;42(3):200–5.
100. Villeneuve PJ, Johnson KC, Mao Y, Hanley AJ. Environmental tobacco smoke and the risk of pancreatic cancer: findings from a Canadian population-based case-control study. Can J Public Health. 2004;95(1):32–7.
101. Tranah GJ, Holly EA, Wang F, Bracci PM. Cigarette, cigar and pipe smoking, passive smoke exposure, and risk of pancreatic cancer: a population-based study in the San Francisco Bay Area. BMC Cancer. 2011;11:138.
102. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, vol. 96. Lyon: International Agency for Research on Cancer; 2010. Alcohol consumption and ethyl carbamate.
103. Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni Jr JF. Lifestyle risk factors for pancreatic cancer in Louisiana: a case-control study. Am J Epidemiol. 1988;128(2):324–36.
104. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. Int J Cancer. 1989;43(3):415–21.
105. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. Am J Public Health. 1989;79(8):1016–9.
106. Hassan MM, Bondy ML, Wolff RA, et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol. 2007; 102(12):2696–707.
107. Suzuki T, Matsuo K, Sawaki A, et al. Alcohol drinking and one-carbon metabolism-related gene polymorphisms on pancreatic cancer risk. Cancer Epidemiol Biomarkers Prev. 2008;17(10):2742–7.
108. Talamini R, Polesel J, Gallus S, et al. Tobacco smoking, alcohol consumption and pancreatic cancer risk: a case-control study in Italy. Eur J Cancer. 2010;46(2):370–6.
109. Heuch I, Kvale G, Jacobsen BK, Bjelke E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br J Cancer. 1983; 48(5):637–43.
110. Zheng W, McLaughlin JK, Gridley G, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer Causes Control. 1993;4(5):477–82.
111. Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev. 1997;6(12):1081–6.
112. Heinen MM, Verhage BA, Ambergen TA, Goldbohm RA, van den Brandt PA. Alcohol consumption and risk of pancreatic cancer in the Netherlands cohort study. Am J Epidemiol. 2009;169(10): 1233–42.
113. Jiao L, Silverman DT, Schairer C, et al. Alcohol use and risk of pancreatic cancer: the NIH-AARP diet and health study. Am J Epidemiol. 2009;169(9):1043–51.
114. Silverman DT, Brown LM, Hoover RN, et al. Alcohol and pancreatic cancer in blacks and whites in the United States. Cancer Res. 1995;55(21):4899–905.
115. Lucenteforte E, La Vecchia C, Silverman D, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012; 23(2):374–82.
116. MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G. Coffee and cancer of the pancreas. N Engl J Med. 1981;304(11):630–3.
117. Turati F, Galeone C, Talamini R, et al. Coffee, decaffeinated coffee, tea, and pancreatic cancer risk: a pooled-analysis of two Italian case-control studies. Eur J Cancer Prev. 2011;20(4):287–92.
118. Dong J, Zou J, Yu XF. Coffee drinking and pancreatic cancer risk: a meta-analysis of cohort studies. World J Gastroenterol. 2011;17(9):1204–10.
119. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of

cancer: a global perspective. Washington, DC: AICR; 2007. p. 211–42.
120. Mills PK, Beeson WL, Abbey DE, Fraser GE, Phillips RL. Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. Cancer. 1988;61(12):2578–85.
121. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. Int J Cancer. 1994;58(1):46–9.
122. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. Am J Epidemiol. 2002;155(9):783–92.
123. Silverman DT, Swanson CA, Gridley G, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. J Natl Cancer Inst. 1998;90(22):1710–9.
124. Nkondjock A, Krewski D, Johnson KC, Ghadirian P. Dietary patterns and risk of pancreatic cancer. Int J Cancer. 2005;114(5): 817–23.
125. Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. Cancer Epidemiol Biomarkers Prev. 2005;14(9):2093–7.
126. Stolzenberg-Solomon RZ, Albanes D, Nieto FJ, et al. Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers. J Natl Cancer Inst. 1999;91(6):535–41.
127. Howe GR, Ghadirian P, Bueno de Mesquita HB, et al. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. Int J Cancer. 1992;51(3): 365–72.
128. Zatonski W, Przewozniak K, Howe GR, Maisonneuve P, Walker AM, Boyle P. Nutritional factors and pancreatic cancer: a case-control study from south-west Poland. Int J Cancer. 1991;48(3):390–4.
129. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. Nutrients and pancreatic cancer: a population-based case-control study. Cancer Causes Control. 1991;2(5):291–7.
130. Nkondjock A, Ghadirian P, Johnson KC, Krewski D. Dietary intake of lycopene is associated with reduced pancreatic cancer risk. J Nutr. 2005;135(3):592–7.
131. Gong Z, Holly EA, Wang F, Chan JM, Bracci PM. Intake of fatty acids and antioxidants and pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. Int J Cancer. 2010;127(8):1893–904.
132. Larsson SC, Hakanson N, Permert J, Wolk A. Meat, fish, poultry and egg consumption in relation to risk of pancreatic cancer: a prospective study. Int J Cancer. 2006;118(11):2866–70.
133. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. J Natl Cancer Inst. 2005;97(19):1458–65.
134. Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. Cancer Causes Control. 2007;18(10):1153–67.
135. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. Am J Epidemiol. 2003;157(12):1115–25.
136. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control. 2000;11(10):915–23.
137. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer. 2011;47:1928–37.
138. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med. 1993;328(20):1433–7.
139. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. Am Fam Physician. 2006;73(3):485–92.
140. Lauwers GY, Mino-Kenudson M, Rubin R. The pancreas. In: Rubin R, Strayer D, editors. Rubin's pathology: clinicopathologic foundations of medicine. 5th ed. Baltimore: Wolters Kluwer/ Lippincott Williams& Wilkins; 2008.
141. Malesci A, Montorsi M, Mariani A, et al. Clinical utility of the serum CA 19-9 test for diagnosing pancreatic carcinoma in symptomatic patients: a prospective study. Pancreas. 1992;7(4): 497–502.
142. Montgomery RC, Hoffman JP, Riley LB, Rogatko A, Ridge JA, Eisenberg BL. Prediction of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas. Ann Surg Oncol. 1997;4(7):551–6.
143. Koopmann J, Buckhaults P, Brown DA, et al. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other periampullary cancers. Clin Cancer Res. 2004;10(7):2386–92.
144. Koopmann J, Rosenzweig CN, Zhang Z, et al. Serum markers in patients with resectable pancreatic adenocarcinoma: macrophage inhibitory cytokine 1 versus CA19-9. Clin Cancer Res. 2006;12(2):442–6.
145. Koopmann J, Fedarko NS, Jain A, et al. Evaluation of osteopontin as biomarker for pancreatic adenocarcinoma. Cancer Epidemiol Biomarkers Prev. 2004;13(3):487–91.
146. Zhou W, Sokoll LJ, Bruzek DJ, et al. Identifying markers for pancreatic cancer by gene expression analysis. Cancer Epidemiol Biomarkers Prev. 1998;7(2):109–12.
147. Argani P, Iacobuzio-Donahue C, Ryu B, et al. Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by Serial Analysis of Gene Expression (SAGE). Clin Cancer Res. 2001;7(12):3862–8.
148. Chen R, Pan S, Cooke K, et al. Comparison of pancreas juice proteins from cancer versus pancreatitis using quantitative proteomic analysis. Pancreas. 2007;34(1):70–9.
149. Gronborg M, Bunkenborg J, Kristiansen TZ, et al. Comprehensive proteomic analysis of human pancreatic juice. J Proteome Res. 2004;3(5):1042–55.
150. Rosty C, Goggins M. Early detection of pancreatic carcinoma. Hematol Oncol Clin North Am. 2002;16(1):37–52.
151. Hruban RH, Goggins M, Parsons J, Kern SE. Progression model for pancreatic cancer. Clin Cancer Res. 2000;6(8):2969–72.
152. Wilentz RE, Iacobuzio-Donahue CA, Argani P, et al. Loss of expression of Dpc4 in pancreatic intraepithelial neoplasia: evidence that DPC4 inactivation occurs late in neoplastic progression. Cancer Res. 2000;60(7):2002–6.
153. Mazaki T, Masuda H, Takayama T. Polymorphisms and pancreatic cancer risk: a meta-analysis. Eur J Cancer Prev. 2011;20:169–83.
154. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell. 1988;53(4):549–54.
155. Aspinall RJ, Lemoine NR. Gene therapy for pancreatic and biliary malignancies. Ann Oncol. 1999;10 Suppl 4:188–92.
156. Schutte M, Hruban RH, Geradts J, et al. Abrogation of the Rb/p16 tumor-suppressive pathway in virtually all pancreatic carcinomas. Cancer Res. 1997;57(15):3126–30.
157. Cowgill SM, Muscarella P. The genetics of pancreatic cancer. Am J Surg. 2003;186(3):279–86.
158. Sohn TA, Yeo CJ. The molecular genetics of pancreatic ductal carcinoma: a review. Surg Oncol. 2000;9(3):95–101.
159. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol. 2006;20(2): 197–209.
160. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet. 2004;363(9414):1049–57.
161. Jiao L, Bondy ML, Hassan MM, et al. Glutathione S-transferase gene polymorphisms and risk and survival of pancreatic cancer. Cancer. 2007;109(5):840–8.

162. Lee HC, Yoon YB, Kim CY. Association between genetic polymorphisms of the cytochromes P-450 (1A1, 2D6, and 2E1) and the susceptibility to pancreatic cancer. Korean J Intern Med. 1997;12(2):128–36.
163. Bartsch H, Malaveille C, Lowenfels AB, Maisonneuve P, Hautefeuille A, Boyle P. Genetic polymorphism of N-acetyltransferases, glutathione S-transferase M1 and NAD(P)H:quinone oxidoreductase in relation to malignant and benign pancreatic disease risk. The International Pancreatic Disease Study Group. Eur J Cancer Prev. 1998;7(3):215–23.
164. Liu G, Ghadirian P, Vesprini D, et al. Polymorphisms in GSTM1, GSTT1 and CYP1A1 and risk of pancreatic adenocarcinoma. Br J Cancer. 2000;82(10):1646–9.
165. Duell EJ, Holly EA, Bracci PM, Liu M, Wiencke JK, Kelsey KT. A population-based, case-control study of polymorphisms in carcinogen-metabolizing genes, smoking, and pancreatic adenocarcinoma risk. J Natl Cancer Inst. 2002;94(4):297–306.
166. Ockenga J, Vogel A, Teich N, Keim V, Manns MP, Strassburg CP. UDP glucuronosyltransferase (UGT1A7) gene polymorphisms increase the risk of chronic pancreatitis and pancreatic cancer. Gastroenterology. 2003;124(7):1802–8.
167. Piepoli A, Gentile A, Valvano MR, et al. Lack of association between UGT1A7, UGT1A9, ARP, SPINK1 and CFTR gene polymorphisms and pancreatic cancer in Italian patients. World J Gastroenterol. 2006;12(39):6343–8.
168. Li D, Jiao L, Li Y, et al. Polymorphisms of cytochrome P4501A2 and N-acetyltransferase genes, smoking, and risk of pancreatic cancer. Carcinogenesis. 2006;27(1):103–11.
169. Verlaan M, Drenth JP, Truninger K, et al. Polymorphisms of UDP-glucuronosyltransferase 1A7 are not involved in pancreatic diseases. J Med Genet. 2005;42(10):e62.
170. Vrana D, Pikhart H, Mohelnikova-Duchonova B, et al. The association between glutathione S-transferase gene polymorphisms and pancreatic cancer in a central European Slavonic population. Mutat Res. 2009;680(1–2):78–81.
171. Jiao L, Bondy ML, Hassan MM, et al. Selected polymorphisms of DNA repair genes and risk of pancreatic cancer. Cancer Detect Prev. 2006;30(3):284–91.
172. Jiao L, Hassan MM, Bondy ML, et al. XRCC2 and XRCC3 gene polymorphism and risk of pancreatic cancer. Am J Gastroenterol. 2008;103(2):360–7.
173. Jiao L, Hassan MM, Bondy ML, Abbruzzese JL, Evans DB, Li D. The XPD Asp312Asn and Lys751Gln polymorphisms, corresponding haplotype, and pancreatic cancer risk. Cancer Lett. 2007;245(1–2):61–8.
174. Duell EJ, Holly EA, Bracci PM, Wiencke JK, Kelsey KT. A population-based study of the Arg399Gln polymorphism in X-ray repair cross- complementing group 1 (XRCC1) and risk of pancreatic adenocarcinoma. Cancer Res. 2002;62(16):4630–6.
175. McWilliams RR, Bamlet WR, Cunningham JM, et al. Polymorphisms in DNA repair genes, smoking, and pancreatic adenocarcinoma risk. Cancer Res. 2008;68(12):4928–35.
176. Wang L, Lin DX, Lu XH, Miao XP, Li H. Polymorphisms of the DNA repair genes XRCC1 and XPC: relationship to pancreatic cancer risk. Wei Sheng Yan Jiu. 2006;35(5):534–6.
177. Li D, Suzuki H, Liu B, et al. DNA repair gene polymorphisms and risk of pancreatic cancer. Clin Cancer Res. 2009;15(2):740–6.
178. Reid-Lombardo KM, Fridley BL, Bamlet WR, Cunningham JM, Sarr MG, Petersen GM. Inflammation-related gene variants as risk factors for pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2011;20(6):1251–4.
179. Duell EJ, Casella DP, Burk RD, Kelsey KT, Holly EA. Inflammation, genetic polymorphisms in proinflammatory genes TNF-A, RANTES, and CCR5, and risk of pancreatic adenocarcinoma. Cancer Epidemiol Biomarkers Prev. 2006;15(4):726–31.
180. Miyasaka K, Kawanami T, Shimokata H, Ohta S, Funakoshi A. Inactive aldehyde dehydrogenase-2 increased the risk of pancreatic cancer among smokers in a Japanese male population. Pancreas. 2005;30(2):95–8.
181. Kanda J, Matsuo K, Suzuki T, et al. Impact of alcohol consumption with polymorphisms in alcohol-metabolizing enzymes on pancreatic cancer risk in Japanese. Cancer Sci. 2009;100(2):296–302.
182. Li D, Ahmed M, Li Y, et al. 5,10-Methylenetetrahydrofolate reductase polymorphisms and the risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2005;14(6):1470–6.
183. Matsubayashi H, Skinner HG, Iacobuzio-Donahue C, et al. Pancreaticobiliary cancers with deficient methylenetetrahydrofolate reductase genotypes. Clin Gastroenterol Hepatol. 2005;3(8):752–60.
184. Wang L, Miao X, Tan W, et al. Genetic polymorphisms in methylenetetrahydrofolate reductase and thymidylate synthase and risk of pancreatic cancer. Clin Gastroenterol Hepatol. 2005;3(8):743–51.
185. Matsubayashi H, Fukushima N, Sato N, et al. Polymorphisms of SPINK1 N34S and CFTR in patients with sporadic and familial pancreatic cancer. Cancer Biol Ther. 2003;2(6):652–5.
186. Lempinen M, Paju A, Kemppainen E, et al. Mutations N34S and P55S of the SPINK1 gene in patients with chronic pancreatitis or pancreatic cancer and in healthy subjects: a report from Finland. Scand J Gastroenterol. 2005;40(2):225–30.
187. Teich N, Schulz HU, Witt H, Bohmig M, Keim V. N34S, a pancreatitis associated SPINK1 mutation, is not associated with sporadic pancreatic cancer. Pancreatology. 2003;3(1):67–8.
188. Dong X, Li Y, Chang P, et al. Glucose metabolism gene variants modulate the risk of pancreatic cancer. Cancer Prev Res (Phila). 2011;4(5):758–66.
189. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet. 2009;41(9):986–90.
190. Petersen GM, Amundadottir L, Fuchs CS, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet. 2010;42(3):224–8.

Cancers of the Intestine, Liver, and Biliary Tract

6

Paolo Boffetta, Doriane A. Gouas, André Nogueira da Costa, Behnoush Abedi-Ardekani, and Pierre Hainaut

Keywords
Colorectal cancer • Small intestinal cancer • Liver cancer • Hepatocellular carcinoma • Cholangiocarcinoma • Ulcerative colitis • Crohn's disease • Asbestos • Hepatic angiosarcoma • Vinyl chloride • Hepatitis B virus (HBV) • Hepatitis C virus (HCV)

Introduction

This chapter reviews the occupational risk factors of cancers of the intestine, comprising the small intestine, the colon, and the rectum, and of cancers of the liver and the biliary tract. In addition, the general epidemiology of these neoplasms is reviewed, to put the – rather limited – data on occupational risk factors in a broader context. Finally, in the case of primary liver cancer, a review of molecular and genetic mechanisms is included, to reflect the increasing knowledge of these aspects of an important disease, which eventually might have implications for prevention of occupational-related cases.

Cancer of the Intestine

Cancer of the intestine is the most frequent human neoplasm in nonsmokers of both sexes combined, and its rates are high in particular in developed countries. Most cancers of the intestine occur in the large intestines, while cancer of the small intestine is rare. Of colorectal cancers, approximately two thirds originate from the colon and one third from the rectum and the rectosigmoid junction. Most cancers of the intestine are of adenocarcinoma type, that is, originating from the glandular cells. Other histological types include neuroendocrine tumors, sarcomas, and lymphomas.

When taken together, cancers of the colon and rectum accounted in 2012 for an estimated 1,360,000 new cases and 694,000 deaths worldwide [1]. They represent the third most frequent malignant disease in terms of incidence and the fourth for mortality.

Cancer of the Small Intestine

Age-standardized incidence rates of small intestinal cancer are in most populations below one case per 100,000 persons in both genders. The neoplasm is more common in men than in women, with a ratio in the order of 1.5–3. Its occurrence is correlated with the incidence of colon cancer. Adenocarcinomas account for approximately 50 % of neoplasms of the small intestine. They originate mainly in the duodenum and proximal jejunum and are preceded by formation of adenoma. Various hereditary syndromes such as familial adenomatous polyposis and Peutz-Jeghers syndrome are characterized by multiple hamartomatous adenomas of the small intestine and, to a less extent, of the colon: these patients carry an increased risk of adenocarcinoma of the small intestine. Similarly, patients with Crohn's disease have a tenfold increased risk of small intestine adenocarcinoma [2]. Malignant lymphomas represent about one fourth of neoplasms of the small intestine. Patients with celiac sprue are at increased risk of T-cell lymphomas. Most B- cell lymphomas of the intestine are thought to arise from the

P. Boffetta, MD, MPH (✉)
Institute for Translational Epidemiology,
Icahn School of Medicine at Mount Sinai,
One Gustave L. Levy Place, New York, NY 10029, USA
e-mail: paolo.boffetta@mssm.edu

D.A. Gouas, MS • A.N. da Costa, PhD • B. Abedi-Ardekani, MD
P. Hainaut, PhD
Molecular Carcinogenesis Group, International Agency for Research on Cancer, Lyon, France

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_6,

mucosa-associated lymphoid tissue. Neuroendocrine tumors, which originate from the enteroendocrine (argentaffin) cells, are another important histological type. Limited data are available on the risk factors for this type of neoplasm. The evidence for a role of environmental factors, such as tobacco smoking, alcohol, and diet, in the genesis of small intestine neoplasms is at present inconclusive, although a role of overweight/obesity seems plausible. No occupational causes are known for cancer of the small intestine.

Cancer of the Colon

The highest rates of colon cancer (around or above 30/100,000 in men and 25/100,000 in women) are recorded in high-income countries, while rates in developing countries are lower (5–15/100,000) but they are increasing [3]. Studies of migrant populations have shown that the risk of colon cancer approaches that of the country of adoption within one generation; the incidence is higher in urban than in rural populations. The predominant histological type of malignant neoplasms of the colon is adenocarcinoma. This neoplasm is usually preceded by a polyp, or adenoma, less frequently by a small area of flat mucosa exhibiting various grades of dysplasia. The malignant potential of an adenoma is increased by a surface diameter greater than 1 cm, by villous (rather than tubular) organization, and by severe cellular dysplasia. Carriers of one adenoma larger than 1 cm have a 2–4 times increased risk of developing colon cancer; this risk is further doubled in carriers of multiple adenomas.

Migrant studies suggest that lifestyle factors are responsible for a substantial proportion of colorectal cancer, and the focus has mainly been on changes in diet; however, recent evidence from perspective studies provides only limited evidence in favor of a role of specific foods and nutrients [4]. An etiologic role of overweight/obesity and of limited physical activity seems established [4]. The strongest evidence concerns an increased risk for high intake of meat and of smoked, salted, or processed meat (and possibly other foods). A protective role of high intake of fruits and vegetables has been reported in several studies but is still open to discussion. Several studies have associated tobacco smoking with an increased risk of colonic adenoma. For colon cancer, a modest increased risk following prolonged heavy smoking has been shown in some of the largest prospective studies [5]. An increased risk in the order of 50 % moderate RR is observed for heavy alcohol drinking [6].

Use of aspirin and other anti-inflammatory drugs is likely to reduce the incidence of colorectal cancer [7]. Patients with ulcerative colitis and Crohn's disease are at increased risk of colon cancer [7]. Diabetes and cholecystectomy have been associated with a moderate (1.5–2-fold) increased risk of colon cancer [7]. Patients with one cancer of the colon have a double risk to develop a second primary tumor in the colon or rectum, and in women, an association has been shown also with cancers of the endometrium, ovary, and breast, possibly due to shared hormonal or dietary factors.

There are several rare hereditary conditions that are characterized by a very high incidence of colon cancer [7]. In particular, familial adenomatous polyposis, due to inherited or de novo mutation in the adenomatous polyposis colon gene on chromosome 5, is characterized by a very high number of colonic adenomas and a cumulative incidence of colon or rectal cancer close to 100 % by age 55. Other, rarer, diseases characterized by colonic polyposis, among other features, are Gardner's syndrome, Turcot syndrome, and juvenile polyposis. All these hereditary conditions, although very serious for the affected patients, account for no more than 1 % of colon cancers in the general population. In addition, two syndromes characterized by hereditary nonpolyposis colon cancer (Lynch syndrome), that is, with increased familial risk of colon cancer in the absence of adenomas, have also been described. Lynch syndrome I is characterized by increased risk of cancer of the proximal (right) colon and is due to inherited mutation in one of the genes involved in DNA mismatch repair. Patients of Lynch syndrome II have also an increased risk of extra-colonic neoplasms, mainly of the endometrium and the breast. As a whole, hereditary nonpolyposis colon cancer may account for a sizeable proportion of cases of colon cancer in Western populations. In addition to these hereditary conditions, first-degree relatives of colon cancer patients have a two- to threefold increased risk of developing a cancer of the colon or the rectum.

Cancer of the Rectum

The distribution of cancer of the rectum, including the rectosigmoid junction and the anus, parallels the distribution of colon cancer: the highest rates are recorded in Oceania, North America, and Central Europe and are in the order of 20/100,000 in men and 10/100,000 in women [3]. In most populations, incidence rates have been stable in recent decades. The male-to-female ratio is close to 2.

Most biological and epidemiological features of rectal cancer resemble those described for colon cancer, including the preneoplastic role of adenomas and nonpolypoid dysplastic mucosa, the presence of familial syndromes, the increased risk among patients with chronic inflammatory bowel diseases, and the likely protective role of dietary factors and physical activity. In addition, the association with heavy alcohol drinking appears to be stronger for rectal cancer than for colon cancer [6].

Asbestos

There is some evidence that inhalation exposure to asbestos increases the risk of colorectal cancer (most studies did not report results separately for the two organs). A two- to three-fold increased mortality was reported in early studies of insulator workers [8]: such strong relative risks have generally not been replicated, although several other cohorts of asbestos workers detected a small increase in incidence or mortality, with RR in the order of 1.2–1.8. Other cohort studies, however, failed to replicate these findings. Meta-analyses concluded in favor of a weak association [9]. A recent review by IARC [10] included 41 occupational cohorts and 13 case-control studies: the conclusion was that a positive association has been observed between asbestos exposure and colorectal cancer, but the evidence was not sufficiently strong to conclude for a causal association. There is some suggestion that the association might be stronger for colon cancer than for rectal cancer. Data on occupational exposure to asbestos in drinking water (e.g., workers settled in remote areas using asbestos tanks for drinking water storage) are sparse [11]; overall, they do not support the hypothesis of an increased risk from this route of exposure.

Other Occupational Agents

With the exception of asbestos, no occupational agents have consistently been reported in the literature to be associated with colorectal cancer. Occupations which may involve exposure to non-occupational risk factors such as excessive alcohol drinking (e.g., brewery workers [12]) and lack of physical activity (e.g., sedentary jobs [7]) have been reported to entail a risk of these cancers in some studies. In a systematic analysis of over 15 million residents from the Nordic countries, involving over 100,000 cases of colorectal cancer, there was limited variation in the incidence of these diseases among occupational groups in both men and women [13]. The occupation with the higher risk of colon cancer was chimney sweeping (SIR 1.52; 95 % CI 1.25–1.84, based on 104 exposed cases): a similar finding was reported in a Swedish cohort of chimney sweeps, which partially overlaps with the census analysis (SIR 1.36, 95 % CI 1.02–1.76).

Cancer of the Liver

Anatomy of the Liver

The liver is a pyramid-shaped organ divided into right and left lobes. Each lobe is made up of microscopic structural units called lobules, which are roughly hexagonal comprising rows of liver cells (hepatocytes) that radiate out from a central vein. Liver has a dual blood supply with the hepatic artery supplying oxygen-rich blood and the portal vein carrying nutrient-rich blood from intestine to liver. Hepatocytes are arranged in rows, the so-called hepatic cords, and lie adjacent to the delicate vascular channels called sinusoids. The sinusoids are lined by endothelial cells, which have fenestrated membranes. The space between hepatocytes and endothelial cells is called "space of Disse." Close contact between hepatocytes and blood facilitates metabolic exchanges occurring in the liver. On the other hand, liver secretes bile, which is transported by the fine branches of the intrahepatic biliary tract (biliary tree) and collects into the gallbladder, which secretes the stored bile into duodenum and facilitates fat digestion. The group of bile duct, branches of hepatic artery, and portal vein define the portal triad, a major landmark of liver histology.

Hepatocytes are the predominant cell type of the liver parenchyma and represent about 80 % of the liver mass. These cells are round and mononuclear and contain an abundance of cellular organelles such as smooth and rough endoplasmic reticulum and Golgi apparatus. These organelles support the specialized metabolic and secretory functions of hepatocytes. Hepatocytes also contain high numbers of mitochondria.

Pathology

Hepatocellular Carcinoma

The macroscopic appearance of advanced HCC varies with the presence of cirrhosis and the size of the tumor. Macroscopically, small HCC is defined as measuring less than 2 cm in diameter with vaguely nodular appearance, which is difficult to distinguish from surrounding cirrhotic liver. Tumors arising in a non-cirrhotic liver usually grow as single large mass, occasionally with satellite nodules (massive or expanding type), whereas those associated with cirrhosis often grow as multiple discrete nodules (nodular type) or numerous minute nodules (diffuse type) that may be indistinguishable from cirrhosis. The liver is enlarged by one or more tumor nodules that are soft and fleshy and variegated, with green bile-stained, pale yellow cut surface, usually associated with areas of hemorrhage, necrosis, and fibrosis. Invasion of the branches of the portal or hepatic veins is common in larger tumors. Involvement of major bile ducts, with intra-biliary growth, can lead to obstructive jaundice. Staging criteria depend on the size and number of tumor nodules and presence or absence of vascular invasion.

The microscopic appearance of HCC depends on the degree of differentiation. Grading is based on the parenchymal architecture, nuclear and cytoplasmic features, and cell size. The current World Health Organization (WHO) system divides tumors into well-differentiated, moderately

differentiated, poorly differentiated, and undifferentiated grades [14]. Well-differentiated tumors might be difficult to distinguish from nonmalignant neoplastic proliferations such as hepatic adenoma, while undifferentiated tumors show little evidence of hepatocellular differentiation. Most HCCs are moderately differentiated (grades 2–3) with more than one histological grade present within a given tumor. The clinical manifestations of HCC are seldom characteristic. In Western countries, they are often masked by those related to the underlying cirrhosis or chronic hepatitis. In regions of high incidence, many patients may have no prior clinical history of liver disease, although cirrhosis is often detected at autopsy. The most common presenting symptoms are abdominal pain, nausea, fullness, or worsening of symptoms attributed to cirrhosis.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a malignant tumor of the biliary tree, within (intrahepatic) or outside (extrahepatic) the liver, comprising every section from the ampulla of Vater to the common bile duct, the cystic duct, the hepatic duct, and the bile ductules where the majority are adenocarcinoma [15].

Extrahepatic CCA is a rare tumor arising from right or left hepatic ducts. It usually appears as firm, gray nodules within the bile duct wall. Alternatively, it can present as either diffusely infiltrative or papillary or polypoid lesion.

Intrahepatic CCA arises from any portion of intrahepatic bile ducts and may track along the portal tract system to create a treelike tumor mass within a portion of the liver. Histologically, CCA resembles adenocarcinomas arising in other parts of the body. CCA may be grossly classified into three types: mass-forming (MF), periductal infiltrating (PI), and intraductal growth (IG) types. Most CCA are well- to moderately differentiated sclerosing adenocarcinomas with defined glandular and tubular structures lined by cuboidal to low columnar epithelial cells. Two types of precursor lesions have been proposed for intrahepatic CCA: flat biliary intraepithelial neoplasia (BillN) and intraductal papillary neoplasms (IPN) of the bile duct. Intrahepatic CCA has a poor prognosis because of early invasion, widespread metastasis, and lack of effective therapeutic strategies. The general clinical features of CCA are somehow similar to those of HCC although architectural and biomarker patterns are clearly different.

Hepatic Angiosarcoma

Although being the most common sarcoma arising in the liver, hepatic angiosarcoma (HAS) is a very rare tumor, which develops in endothelial cells that line the blood vessels of the liver [16]. Macroscopically, the tumor is often multifocal and involves the entire liver. Cut surface shows a mixture of tan-gray firm areas with large hemorrhagic foci. On microscopic examination, variably sized, dilated spaces are seen in the liver parenchyma, lined by highly atypical endothelial cells. The adjacent liver cords show varying degrees of atrophy and destruction. Epithelioid hemangioendothelioma, Kaposi sarcoma, fibrosarcoma, and leiomyosarcoma are among the differential diagnoses. HAS has a poor prognosis and the majority of patients die within 6 months of diagnosis.

Epidemiology

The epidemiology of liver cancer is made complex by the large number of secondary tumors which arise in the organ and are difficult to separate from primary liver cancers without histological verification. The most common histological type of primary liver cancer is hepatocellular carcinoma (HCC). Other forms include hepatoblastoma (in children), cholangiocarcinoma (originating from the intrahepatic biliary ducts), and angiosarcoma (from the intrahepatic blood vessels). Most HCCs originate from cirrhotic tissue.

The incidence of liver cancer is high in all low-resource regions of the world, with the exception of Northern Africa and Western Asia. The highest rates (above 40/100,000 in men and above 10/100,000 in women) are recorded in Thailand, Japan, and certain parts of China. In most high-resource countries, age-standardized rates are below 5/100,000 in men and 2.5/100,000 in women. Intermediate rates (5–10/100,000 in men) are observed in areas of Southern and Central Europe [3]. The estimated worldwide number of new cases of liver cancer in 2012 is 782,000, of which more than 80 % are from developing countries (51 % from China alone) [1]. Given the poor survival from this disease, the estimated number of deaths is similar to that of new cases (746,000): liver cancer is the second most frequent cause of neoplastic death worldwide.

Hepatocellular Carcinoma

Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are the main causes of HCC. The risk increases with early age at infection (in high-risk countries, most HBV infections occur perinatally or in early childhood), and the presence of liver cirrhosis is a pathogenic step. HBV is the main agent in China, Southeast Asia, and Africa, while HCV is the predominant virus in Japan and Southern Europe. The most frequent routes of HCV transmission are parenteral and sexual, while perinatal infection is rare. The estimated risk of developing HCC among infected subjects, relative to uninfected, is in the order of 15–20 for both infections. On a global scale, the fraction of liver cancer cases attributable to HBV is 54 %; the one attributable to HCV is 31 % [17].

Contamination of foodstuff with aflatoxins, a group of mycotoxins produced by fungi of the *Aspergillus* genus,

which originates mainly from improper storage of cereals, peanuts, and other vegetables, is prevalent in Africa, Southeast Asia, and China and is an important cause of HCC in these populations. Excessive alcohol intake increases the risk of HCC; the most likely mechanism is through development of cirrhosis, although alternative mechanisms such as alteration in activation and detoxification of carcinogens may also play a role. The association between tobacco smoking and HCC is now established, with an RR of the order of 1.5–2 [5]. Other known causes of HCC include overweight/obesity, history of diabetes, use of oral contraceptives, and iron overload (in patients with hemochromatosis or other disorders of iron metabolism).

Other Types of Liver Cancer

Infestation with the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, is the main known cause of CCA, a type of liver cancer which is very frequent in infested areas in Southeast Asia. Infection occurs via consumption of improperly cooked fish. Exposure to thorotrast, a contrast medium containing radioactive thorium used for angiography in Europe and Japan during 1930–1955, resulted in an increase of CCA and of HAS.

Occupational Risk Factors

Despite the fact that the liver is the primary organ involved in the metabolism of many exogenous chemicals, including potential carcinogens, little is known on potential occupational causes of this disease. An increased risk of HCC has been reported in cohort studies of workers exposed to vinyl chloride; however, since vinyl chloride is an established risk factor of HAS (see below), it is important to avoid diagnostic misclassification between the types of liver cancer. A meta-analysis of two multicenter cohort studies of vinyl chloride-exposed workers [18, 19] resulted in a meta-SMR of 1.35 (95% CI, 1.04–4.39) for liver cancer other than HAS [20]. The epidemiological evidence for an association with trichloroethylene exposure is limited [21], but a recent study based on individuals undergoing biomonitoring in three Nordic countries reported an association [22]. There is no consistent evidence for tetrachloroethylene, although a weak association was reported in a recent study based on Nordic census data [23]. An increased risk of liver cancer mortality was reported in a cohort study of cellulose fiber production workers exposed to methylene chloride [24], which however was not confirmed by other study (see [25] for review and meta-analysis).

Workers exposed to vinyl chloride, a monomer used in the chemical industry for production of the plastic polymer, polyvinyl chloride, experience an increased risk of HAS. This occupational carcinogen was first identified through the report of a cluster of cases of HAS among US production workers [26]. Several studies have subsequently been conducted in Europe, North America, and Asia [20], including two large multicenter cohorts [18, 19], which confirmed the presence of HAS cases among workers exposed to vinyl chloride. Since HAS is a very rare disease, the fraction of cases attributable to vinyl chloride in potentially exposed workers is essentially 100 %. The identification of this hazard has led to a drastic reduction in occupational exposure to vinyl chloride, and no cases of HAS have been reported among workers employed after the implementation of these measures: the available cohort studies, however, might not have adequate power to exclude the presence of a small excess risk.

Mechanisms of Liver Cancer

Hepatocellular Carcinoma

The development of HCC proceeds through multiple genetic pathways depending upon the particular combination of risk factors involved. The two most common types of genetic alterations occur in *TP53* (encoding the tumor suppressor protein p53, 30–70 %) and in components of the oncogenic Wnt/β (beta)-catenin pathway (20–50 %). Other commonly affected genes include regulators of the TGFβ (beta) signaling pathways such as SMAD2, SMAD4, the gene encoding the IGF2 receptor (IGFR), and genes involved in growth control through the RB1 (retinoblastoma) pathway. A model proposed by Laurent-Puig and Zucman-Rossi identifies two broad categories of HCC [27]. The first, characterized by chromosome instability, contains HCC occurring in a context of chronic infection by HBV with *TP53* mutations and often shows a poorly differentiated phenotype. The second, characterized by chromosome stability, is more common among non-HBV-infected HCC, with mutations in the Wnt/β (beta)-catenin pathway, and often consists of large tumors (Fig. 6.1).

HBV-Induced HCC

Several lines of evidence support the direct involvement of HBV in hepatocarcinogenesis. First, HBV genome integration into the host cell genome has been associated with host DNA microdeletions [28] that can target cancer-relevant genes including telomerase reverse transcriptase (*TERT*), platelet-derived-growth-factor receptor-β (*PDGFRβ*), and mitogen-activated protein kinase 1 (MAPK1), among others [29]. Second, the viral oncoprotein HBx presents transcriptional activity that can alter the expression of growth-control genes, such as SRC tyrosine kinases, Ras, Raf, MAPK, ERK, JNK, and others [30]. Third, HBx can bind and inactivate the tumor suppressor p53 in vitro, thereby increasing cellular proliferation and survival and compromising DNA-damage checkpoints [31, 32]. The carcinogenic potential of HBx has

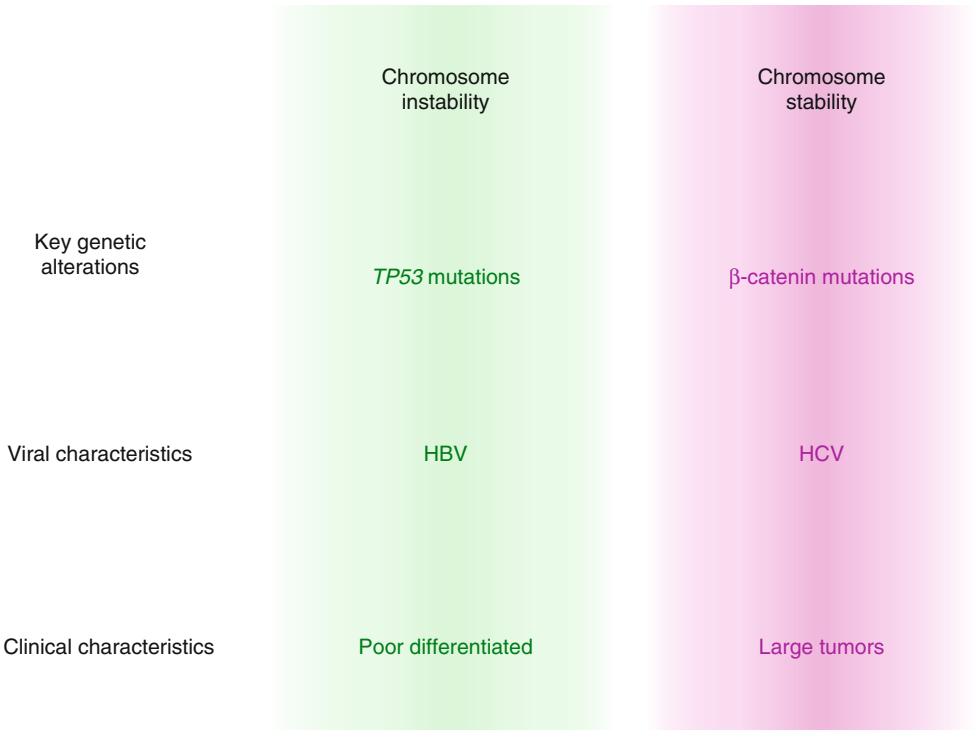


Fig. 6.1 Development of HCC through multiple genetic pathways depending upon the particular combination of risk factors involved (Adapted from Boffetta et al. [20])

been demonstrated in HBx transgenic mice, 90 % of which develop HCC [32, 33]. Another mechanism of HBV-induced HCC involves inflammatory and regenerative responses to chronic infection. The T-cell immune response contributes to chronic cycles of hepatocyte necrosis/inflammation/regeneration, which in turn promote the propagation of oncogenic lesions and telomere erosion, generating genomic instability [34]. Moreover, accumulation of viral proteins in the endoplasmic reticulum (ER) causes ER stress resulting into oxidative stress and generation of free radicals contributing to the liver destruction/regeneration cycles [35]. Finally, mutations in HBV enhance viral replication and the severity of hepatitis and virus escape from immune response, leading to increased hepatocyte damage and liver disease.

Aflatoxin B_1-Induced HCC

Aflatoxin B_1 (AFB_1) is a mycotoxin produced by *Aspergillus* sp. fungus (e.g., *A. flavus*), which contaminates the staple diet in many low-resource areas of sub-Saharan Africa, Southeast Asia, and Latin America. Metabolites of AFB_1 bind specifically to the third base of codon 249 of *TP53* gene, resulting into a specific *TP53* mutation (AG**G** to AG**T**, *R249S*, mutant protein p.R249S) [36]. High exposure to AFB_1 often occurs in regions where chronic HBV infection is endemic and the two risk factors act synergistically in the development of HCC. Subjects exposed to both chronic HBV and AFB_1 present a five- to tenfold increased risk of developing HCC compared with subjects exposed to either factor alone [36, 37]. A recent study on HCC in the Gambia, West Africa, has reported that cirrhosis was detected in only 60–65 % of HCC patients presenting markers of exposure to both factors, a relatively low proportion in comparison with industrialized countries where about 90 % of HCCs develop in a context of liver cirrhosis [38]. A model for the cooperation between chronic HBV infection and exposure to AFB_1 (Fig. 6.2) suggests that the *R249S* mutation caused by AFB_1 may downregulate p53-dependent apoptosis, thus decreasing cell destruction caused by chronic hepatitis while increasing genetic instability and risk of acquisition of additional mutations. At the molecular level, the mutant p.R249S protein interacts with the viral oncoprotein HBx [39, 40]. Gouas et al. have shown that p.R249S and HBx were able to form a complex and to play a role in the proliferation of a HCC cell line [40]. In another study, Jiang et al. have shown that tumor-derived HBx mutants in cooperation with p. R249S could alter cell proliferation and chromosome stability of normal human hepatocytes [39].

HCV-Induced HCC

HCV causes more chronic infections than HBV (60–80 % vs. 10 % for HBV) and has a greater propensity to promote liver cirrhosis (see Fig. 6.2). In contrast with HBV, HCV is an RNA virus without DNA intermediate form and does not integrate into host genomes [41]. HCV induces hepatocarcinogenesis through continuous cycles of hepatocyte destruction/regeneration caused by the immune response to the virus, which provides a context for the accumulation and propagation of mutations. On the other hand, various immune-evasion

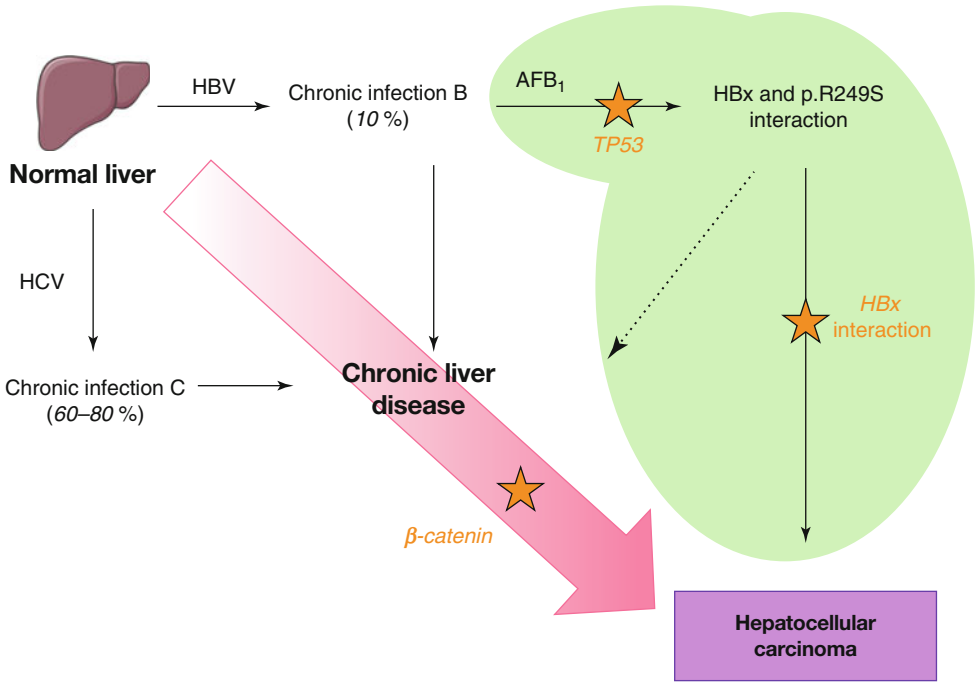


Fig. 6.2 A model of hepatocarcinogenesis driven by different etiologic contexts. The main route to HCC, represented by the large diagonal arrow, generally involves a long phase of precursor, chronic liver disease. Progression from chronic liver disease into HCC involves activation of oncogenic signals (e.g., ß-catenin) as primary mechanisms and inactivation of the suppressive response to oncogenic stress (e.g., inactivation of the p53/p14arf connection) as a secondary mechanism. In contrast, in the case of chronic exposure to AFB_1, the early formation of *R249S* mutations and the cooperation between HBx and the mutant p.R249S protein may enhance progression to HCC without the need for a protracted phase of chronic liver disease (pathway highlighted in *green*)

mechanisms by HCV proteins have been described. NS3 and NS4A HCV proteins use their protease function to cleave and activate components that are essential for immune response signaling [42, 43]. In addition, NS5A has been proposed to interact with and to sequester it to the perinuclear space [44]. Overall, the pathogenetic interactions between the immune system and HCV-induced HCC are complex and not fully understood. A further factor of complexity is that, in a proportion of patients, both infections by HBV and HCV may coexist, sometimes with HBV being in an occult form (serologically silent but detectable at DNA level).

Alcohol-Induced HCC

Chronic alcohol intake is a major cause of liver damage that may lead to HCC. First, metabolites of alcohol such as acetaldehyde may have a direct mutagenic effect on hepatocytes, although molecular hallmarks of this type of mutation have not been clearly identified so far. Second, alcohol overload generates a massive metabolic stress for liver cells and enhances the development of metabolic diseases. Third, alcohol may increase the production of proinflammatory cytokines with deleterious effects on hepatocyte survival [45, 46]. The notion that alcohol may have specific effects on the transformation of hepatocytes is supported by observation of different patterns of gene methylation in alcohol-related HCC as compared to HCC occurring in a context of chronic HBV or HCV [47]. Overall, these various mechanisms, acting either separately or in synergy, may confer to alcohol the properties of a pleiotropic carcinogen for liver cells.

Iron Overload-Induced HCC

Increased iron absorption and accumulation by liver cells induce extreme oxidative stress caused by iron-catalyzed Fenton reactions. The resulting reactive oxygen species induce DNA damage and promote inflammation leading to chronic hepatocyte destruction/regeneration cycles, cirrhosis, and ultimately HCC. Increased oxidative stress associated with iron overload (hereditary hemochromatosis) has been associated with *TP53* mutations in HCC [48].

Cholangiocarcinoma

Carcinogenesis in the bile ducts caused by chronic infection with liver flukes involves chronic inflammation and oxidative stress. So far, no specific mutagenic mechanism other than overproduction of NO species and inflammatory stress has been documented. *TP53* mutations often occur in CCA in a context of chronic infection by *Opisthorchis viverrini*. The majority of these mutations are C to T transitions occurring at CpG dinucleotides, a type of mutation common in cancers occurring in high inflammatory contexts. A recent survey of deregulated tyrosine

phosphorylation in a small set of CCA cases has identified fusion products of ROS tyrosine kinase, leading to its activation, in 2/23 cases (9 %) [49]. Established mechanistic events for HBV and HCV in the development of CCA include inflammation, liver cirrhosis, chronic hepatitis, and liver fibrosis [50].

Hepatic Angiosarcoma

HAS associated with exposure to vinyl chloride has been shown to harbor specific mutations in *TP53* (mutations at A:T base pairs) [51]. The same type of mutation has been observed in liver angiosarcomas of rats exposed to vinyl chloride [51, 52]. *KRAS* mutations appear to be common in thorotrast and vinyl chloride-associated HAS [53].

Susceptibility to Liver Cancer

Inherited Disorders

Inherited disorders that cause chronic liver inflammation, fibrosis, and cirrhosis may lead to the development of HCC. These disorders are diverse and their relative risk for HCC development is not clearly defined. The most common form is hereditary hemochromatosis (HH), a genetic disorder of iron metabolism leading to excessive iron absorption and accumulation in the liver. The clinical manifestations of HH include cardiomyopathy, diabetes, liver fibrosis, and cirrhosis that are precursors for HCC. The annual incidence of HCC is 4 % in HH patients with established cirrhosis. Genetic studies have linked HH to mutations in *HFE* (hemochromatosis gene, 6q22) and to rare defects in *TRF2* (transferrin receptor 2), *HAMP* (hepcidin), *SLC40A1* (ferroportin), or *HFE* (HFE2) [54]. HH is inherited as autosomal recessive trait. Most HH cases are homozygote carriers of the founder mutation C282Y in *HFE* [55]. This mutation is detected in up to 0.8 % of the population in Northern European countries, where HH appears to be particularly frequent. Nevertheless, the penetrance of this mutation is partial and only a minority of homozygote carriers develops HH, suggesting a strong influence of lifestyle and/or genetic modifiers.

Rare occurrence of HCC has been observed in several inherited syndromes [54]. These include Fanconi anemia, a genetically complex disease caused by mutations in genes that participate in repair of DNA inter-strand cross-links and control of genetic stability, and Werner syndrome, a premature aging disease caused by mutations in WRN (8p11.2-p12), encoding a DNA helicase of the RecQ family. Wilson disease, a disorder of copper metabolism, promotes the development of liver abnormalities including steatosis, cirrhosis, and, in rare instances, HCC. Among inherited metabolic disorders, alpha-1 anti-trypsin deficiency (AAT) and tyrosinemia type 1 (TT1) are diversely associated with HCC. Hereditary TT1 is an autosomal recessive disease caused by mutations disrupting fumarylacetoacetate hydrolase (FAH), the last enzyme in the catabolic pathway of tyrosine (15q24-q25). Accumulation of catabolic tyrosine intermediates causes devastating damage in children resulting in either acute liver failure or chronic liver disease and to HCC, which occurs in about 40 % of patients who survive beyond 2 years of age.

Genetic Polymorphisms

A number of studies on individual genetic polymorphisms have identified associations between specific single-nucleotide polymorphisms and the risk of HCC. However, these studies are heterogeneous in their design and etiologic context, making it difficult to identify reproducible associations. In regions of high exposure to AFB_1, a significantly increased risk of HCC has been observed in relation with polymorphisms in enzymes involved in AFB_1 metabolism and detoxification or in the repair of AFB_1-induced DNA adducts. A case-control study in the Gambia has shown a cumulative risk associated with increasing number of "at-risk" alleles in AFB_1 metabolism and DNA repair pathways.

A recent review and meta-analysis of SNPs associated with HCC has identified six SNPs in five genes [56]. These SNPs are rs1800562 of *HFE*, rs17868323, and rs11692021 of the UDP glycosyltransferase *UGT1A7*, rs2279744 of *MDM2* (encoding a negative regulator of the tumor suppressor p53; this SNP, commonly identified as SNP309, modifies a regulatory site in *MDM2* promoter), rs1143627 of *IL-1B*, and rs4880 of *MnSOD*. However, only two SNPs (rs1800562 of *HFE* and rs2279744 of *MDM2*) appeared to pass the false-positive report probability threshold (FPRP <0.20).

Genetic Variations in Hepatitis Viruses

Two types of genotypic variations in HBV have an impact on the clinical course of HBV-related diseases including HCC. First, the course of liver diseases differs according to HBV genotypes. Second, recurrent mutations in HBV are associated with increased risk of progression to cirrhosis and HCC. These mutations include mutations in the basal core promoter (BCP; A1762T/G1764A) and in the open-reading frames encoding preS1/preS2/S and pre-C/C (reviewed in [57]).

Studies in Taiwan have shown that genotype C is associated with more severe liver disease than other genotypes in this population (e.g., genotype B) [58, 59]. In Alaska, the median age at HCC diagnosis has been shown to be lower in patients with genotype F, which is endemic to America, than with other genotypes (22.5 vs. 60 years, respectively; $P = 0.002$). The BCP mutations occur in a region that overlaps with the *HBX* gene, resulting to amino acid substitutions in the oncogenic protein HBx (K130M and V131I). These mutations have been proposed as prognostic markers for the development of HCC [60]. On the other hand, deletions in pre-S have been reported in integrated HBV DNA in HCC

cells. These deletions are thought to impair HBsAg secretion, causing ER and oxidative stress [61, 62].

Cancer of Extrahepatic Biliary Tract

Cancers of the extrahepatic biliary ducts are of the adenocarcinoma type. Incidence rates of biliary tract cancer are high (above 3/100,000 in men and above 5/100,000 in women) in Central Europe, South America, Japan, and Western Asia. In the USA, rates are higher among people of American-Indian, Hispanic, and Japanese origin than in other groups [3]. Most of the geographical variation is accounted for by cancer of the gallbladder, which represents the majority of biliary tract cancers. Rates of gallbladder cancer in women are generally higher than in men.

The main known risk factor for cancer of the gallbladder is presence of gallstones. The RR is in the order of 3, and it is higher in patients with large (>3 cm in diameter) rather than small (<1 cm) stones. In Western populations, most gallstones are formed by cholesterol, and their formation is associated with hypersecretion and saturation of cholesterol in the bile. The possible causes of cholesterol saturation (obesity, multiple pregnancies, and other hormonal factors) are also associated with increased risk of gallbladder cancer. An additional role of gallbladder hypomotility in stone formation is likely. In Asia, the main types of gallstone are formed by bilirubin salts and have as risk factor bacterial infection of the biliary system: their association with gallbladder cancer, however, is not clear [63].

Other suspected risk factors for gallbladder cancer include chronic inflammation, biliary stasis, and infection, in particular status of chronic typhoid and paratyphoid carrier, history of gastric resection, reproductive history resulting in increased exposure to endogenous estrogens and progesterone, obesity, and, possibly, increased energy intake. It is likely that these factors act through gallstone formation, although the available data do not allow a conclusion with respect to their possible role in gallbladder carcinogenesis.

Fewer data are available on risk factors for cancer of extrahepatic biliary ducts. Infestation with the liver flukes causing intrahepatic CCA and history of ulcerative colitis are established risk factors but explain only a small proportion of these cancers. Tobacco smoking and diabetes have been suggested as additional causes.

Occupational Risk Factors

Little is known on potential occupational risk factors of biliary tract cancer. An early analysis of census data from Sweden identified a few occupations at increased risk, including textile workers [64]: this association was confirmed in a cohort study from Lithuania [65]. A recent systematic analysis of over 15 million residents from the Nordic countries, including over 8,500 cases among men and 19,000 cases among women, did not confirm the increased risk among textile workers [66]. In this study, high-risk groups were cooks and drivers among men and building caretakers among women.

Conclusion

Despite the important contribution of cancers of the intestine, the liver, and the biliary tract to the global cancer burden, our understanding of their occupational causes is rather limited (the only established occupational carcinogen for this group of neoplasms is vinyl chloride). While for colorectal and gallbladder cancers there is also an incomplete understanding of other underlying causes, knowledge on the etiology of liver cancers, in particular HCC, is rather extensive. The particular combination of viral, environmental, lifestyle, and metabolic risk factors appears to have a major impact on the molecular mechanisms by which HCC occurs and develops and offers important avenues for its prevention, primarily through control of chronic HBV and HCV infection.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11. Lyon: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr.
2. Beebe-Dimer J, Schottenfeld D. Cancers of the small intestine. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 2006. p. 801–8.
3. Forman D, Bray F, Brewster DH, et al., editors. Cancer incidence in five continents, vol. X. Lyon: International Agency for Research on Cancer; 2013. Available from: http://ci5.iarc.fr.
4. World Cancer Research Fund/ American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research; 2007.
5. International Agency for Research on Cancer. Tobacco smoke. In: IARC monographs on the evaluation of the carcinogenic risks to humans, Tobacco smoke and involuntary smoking, vol. 83. Lyon: International Agency for Research on Cancer; 2004. p. 51–1187.
6. Fedirko V, Tramacere I, Bagnardi V, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol. 2011;22:1958–72.
7. Giovannucci E, Wu K. Cancers of the colon and rectum. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 2006. p. 809–29.
8. Selikoff IJ, Churg J, Hammond EC. Asbestos exposure and neoplasia. JAMA. 1964;188:22–6.
9. Institute of Medicine. Asbestos: selected cancers. Washington, DC: National Academy Press; 2006.
10. International Agency for Research on Cancer. Asbestos. In: IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens, part C: arsenic, metals, fibres, and dusts, vol. 100. Lyon: International Agency for Research on Cancer; 2012. p. 219–310.

11. Kjarheim K, Ulvestad B, Martinsen JI, Andersen A. Cancer of the gastrointestinal tract and exposure to asbestos in drinking water among lighthouse keepers (Norway). Cancer Causes Control. 2005;16:593–8.
12. Thygesen LC, Albertsen K, Johansen C, Grønbaek M. Cancer incidence among Danish brewery workers. Int J Cancer. 2005;116: 774–8.
13. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48:646–790.
14. Theise ND, Curado MP, Franceschi S, Hytiroglou P, Kudo M, Park YN, Sakamoto M, Torbenson M, Wee A. WHO classification of tumours of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. Hepatocellular carcinoma. 4th ed. Lyon: International Agency for Research on Cancer; 2010. p. 205–16.
15. Nakanuma Y, Curado MP, Franceschi S, Gores G, Paradis V, Sripa B, Tsui WMS, Wee A. WHO classification of tumours of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. Intrahepatic cholangiocarcinoma. 4th ed. Lyon: International Agency for Research on Cancer; 2010. p. 217–24.
16. Miettinen M, Fletcher CDM, Kindblom LG, Zimmermann A, Tsui WMS. WHO classification of tumours of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. Mesenchymal tumours of the liver. 4th ed. Lyon: International Agency for Research on Cancer; 2010. p. 241–50.
17. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006;118:3030–44.
18. Mundt KA, Dell LD, Austin RP, et al. Historical cohort study of 10 109 men in the North American vinyl chloride industry, 1942–72: update of cancer mortality to 31 December 1995. Occup Environ Med. 2000;57:774–81.
19. Ward E, Boffetta P, Andersen A, et al. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. Epidemiology. 2001;12:710–8.
20. Boffetta P, Matisane L, Mundt KA, Dell LD. Metaanalysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health. 2003;29:220–9.
21. Guha N, Loomis D, Grosse Y, et al. Carcinogenicity of trichloroethylene, tetrachloroethylene, some other chlorinated solvents, and their metabolites. Lancet Oncol. 2012;13:1192–3.
22. Hansen J, Sallmén M, Seldén AI, et al. Risk of cancer among workers exposed to trichloroethylene: analysis of three Nordic cohort studies. J Natl Cancer Inst. 2013;105:869–77.
23. Vlaanderen J, Straif K, Pukkala E, et al. Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries. Occup Environ Med. 2013;70:393–401.
24. Lanes SF, Rothman KJ, Dreyer NA, Soden KJ. Mortality update of cellulose fiber production workers. Scand J Work Environ Health. 1993;19:426–8.
25. Liu T, Xu QE, Zhang CH, Zhang P. Occupational exposure to methylene chloride and risk of cancer: a meta-analysis. Cancer Causes Control. 2013;24:2037–49.
26. Block JB. Angiosarcoma of the liver following vinyl chloride exposure. JAMA. 1974;229:53–4.
27. Laurent-Puig P, Zucman-Rossi J. Genetics of hepatocellular tumors. Oncogene. 2006;25:3778–86.
28. Tokino T, Tamura H, Hori N, Matsubara K. Chromosome deletions associated with hepatitis B virus integration. Virology. 1991;185: 879–82.
29. Murakami Y, Saigo K, Takashima H, Minami M, Okanoue T, Brechot C, Paterlini-Brechot P. Large scaled analysis of hepatitis B virus (HBV) DNA integration in HBV related hepatocellular carcinomas. Gut. 2005;54:1162–8.
30. Tarn C, Lee S, Hu Y, Ashendel C, Andrisani OM. Hepatitis B virus X protein differentially activates RAS-RAF-MAPK and JNK pathways in X-transforming versus non-transforming AML12 hepatocytes. J Biol Chem. 2001;276:34671–80.
31. Feitelson MA, Sun B, Satiroglu Tufan NL, Liu J, Pan J, Lian Z. Genetic mechanisms of hepatocarcinogenesis. Oncogene. 2002;21: 2593–604.
32. Ueda H, Ullrich SJ, Gangemi JD, Kappel CA, Ngo L, Feitelson MA, Jay G. Functional inactivation but not structural mutation of p53 causes liver cancer. Nat Genet. 1995;9:41–7.
33. Kim CM, Koike K, Saito I, Miyamura T, Jay G. HBx gene of hepatitis B virus induces liver cancer in transgenic mice. Nature. 1991; 351:317–20.
34. Chisari FV, Isogawa M, Wieland SF. Pathogenesis of hepatitis B virus infection. Pathol Biol (Paris). 2010;58:258–66.
35. Wang HC, Huang W, Lai MD, Su IJ. Hepatitis B virus pre-S mutants, endoplasmic reticulum stress and hepatocarcinogenesis. Cancer Sci. 2006;97:683–8.
36. Gouas D, Shi H, Hainaut P. The aflatoxin-induced TP53 mutation at codon 249 (R249S): biomarker of exposure, early detection and target for therapy. Cancer Lett. 2009;286:29–37.
37. Kew MC. Synergistic interaction between aflatoxin B1 and hepatitis B virus in hepatocarcinogenesis. Liver Int. 2003;23:405–9.
38. Umoh NJ, Lesi OA, Mendy M, Bah E, Akano A, Whittle H, Hainaut P, Kirk GD. Aetiological differences in demographical, clinical and pathological characteristics of hepatocellular carcinoma in The Gambia. Liver Int. 2011;31:215–21.
39. Jiang W, Wang XW, Unger T, Forgues M, Kim JW, Hussain SP, Bowman E, Spillare EA, Lipsky MM, Meck JM, Cavalli LR, Haddad BR, Harris CC. Cooperation of tumor-derived HBx mutants and p53-249(ser) mutant in regulating cell proliferation, anchorage-independent growth and aneuploidy in a telomerase-immortalized normal human hepatocyte-derived cell line. Int J Cancer. 2010;127: 1011–20.
40. Gouas DA, Shi H, Hautefeuille AH, Ortiz-Cuaran SL, Legros PC, Szymanska KJ, Galy O, Egevad LA, Abedi-Ardekani B, Wiman KG, Hantz O, de Fromentel CC, Chemin IA, Hainaut PL. Effects of the TP53 p.R249S mutant on proliferation and clonogenic properties in human hepatocellular carcinoma cell lines: interaction with hepatitis B virus X protein. Carcinogenesis. 2010;31:1475–82.
41. Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. Nat Rev Immunol. 2005;5:215–29.
42. Foy E, Li K, Sumpter Jr R, Loo YM, Johnson CL, Wang C, Fish PM, Yoneyama M, Fujita T, Lemon SM, Gale Jr M. Control of antiviral defenses through hepatitis C virus disruption of retinoic acid-inducible gene-I signaling. Proc Natl Acad Sci U S A. 2005;102: 2986–91.
43. Li K, Foy E, Ferreon JC, Nakamura M, Ferreon AC, Ikeda M, Ray SC, Gale Jr M, Lemon SM. Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF. Proc Natl Acad Sci U S A. 2005;102: 2992–7.
44. Majumder M, Ghosh AK, Steele R, Ray R, Ray RB. Hepatitis C virus NS5A physically associates with p53 and regulates p21/waf1 gene expression in a p53-dependent manner. J Virol. 2001;75: 1401–7.
45. McClain CJ, Hill DB, Song Z, Deaciuc I, Barve S. Monocyte activation in alcoholic liver disease. Alcohol. 2002;27:53–61.
46. Hoek JB, Pastorino JG. Ethanol, oxidative stress, and cytokine-induced liver cell injury. Alcohol. 2002;27:63–8.
47. Lambert MP, Paliwal A, Vaissiere T, Chemin I, Zoulim F, Tommasino M, Hainaut P, Sylla B, Scoazec JY, Tost J, Herceg Z. Aberrant DNA methylation distinguishes hepatocellular carcinoma associated with HBV and HCV infection and alcohol intake. J Hepatol. 2011;54:705–15.
48. Marrogi AJ, Khan MA, van Gijssel HE, Welsh JA, Rahim H, Demetris AJ, Kowdley KV, Hussain SP, Nair J, Bartsch H, Okby N, Poirier MC, Ishak KG, Harris CC. Oxidative stress and p53

mutations in the carcinogenesis of iron overload-associated hepatocellular carcinoma. J Natl Cancer Inst. 2001;93:1652–5.
49. Gu TL, Deng X, Huang F, Tucker M, Crosby K, Rimkunas V, Wang Y, Deng G, Zhu L, Tan Z, Hu Y, Wu C, Nardone J, MacNeill J, Ren J, Reeves C, Innocenti G, Norris B, Yuan J, Yu J, Haack H, Shen B, Peng C, Li H, Zhou X, Liu X, Rush J, Comb MJ. Survey of tyrosine kinase signaling reveals ROS kinase fusions in human cholangiocarcinoma. PLoS One. 2011;6:e15640.
50. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. Group WHOIAfRoCMW. A review of human carcinogens–Part B: biological agents. Lancet Oncol. 2009;10:321–2.
51. Hollstein M, Marion MJ, Lehman T, Welsh J, Harris CC, Martel-Planche G, Kusters I, Montesano R. p53 mutations at A:T base pairs in angiosarcomas of vinyl chloride-exposed factory workers. Carcinogenesis. 1994;15:1–3.
52. Barbin A, Froment O, Boivin S, Marion MJ, Belpoggi F, Maltoni C, Montesano R. p53 gene mutation pattern in rat liver tumors induced by vinyl chloride. Cancer Res. 1997;57:1695–8.
53. Przygodzki RM, Finkelstein SD, Keohavong P, Zhu D, Bakker A, Swalsky PA, Soini Y, Ishak KG, Bennett WP. Sporadic and thorotrast-induced angiosarcomas of the liver manifest frequent and multiple point mutations in K-ras-2. Lab Invest. 1997;76:153–9.
54. Dragani TA. Risk of HCC: genetic heterogeneity and complex genetics. J Hepatol. 2010;52:252–7.
55. Jin F, Xiong WJ, Jing JC, Feng Z, Qu LS, Shen XZ. Evaluation of the association studies of single nucleotide polymorphisms and hepatocellular carcinoma: a systematic review. J Cancer Res Clin Oncol. 2011;137:1095–104.
56. Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, McLaren CE, Bahlo M, Nisselle AE, Vulpe CD, Anderson GJ, Southey MC, Giles GG, English DR, Hopper JL, Olynyk JK, Powell LW, Gertig DM. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med. 2008;358:221–30.
57. Pujol FH, Navas MC, Hainaut P, Chemin I. Worldwide genetic diversity of HBV genotypes and risk of hepatocellular carcinoma. Cancer Lett. 2009;286:80–8.
58. Yu MW, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, Shih WL, Kao JH, Chen DS, Chen CJ. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. J Natl Cancer Inst. 2005;97:265–72.
59. Yang HI, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, Wang LY, Lu SN, You SL, Chen DS, Liaw YF, Chen CJ, Group R-HS. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. J Natl Cancer Inst. 2008;100:1134–43.
60. Kuang SY, Jackson PE, Wang JB, Lu PX, Munoz A, Qian GS, Kensler TW, Groopman JD. Specific mutations of hepatitis B virus in plasma predict liver cancer development. Proc Natl Acad Sci U S A. 2004;101:3575–80.
61. Fang ZL, Sabin CA, Dong BQ, Wei SC, Chen QY, Fang KX, Yang JY, Huang J, Wang XY, Harrison TJ. Hepatitis B virus pre-S deletion mutations are a risk factor for hepatocellular carcinoma: a matched nested case-control study. J Gen Virol. 2008;89:2882–90.
62. Gao ZY, Li T, Wang J, Du JM, Li YJ, Li J, Lu FM, Zhuang H. Mutations in preS genes of genotype C hepatitis B virus in patients with chronic hepatitis B and hepatocellular carcinoma. J Gastroenterol. 2007;42:761–8.
63. Hsing AW, Rashid A, Devesa SS, Fraumeni JF. Biliary tract cancer. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 2006. p. 787–800.
64. Malker HS, McLaughlin JK, Malker BK, et al. Biliary tract cancer and occupation in Sweden. Br J Ind Med. 1986;43:257–62.
65. Kuzmickiene I, Didziapetris R, Stukonis M. Cancer incidence in the workers cohort of textile manufacturing factory in Alytus, Lithuania. J Occup Environ Med. 2004;46:147–53.
66. Gamble J. Risk of gastrointestinal cancers from inhalation and ingestion of asbestos. Regul Toxicol Pharmacol. 2008;52(Suppl):S124–53.

Sinonasal Cancer

7

Kirsti Husgafvel-Pursiainen, Matthieu Carton, Danièle Luce, C. Henrik J. Wolff, Reetta Holmila, Vivi Schlünssen, Jette Bornholdt, and Johnni Hansen

Keywords
Sinonasal cancer • Epidemiology • Pathology • Occupational factors • Wood dust exposure • Genotoxicity • Molecular markers • Mechanisms of carcinogenesis

Introduction

Sinonasal cancer, the cancer of the nose and paranasal cavities (ICD 10 codes C30.0 and C31.0 to C31.9), is a rare form of cancer. Its incidence varies between men (0.5–1.5 new cases annually per 100,000) and women (0.1–0.6/100,000) and also from country to country. For example, age-standardized incidence rates among men during 1998–2002 in some European countries were 0.8–1.6 in France, 0.4–1.4 in Italy, 0.9 in Denmark, 0.8 in the Netherlands, 0.8 in Norway, 0.3–0.7 in the UK, 0.5–0.6 in Germany, 0.5 in Finland, and 0.4 in Sweden; in the USA the incidence rate was 0.7 (in Blacks) and 0.6 (in Whites). The corresponding rates in each country were lower for women [1]. There has also been some variation in the incidence rates over time [2–4]. It is currently seen that by far the most important factor explaining such variation in incidence is exposure, in particular occupational exposure, whereas individual factors, such as genetic susceptibility, play only a very minor role [2, 4].

Anatomically, the sinonasal region is located in the mid-portion of the face and is composed of the centrally located paired nasal cavities surrounded by paired paranasal sinuses (maxillary, frontal, ethmoidal, and sphenoidal) (Fig. 7.1) [5]. The airspace within the sinuses is connected to that of the nasal cavities via narrow passages.

In the most anterior part of the nasal cavity, the superior and lateral walls are composed of the soft tissues of the nasal wings; this area is called the nasal vestibule. The lining of the vestibule consists of an extension of the skin with keratinizing stratified epithelium and secondary appendages. This lining extends 1–2 cm from the external rim of the nose into the nostrils. The mucocutaneous junction is the location where the respiratory mucosa (referred to as the Schneiderian membrane) begins. The nasal cavity with the turbinates and the paranasal sinuses are lined with this epithelium. The superior, middle, and inferior turbinates (conchae) hang into the nasal lumen along the lateral wall of the nasal cavity. Posteriorly, the turbinates end approximately one cm anterior to the choanal orifice where the nasal cavity leads into the anterior opening of the nasopharynx.

K. Husgafvel-Pursiainen, PhD (✉)
Health and Work Ability, Systems Toxicology,
Finnish Institute of Occupational Health,
Topeliuksenkatu 41a A, FI-00250, Helsinki, Finland
e-mail: kirsti.husgafvel-pursiainen@ttl.fi

M. Carton, MD
UMS 011, Population-based Epidemiologic Cohorts Unit,
Inserm – Versailles St-Quentin University, Villejuif, France

D. Luce, PhD
Inserm UMR 1085 – Irset,
Inserm (French National Institute of Health and Medical Research),
Pointe-à-Pitre, Guadeloupe, French West Indies

C.H.J. Wolff, MD
Health and Work Ability, Systems Toxicology/Pathology,
Finnish Institute of Occupational Health,
Helsinki, Finland

R. Holmila, PhD
Section of Molecular Carcinogenesis, International Agency for Research on Cancer, Lyon, France

V. Schlünssen, MD, PhD
Department of Public Health, Section for Environmental and Occupational Medicine, Aarhus University, Aarhus, Denmark

J. Bornholdt, PhD
Department of Biology, The Bioinformatics Centre,
University of Copenhagen, Copenhagen, Denmark

J. Hansen, PhD
Research Center, Danish Cancer Society,
Copenhagen, Denmark

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_7, © Springer-Verlag London 2014

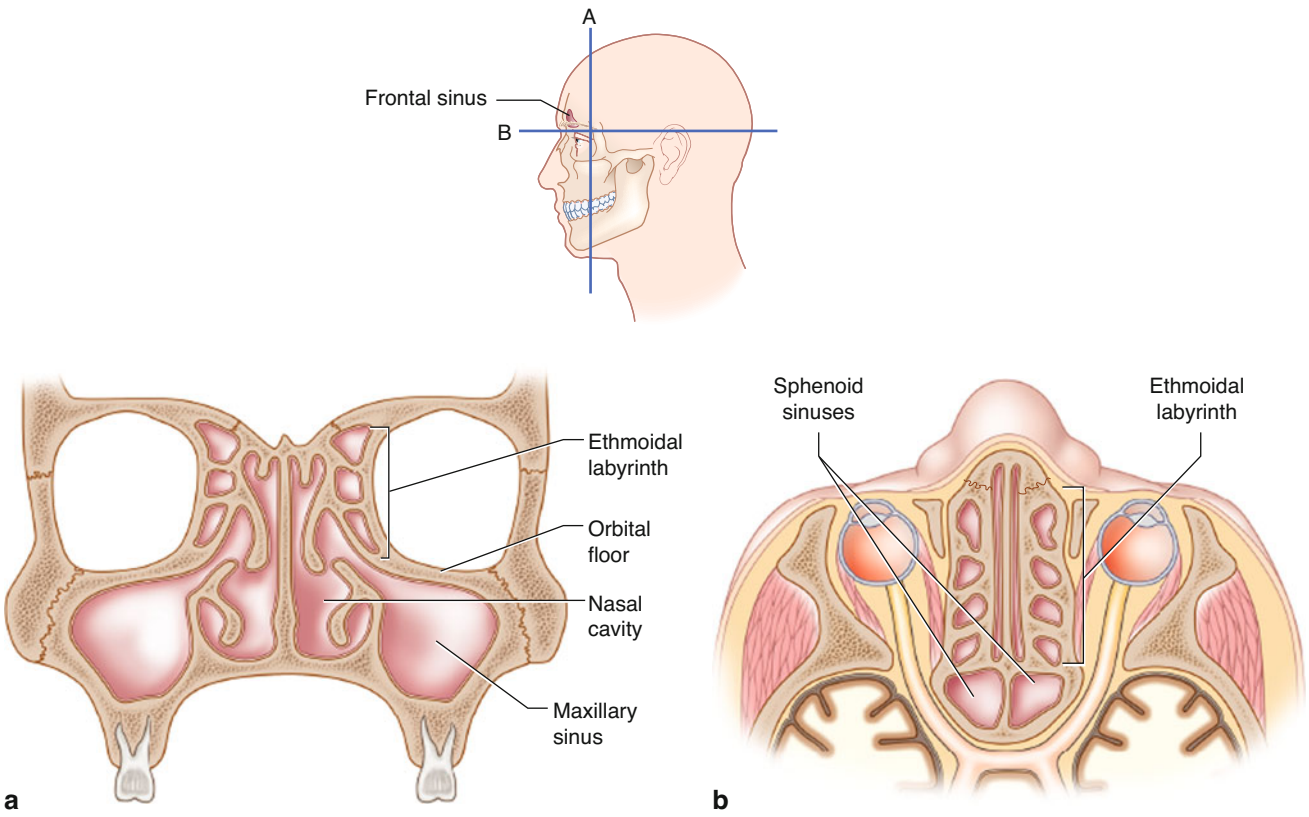


Fig. 7.1 Nasal cavities and paranasal sinuses shown in (**a**) coronal and (**b**) transverse sections. The orientation of the sections is illustrated in the middle where the frontal sinus is also shown. The ethmoidal labyrinth is a frequent target of sinonasal adenocarcinoma (Adapted from Gnepp [5])

The ethmoid labyrinth in the adult is a completely pneumonized complex of 3–18 cells per side. The roof of the labyrinth is adjacent to the anterior cranial fossa. The maxillary sinus is the largest of the sinuses, and it encompasses the majority of the body of the maxilla. The frontal and sphenoidal sinuses (Fig. 7.1) are of less importance for the topic of this chapter; these are described in more detail elsewhere [6].

This chapter will give an overview and discuss studies on sinonasal cancer dealing with epidemiological findings and various occupational risk factors, exposure levels and other exposure characteristics, tumor pathology, the molecular cancer mechanisms likely to be involved in the development of the disease, and, finally, molecular alterations observed in tumors and available as potential molecular markers. The main studies and their findings as well as the principal pathological features of sinonasal tumors are summarized in tables and exemplified in illustrations.

Epidemiology and Occupational Risk Factors

Sinonasal cancer is a rare type of cancer with 0.5–1.5 new cases per year per 100,000 in men and 0.1–0.6/100,000 in women. The incidence has been relatively stable in the last decades but varies markedly between the countries and even within the same country, from one region to another [7, 8] (see Introduction for some detail). Two main histological types of sinonasal cancer (squamous cell carcinomas and adenocarcinoma; see also Section on Pathology) exist with somewhat different etiologies and epidemiology. The 5-year relative survival of sinonasal cancer is about 50–60 % in Europe and the USA [8–12].

Occupational Risk Factors

Several occupational exposures are known to increase the risk of sinonasal cancer. According to the recent review of human carcinogens compiled by the International Agency for Research on Cancer [4, 13–15], wood dust, leather dust, nickel compounds, radium-226, and work in isopropanol production cause sinonasal cancer. Positive associations have also been observed between sinonasal cancer and exposure to chromium VI compounds, to formaldehyde, and work in the textile industry, although the evidence remains limited in humans [16]. The following Section on Exposure Characteristics characterizes the exposures involved, giving more detail in estimated numbers of those exposed at work,

exposure levels, exposure-response relationships, as well as industries and occupations relevant.

Since sinonasal cancer is a rare disease, cohort studies may often lack the statistical power to detect even moderate excess risks. In addition, as many occupational cohort studies are based on mortality data, no reliable information on histology is available. Therefore, most information on risk factors for sinonasal cancer has emerged from case-control studies. For such a rare disease, however, even case-control studies tend to involve a relatively small number of cases (generally less than 100), precluding detection of associations with specific jobs or exposure to specific substances.

This section will thus focus on the results of a pooled reanalysis of 12 case-control studies on sinonasal cancer conducted in seven countries [17–19]. These studies were selected on the basis of the availability of information on histological type, age, sex, smoking, and occupational histories. The pooled dataset consisted of 930 patients with sinonasal cancer (680 men and 250 women) and 3,136 controls (2,349 men and 787 women). The cases included 195 adenocarcinomas (169 men, 26 women) and 432 squamous cell carcinomas (330 men, 102 women). The proportion of adenocarcinomas was distinctly higher in the studies carried out in France (49 %), Italy (between 22 and 69 %), and the Netherlands (25 %) compared to those performed in the USA (between 3 and 14 %). The occupational histories were coded and exposures were assessed through a job-exposure matrix. The main advantage of the pooled analysis is that it provides sufficient statistical power to realistically examine the risks according to histological type, sex, work, exposure category, and exposure duration.

The analyses from the pooled dataset focused on the associations with wood dust [17], formaldehyde, silica, textile dust, coal dust, flour dust, asbestos, man-made vitreous fibers [19], and various occupations and industries [18]. An analysis was also conducted restricted to the 8 European studies included in the pooled dataset, dealing with exposure to wood dust, leather dust, and formaldehyde [20]. The main characteristics of the 12 studies are summarized in Table 7.1. Specific results from the original studies as well as results from case-control studies not included in the pooled dataset (Table 7.2) or from cohort studies will be also presented and discussed when they add relevant information.

Wood Dust

The causal role of exposure to wood dust in the genesis of sinonasal cancer has long been unambiguously established by numerous epidemiological studies, carried out in populations in different geographical origin, who were exposed for different periods and in several fields of activity [2, 4, 14].

Demers and coworkers [17] analyzed the pooled data from 12 case-control investigations presented above and summarized in Table 7.1. Seven categories of woodworkers were investigated. The levels of exposure to wood dust were classified into 4 categories (none, low, medium, and high), corresponding approximately to the following estimated concentrations: equal to zero, less than 1 mg/m^3, between 1 and 5 mg/m^3 and above 5 mg/m^3. The distribution of histological types varied markedly between studies.

Adenocarcinoma

The results from the pooled analysis [17] revealed that there was a sizeable risk of adenocarcinoma (Fig. 7.2). The study showed a high risk in men working with a wood-related job (OR 13.5; 95 % confidence interval [CI] 9.0–20.0). This risk was particularly high in the case of cabinetmakers and men employed in furniture factories (OR 41.1; 95 % CI 24.5–68.7). No increase in the risk of adenocarcinoma was shown for lumberjacks, foresters, or employees in paper pulp plants. The risk for saw mill employees was intermediate (OR 19.7; 95 % CI 11.1–35.1) and slightly lower after eliminating those who had worked in furniture factories (OR 14.9; 95 % CI 8.0–28.7).

For men, the risk of adenocarcinoma increased with the intensity of exposure (OR 0.6, 95 % CI 0.1–4.7 for low exposures; OR 3.1, 95 % CI 1.6–6.1 for moderate exposures; and OR 45.5, 95 % CI 28.3–72.9 for high exposures), and with exposure duration (OR 1.08, 95 % CI 1.07–1.09 per year; OR 5.3, 95 % CI 2.5–11.1 for duration shorter than 5 years; OR 10.7, 95 % CI 5.2–11.8 for duration of 10–19 years; and OR 36.7, 95 % CI 22.0–61.3 for duration of 30 years or more). The data provided evidence for a latency period, in the order of at least 20 years.

The results for women were less conclusive: the increase in the risk of adenocarcinoma for women with wood-related jobs (OR 2.78; 95 % CI 0.75–10.3) was smaller than that seen in men. As with men, the risk was greatest for women employed in furniture factories (OR 4.6; 95 % CI 1.16–18.3). No increase in risk was observed with an increase in the intensity of exposure in women, regardless of the histological type. However, the small number of cases precluded any detailed analysis.

Squamous Cell Carcinoma

The findings from the pooled analysis [17] were more ambiguous for squamous cell cancers than for adenocarcinomas (Fig. 7.2). The risk for women only was approximately doubled, particularly for women who had worked in moderately or highly exposed jobs; an exposure-effect relationship was evident with respect to the exposure duration. It has to be noted that the results for women were based on small numbers. For men, the risk of squamous cell carcinoma was not related to being exposed at the job nor to the intensity or the duration of exposure. Overall, the results showed the risk estimates for squamous cell carcinomas to be distinctly lower than those for adenocarcinomas.

Table 7.1 Main characteristics of the 12 case-control studies included in the pooled analyses by Demers et al. [17], Leclerc et al. [18], 't Mannetje et al. [20], and Luce et al. [19]

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
China (Shanghai)/ Zheng et al. [21]	In-person interview	Asbestos, silica, metal, coal, wood, textile, petroleum products, benzene/paint, chromium, pesticide, formaldehyde, chromium	Population-based cancer registry of Shanghai diagnosed between 01/1988 and 02/1990	Randomly selected from the Shanghai Resident Registry
	Self-reported exposures	Job titles	Men: 39 (16/72)	Men: 269
	Job titles		Women: 21 (18/55)	Women: 145
France/Leclerc et al. [22], Luce et al. [23–25]	Interviewed by trained physicians	Job titles	Diagnosed between 01/1986 and 02/1988 in 27 participating hospitals in France	Selected from patients of the same hospital with cancer from another site and neighborhood of cases
	Detailed occupational history	Industry titles	Men: 167 (49/36)	Men: 320
	Job titles and industries coded ISCO and ISIC	WD, formaldehyde, leather dust, textile dust, flour dust, sugar dust, coal/coke dust, nickel, chromium, chromium VI, welding fumes, soldering fumes, cutting oils, paints, varnishes and lacquers, glues, adhesives	Women: 40(13/45)	Women: 89
	Specific questionnaire for substances, compounds, or procedures			
	Assessment by industrial hygienist			
Germany (Hessen)/ Bolm-Audorff et al. [26]	Occupational history collected through interview	Wood dust, leather dust, welding fumes, pesticides, other dusts (stone, building site, cereal)	Diagnosed between 01/1983 and 12/1985 in hospitals in Hessen	Selected from patient with nonoccupational bone fractures matched for each case on age, sex, and residence
			Men: 33 (9/39)	Men: 33
			Women: 21 (5/33)	Women: 21
Italy (Verona, Vicenza)/Comba et al. [27]	Interviewed or mailed questionnaire	Wood dust, leather dust, metal, textile, mining and construction, farming	Diagnosed between 1982 and 1987 in hospitals of Verona, Vicenza, and Siena provinces	Selected from patient admitted for diseases other than sinonasal diseases, matched for each case on age, sex, and residence
	General occupational history		Men: 55 (25/47)	Men: 184
	Detailed work description in 7 industries		Women: 23 (14/36)	Women: 70
Italy (Brescia)/ Comba et al. [28]	Detailed occupational history	Wood dust, leather dust, metal, textile, mining and construction, farming	Diagnosed between 1980 and 1989 in Brescia Hospital	Selected from patients treated in the same hospital for benign and malignant tumors of the head and neck (excluding cases localization) matched for each case on age, sex
	Specific items concerning work in metal, leather, and wood industries		Men: 23 (22/52)	Men: 70
			Women: 11 (10/50)	Women: 32
Italy (Biella)/ Magnani et al. [29]	Detailed occupational history	Wood dust, leather dust, metal, textile, mining and construction, farming	Diagnosed between 1976 and 1988 among residents of Biella and Cossato	Selected from patient with diagnoses other than respiratory cancer, matched for each case on age, sex
	Specific items concerning work in textile, garment, furniture, shoe, leather, metalworking, agriculture	Formaldehyde (job-exposure matrix and industrial hygienist)	Men: 22 (43/38)	Men: 92
			Women: 4 (33/67)	Women: 19

Table 7.1 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Italy (Vigevano)/ Merler et al. [30]	Occupational history, interviews	Leather dust, solvents, rubber, wood dust, polycyclic aromatic hydrocarbons, nickel, benzene	Diagnosed between 1968 and 1982 and identified through cancer registry	Selected from electoral roll (living controls) and mortality records (dead controls) matched for age, sex, vital status, year of death if dead
	Blind evaluation by 2 occupational physicians on the basis of recorded interviews		Men: 16 Women: 5 Men+Women: 21 (69/6)	Men: 29 Women: 10
The Netherlands/ Hayes et al. [31, 32]	Job history	Wood dust	Diagnosed in men aged 35–79 years between 1978 and 1981 in 6 major hospitals which treat head and neck tumors	Random sample of living and dead males in the Netherlands in 1981 selected from municipal resident registries and records of the Central Bureau of Genealogy
	Interviews by trained interviewers Job titles and industries coded SICM of US Census and tasks with the US DOT Job history reviewed and classified according to level and probability of WD exposure and formaldehyde (blinded to case-control status)	Formaldehyde	Men: 91 (25/55) Women: –	Men: 195 Women: –
Sweden/Hardell et al. [33]	Mailed questionnaire completed by telephone interviews	Asbestos, chlorophenols, DDT, glass fibers, leather work, organic solvents, woodwork, particle board production	Diagnosed between 1970 and 1979 and reported to the Swedish Cancer Registry Men: 44 (7/70) Women: –	Referents of a previous study of soft tissue sarcoma and lymphoma Men: 541 Women: –
USA (Virginia, North Carolina)/ Brinton et al. [34, 35]	Telephone interviews	Wood dust, leather, nickel, chromium, asbestos, petroleum products, formaldehyde	Admitted to four hospitals in North Carolina and Virginia between 1970 and 1980	Selected from living hospital cases matched for year of admission, age, sex, race, and area of residence
	Occupational exposures, medical and family history		Men: 93 (15/61) Women: 67 (17/52)	Men: 181 Women: 106
USA (Los Angeles)/ Mack et Preston-Martin[a]	Telephone interviews		Diagnosed between 1979 and 1985 and reported to a tumor registry	Neighborhoods
	Occupational history, job titles		Men: 64 (3/63) Women: 38 (3/41)	Men: 108 Women: 70
USA (Seattle)/ Vaughan and Davis [36]	Telephone interviews	Wood dust, formaldehyde (study specific JEM)	Diagnosed between 1979 and 1983 and identified from a population-based tumor registry	Selected by random digit dialing and matched for sex and age
	Occupational history, job titles		Men: 33 (3/59) Women: 20 (5/35)	Men: 327 Women: 225

(continued)

Table 7.1 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Pooled analysis of 12 international case-control studies IARC/Demers et al. [17], Luce et al. [19]	Occupational history, job titles, and industries coded by ISCO and ISIC	Wood dust, leather dust, formaldehyde, flour dust, coal dust, silica dust, textile dust, asbestos, mineral wools, ceramic fibers	Cases of the 12 above studies	Controls of the 12 above studies
	Job-exposure matrix		Men: 680 (25/48)	Men: 2,349
			Women: 250 (10/40)	Women: 787
Pooled analysis of eight European case-control studies/'t Mannetje et al. [20]	Occupational history, Job titles and industries coded by ISCO and ISIC	Wood dust, leather, formaldehyde	Cases of the 8 European studies above (France, Germany, Italy, the Netherlands, Sweden)	Controls of the 8 European studies above (France, Germany, Italy, the Netherlands, Sweden)
	Job-exposure matrix	Other high-risk occupations/ industries	Men: 451 (33/44)	Men: 1,464
			Women: 104 (11/39)	Women: 241

[a]Mack W, Preston-Martin S, Case-control study of cancers of the nasal sinuses and nasopharynx among non-Asians in Los Angeles county, 1995, unpublished work
AC adenocarcinomas, *SCC* squamous cell carcinomas

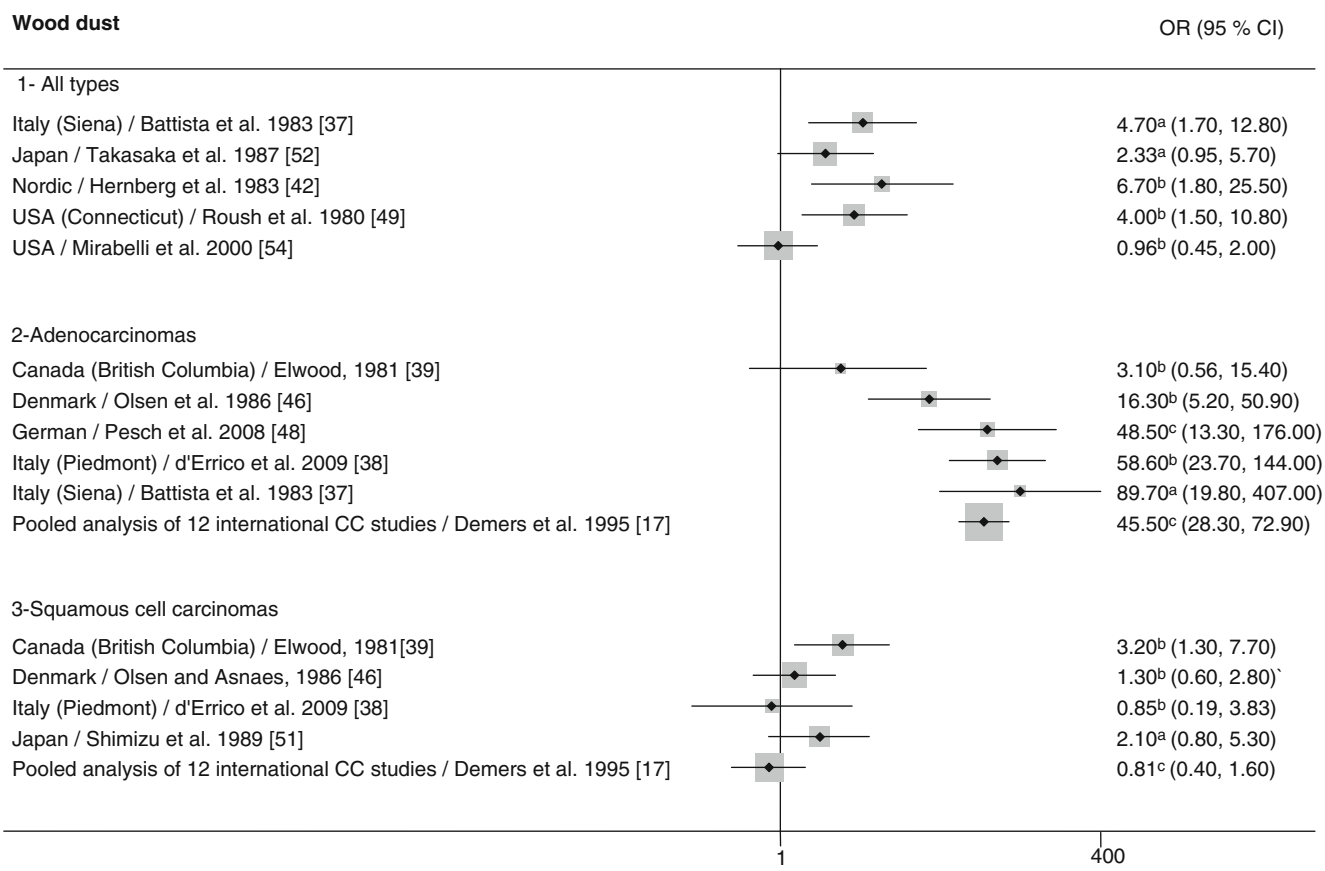
Table 7.2 Main characteristics of other case-control studies (not included in the pooled analyses)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Italy (Siena)/ Battista et al. [37]	Occupational history and specific questions about having ever worked in wood industry, furniture industry, and leather industry	Wood dust, leather	Diagnosed between 1963 and 1981 in Siena hospital	Selected from men admitted for other diseases, matched for age
			Men: 36 (14/47)	Men: 164
			Women: –	Women: –
Italy (Piedmont)/ d'Errico et al. [38]	Occupational history, jobs, and tasks description	Wood dust, leather dust, arsenic, nickel, chromium, PAH, welding fumes, oil mists, formaldehyde, flour, cocoa powder, textile dusts, silica, coal dust, paint mists, strong-acid mists, and organic solvent vapors	Diagnosed or treated between 1996 and 2000 in all Piedmont hospitals	Selected from departments of ENT and orthopedics, frequency matched for age, sex and residence
	Job-exposure matrix		Men: 76 (59/16)	Men: 234
	Exposure evaluated by occupational physicians		Women: 37 (22/68)	Women: 102
Canada (British Columbia)/Elwood [39]	Occupational history	Wood dust	Diagnosed between 1939 and 1977 in the main cancer treatment center in British Columbia	Selected from patients with cancer considered unrelated to smoking or outdoor work, matched for age and year of diagnosis
			Men: 121 (9/50)	Men: 363
			Women: –	Women: –
Japan (Hokkaido)/ Fukuda and Shibata [40], Fukuda et al. [41]	Postal questionnaire	Woodworking (carpenters, joiners, furniture workers, and others woodworkers)	Diagnosed between 1982 and 1986 in all Hokkaido hospitals, aged 40 to 79,	Selected from telephone directory, matched for sex, age, and residence
	Occupational history, history of nasal disease		Men: 81 (?/91)	Men: 162
			Women: 25 (?/83)	Women: 50
Nordic/Hernberg et al. [42]	Telephone interviews	Woodwork, farming, forestry, textile work, metal work, construction work	Diagnosed between 07/1977 and 12/1980 and reported to national cancer registries of Denmark, Finland, and Sweden	Patients with tumors of colon and rectum, matched for country, sex, and age at diagnosis
	Occupational history, tasks, exposure to dust, smoke, fumes, or chemicals	Specific agents: cadmium, chromium, nickel	Men: 110	Men: 110
	Assessment of exposure by an industrial hygienist		Women: 57	Women: 57
			Men+Women: 167 (11/57)	

Table 7.2 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Hong Kong/Ng [43]	Occupational history	Job titles	Diagnosed between 1974 and 1981 and reported to the Cancer Registry in Hong Kong	Two groups: nasopharyngeal carcinomas and other cancers selected in random order from the same registry and matched for treatment center, year of admission, age, sex, race, and resident status
		Industries titles	Men: 157	Men: 159 + 158
			Women: 68	Women: 65 + 68
			Men+Women: 225 (2/53)	
Denmark/Olsen et al. [44], Olsen and Jensen [45], Olsen and Asnaes [46], Olsen [47]	Occupational history	Formaldehyde, wood dust, leather dust, nickel-chromium, chlorophenols, textile dust, asbestos, metal work, man-made mineral fibers, paint, lacquer and glue manufacture, plastic manufacture, silage manufacture	Diagnosed between 1970 and 1982 and identified by the Danish Cancer Registry	Patients with cancers of colon, rectum, prostate/breast diagnosed during the same period
	Exposure assessed by industrial hygienists		Men: 345 (13/69)	Men: 1,631
			Women: 180 (8/66)	Women: 834
Germany/Pesch et al. [48]	Occupational history	Wood dust, varnishes, pigments stains, formaldehyde	Workers of woodworking industries with SNC recognized as occupational disease between 1994 and 2003	Workers of woodworking industries with recognized accidents and falls frequency matched for age
	JEM based on personal measurements in the German woodworking industries: mg/m^3 and mg/m^3.years		Men: 86 (100/0)	Men: 204
			Women: –	Women: –
USA (Connecticut)/ Roush et al. [49, 50]	Job title at 1, 10, 20, 25, 30, 40, 50 years prior to death or until the subject was less than 20 years of age	Nickel, cutting oils, wood dust	Identified through the Connecticut Tumor Registry, aged 35 years or older, and died between 1935 and 1975 in Connecticut	Randomly selected from population of males dying in Connecticut from 1935 to 1975 at age 35 or older
			Men: 198 (10/55)	Men: 605
			Women: –	Women: –
Japan/Shimizu et al. [51]	Occupational history	List of occupations in relation with wood	SCC of maxillary sinus diagnosed in six hospitals in north-eastern Japan between 10/1983 and 10/1985	Random sample of residents in the same area from telephone directories, matched for age and sex
			Men: 45 (0/100)	Men: 90
			Women: 21 (0/100)	Women: 42
Japan/Takasaka et al. [52]	Complete history of experience in woodworking and detailed tasks	List of occupations (forestry worker, coal miner, nickel worker, wood sawyer, chipperman, veneer maker, wood machinist, wood furniture maker and joiner, leather worker, carpenter)	Admitted to Tohoku University Hospital in Japan between 1971 and 1982	Admitted to the same hospital with other otorhinolaryngological diseases, matched for sex, age, and date of admission
			Men: 107 (6/80)	Men: 413
			Women: –	Women: –
USA/Caplan et al. [53], Mirabelli et al. [54], Zhu et al. [55]	Telephone interviews	Pesticides/herbicides, dry cleaning, wood preservatives, wood dust, asbestos, leather, chlorophenols, formaldehyde	Selected from the Selected Cancers Study (Vietnam veterans), born between 1929 and 1953 and reported to eight cancer registries in the USA between 12/1984 and 11/1988	Selected by random digit dialing
	Occupational history		Men: 70 (20/59)	Men: 1,910
	Estimation of exposures by industrial hygienist		Women: –	Women: –

AC adenocarcinomas, *SCC* squamous cell carcinomas



- For each study, when ORs were reported for specific histological types, the OR for the category "All types" is not presented.
- Results from individual studies included in the pooled analysis are not presented.
- Exposure categories:[a]Wood workers or cabinet makers,[b]Wood dust,[c]Wood dust ≥ 5 mg/m^3

Fig. 7.2 Exposure to wood dust. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

Case-control studies not included in the pooled analysis confirmed the role of wood dust exposure in sinonasal cancer risk, the association with exposure to wood dust being much stronger for adenocarcinomas than for squamous cell carcinomas (Fig. 7.2).

Cohort Studies

An elevated risk of sinonasal cancer was also found in cohorts of woodworkers, but there was no information available on histological type. Demers and coworkers [56] performed also a pooled analysis of five cohorts of workers exposed to wood dust. A significant excess in the number of deaths from sinonasal cancer (11 cases; standard mortality ratio [SMR] 3.1; 95 % CI 1.6–5.6) was found, with a clear increase of the SMR with the exposure probability. The excess risk was limited to workers in the furniture industry and no sinonasal cancer deaths were observed in the plywood industry cohorts. The excess risk was limited to those workers who had begun their employment before 1940 and to those whose exposure had begun more than 20 years earlier. In this pooled analysis, the results were strongly influenced by the number of deaths from sinonasal cancer in the group of furniture industry workers from England (ten out of the 11 deaths from sinonasal cancer).

Summary of Studies on Wood Dust

There are epidemiological data indicating that exposure to wood dust is related to extremely high relative risks for sinonasal cancer. Adenocarcinoma represents a variable proportion of sinonasal cancers (between 10 and 50 %, depending on the country). The link between the onset of this histological form and exposure to wood dust is very clear and the association is stronger for adenocarcinomas than for squamous cell carcinomas. Thus, the excess risks reported for all the histological types together could be explained largely by the results relating to adenocarcinoma.

Even though the results for adenocarcinoma were on the whole consistent across the studies, the relative risk was much higher in Europe (especially France and Italy) than in

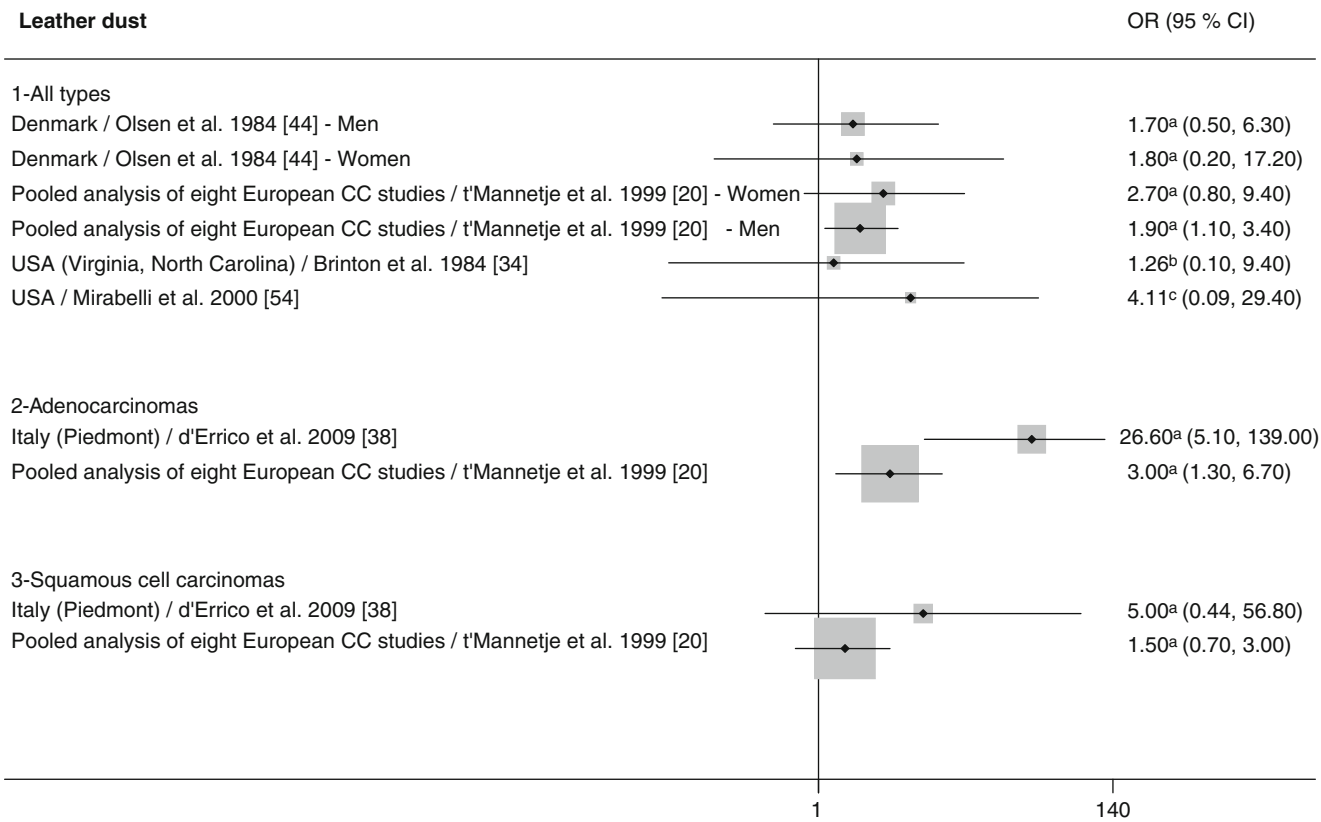
North America and Asia. This difference could be related to the levels of exposure or to the types of wood in use, although no data on the type of wood used were available in the pooled analysis to confirm this hypothesis. However, hardwoods are more widely used in Europe, especially in southern countries, where the proportions of adenocarcinomas among sinonasal cancer cases are higher than in the north.

A large part of the adenocarcinoma cases included in the published studies were related to exposure to hardwood dusts, and the case-control investigations in which the type of wood used was evaluated confirm the suspicion of a stronger association with hardwood dust than with softwood dust [4, 22, 48]. However, it is virtually impossible to distinguish the respective role of each type of wood in the genesis of sinonasal cancer. On the one hand, very few studies have recorded the necessary information, and, on the other, rather often both types of wood are used in furniture factories and also in carpentry and cabinetmaking workshops, the fields of activity in which the risks are highest.

The results of some studies with workers exposed solely or mostly to softwood dusts showed a consistent excess risk, but the magnitude of the excess was small in comparison to hardwood, and the association was primarily with squamous cell carcinoma [4, 57].

Leather Dust

An excess of sinonasal cancers in leather workers, especially in boot and shoe manufacture and repair, has been reported in numerous case-control studies (Fig. 7.3), as well as in cohort or record linkage studies in the United Kingdom [58, 59], the Nordic countries [47, 60], and Italy [61]. The role of leather dust was suggested by the observation of higher risks in jobs exposed to dust and in workers most extensively exposed to leather dust. Leather dust is now considered as a human carcinogen (Group 1) by the IARC [4, 14] with sufficient evidence in humans for the nasal cavity and paranasal sinuses (see also Section on Exposure Characteristics). The association is stronger for



- For each study, when ORs were reported for specific histological types, the OR for the category "All types" is not presented.
- Results from individual studies included in the pooled analysis are not presented.
- Exposure categories: [a]Leather dust, [b]Leather or shoe industries, [c]Leather workers

Fig. 7.3 Exposure to leather dust. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

adenocarcinomas, but some results suggest that other histological types could also be involved. Merler and coworkers [30] showed a very clear relationship between the level of exposure to leather dust and the risk of adenocarcinoma, with an OR of 20.4 (95 % CI 2.7–152.0) for moderate exposures and 88.0 [95 % CI 12.1–642.0] for high exposures. For the other histological types, the OR associated with exposure to leather dust was 6.9 (95 % CI 1.4–34.4).

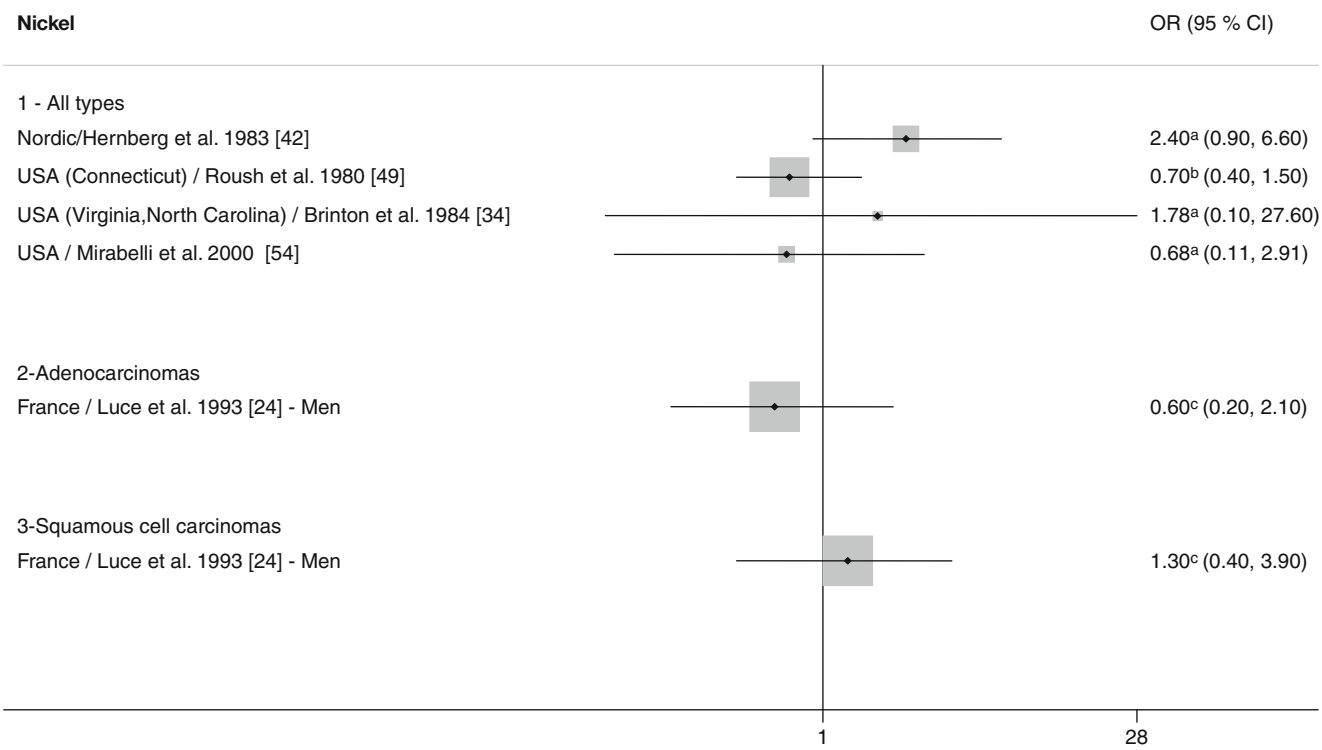
Nickel and Chromium Compounds

The association between the occurrence of sinonasal cancers and exposure to nickel compounds encountered in nickel refining is well recognized. Excesses of sinonasal cancers have also been observed in cohorts of workers exposed to hexavalent chromium [4, 14, 62].

In case-control studies, exposures to nickel and chromium (often simultaneously) have emerged mainly from welding stainless steel, or spray painting, and the levels of exposure were low, which may explain the mainly null results (Figs. 7.4 and 7.5). However, Hernberg and coworkers [42] studying these exposures in these kinds of activities for sinonasal cancer observed an OR of 2.7 (95 % CI 1.1–6.6) for exposure to chromium and of 2.4 (95 % CI 0.9–6.6) for exposure to nickel. Other studies have not confirmed these results. Brinton and coworkers [34] observed a nonsignificantly increased risk of sinonasal cancer in those subjects exposed to chromates (OR 1.49; 95 % CI 0.40–5.60) through the use of these products in construction and painting. Only one male case was exposed to nickel in this study (OR 1.78; 95 % CI 0.10–27.6]. Two studies have examined the histological types separately [24, 38], and no significant association with exposure to chromium and nickel was observed, regardless of histological type. The results with regard to exposure to welding fumes were conflicting [24].

Formaldehyde

Formaldehyde is a probable cause of sinonasal cancer based on sufficient evidence from excess of squamous cell carcinomas in rodents and limited evidence in humans (with an overall evaluation of carcinogenic to humans, Group 1) [13, 63].



- For each study, when ORs were reported for specific histological types, the OR for the category "All types" is not presented.
- Results from individual studies included in the pooled analysis are not presented.
- Exposure categories: [a]Ever exposed, [b]Nickel workers (grinder, filer, turner, molder, welder…), [c]Ever exposed 'Probable or definite'

Fig. 7.4 Exposure to nickel compounds. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

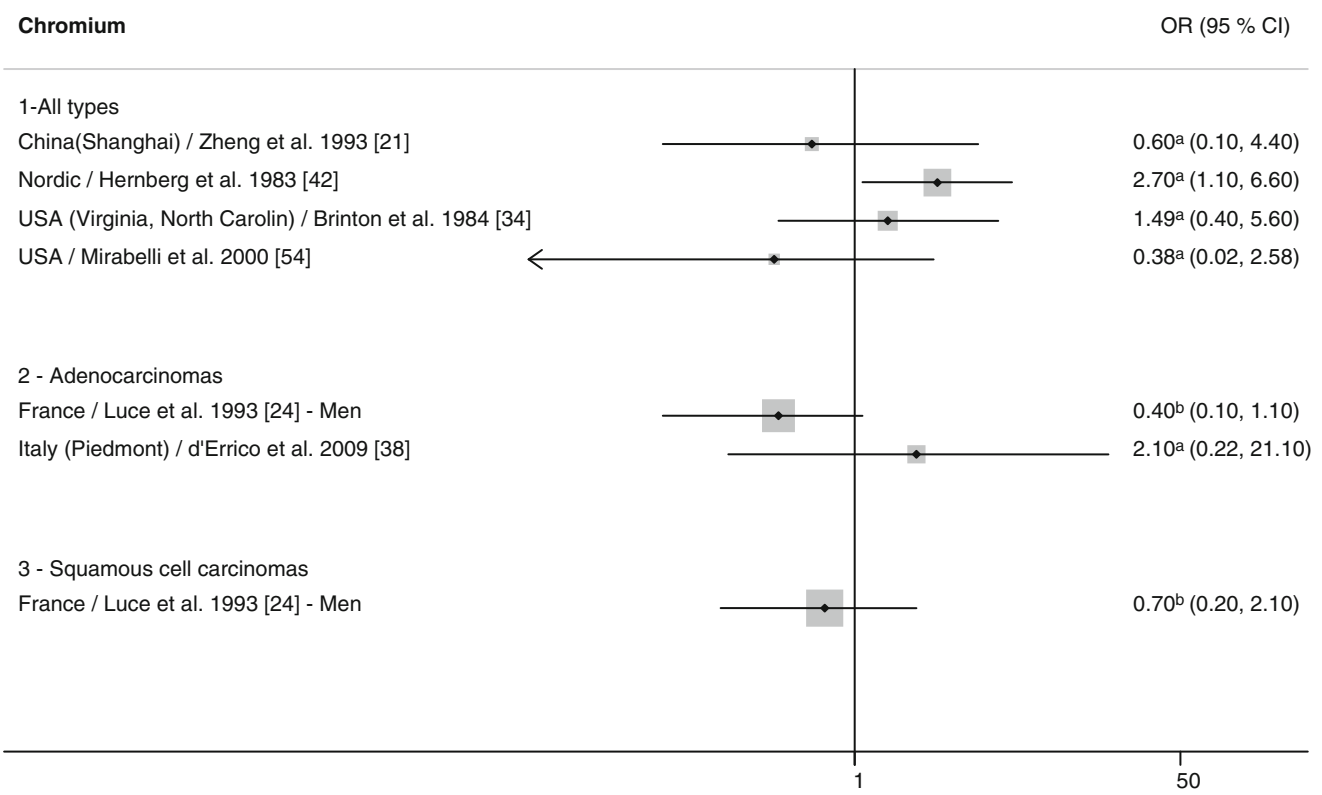


Fig. 7.5 Exposure to chromium compounds. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

Following the reporting of nasal squamous cell carcinogenicity in rats exposed to high doses of formaldehyde in the early 1980s [64], several epidemiological studies have been published [2, 63]. Five cohort studies and one study of proportionate morbidity based on industrial formaldehyde exposure [65–73], and five studies based on exposures among pathologists and embalmers [74–78] have examined the association between formaldehyde and sinonasal cancer. The histological subtypes have not been specified in any of the cohorts. Due to the rarity of the disease, the observed and expected numbers in each study have been very small, and the interpretation of risk is therefore uncertain. A study of proportionate morbidity from Denmark, however, included 13 male and 4 female cases on nasal cavity cancer with corresponding estimated relative risks of 2.3 (95 % CI 1.3–1.4) and 2.4 (95 % CI 0.6–6.0) [69, 70].

The pooled data of 12 case-control studies were analyzed with respect to formaldehyde exposure [19] (Fig. 7.6). Significantly elevated relative risks for adenocarcinomas appeared in the groups with the highest cumulative exposure in both men (OR 3.0; 95 % CI 1.5–5.7) and women (OR 6.2; 95 % CI 2.0–19.7), whereas relative risks for squamous cell carcinomas were not significantly increased (OR 1.2; 95 % CI 0.8–1.8 and OR 1.5; 95 % CI 0.6–3.8 in men and women, respectively). However, in the group with highest probability of formaldehyde exposure, an elevated relative risk of squamous cell carcinomas was observed in men (OR 2.5; 95 % CI 0.6–10.1) and women (OR 3.5; 95 % CI 1.2–10.5). Formaldehyde exposure has also been studied in four case-control studies not included in the pooled analysis (Fig. 7.6) and was found to be associated with an increased risk of sinonasal cancer in two of them.

Textile Workers/Textile Dust

Data from the 12 case-control studies presented above and in Table 7.1 were analyzed according to the occupation and industry [18]. This pooled analysis detected an increased risk of sinonasal adenocarcinoma among women employed in the textile industry (OR 2.6; 95 % CI 1.0–6.6), and a high risk of squamous cell carcinoma for men involved in fiber

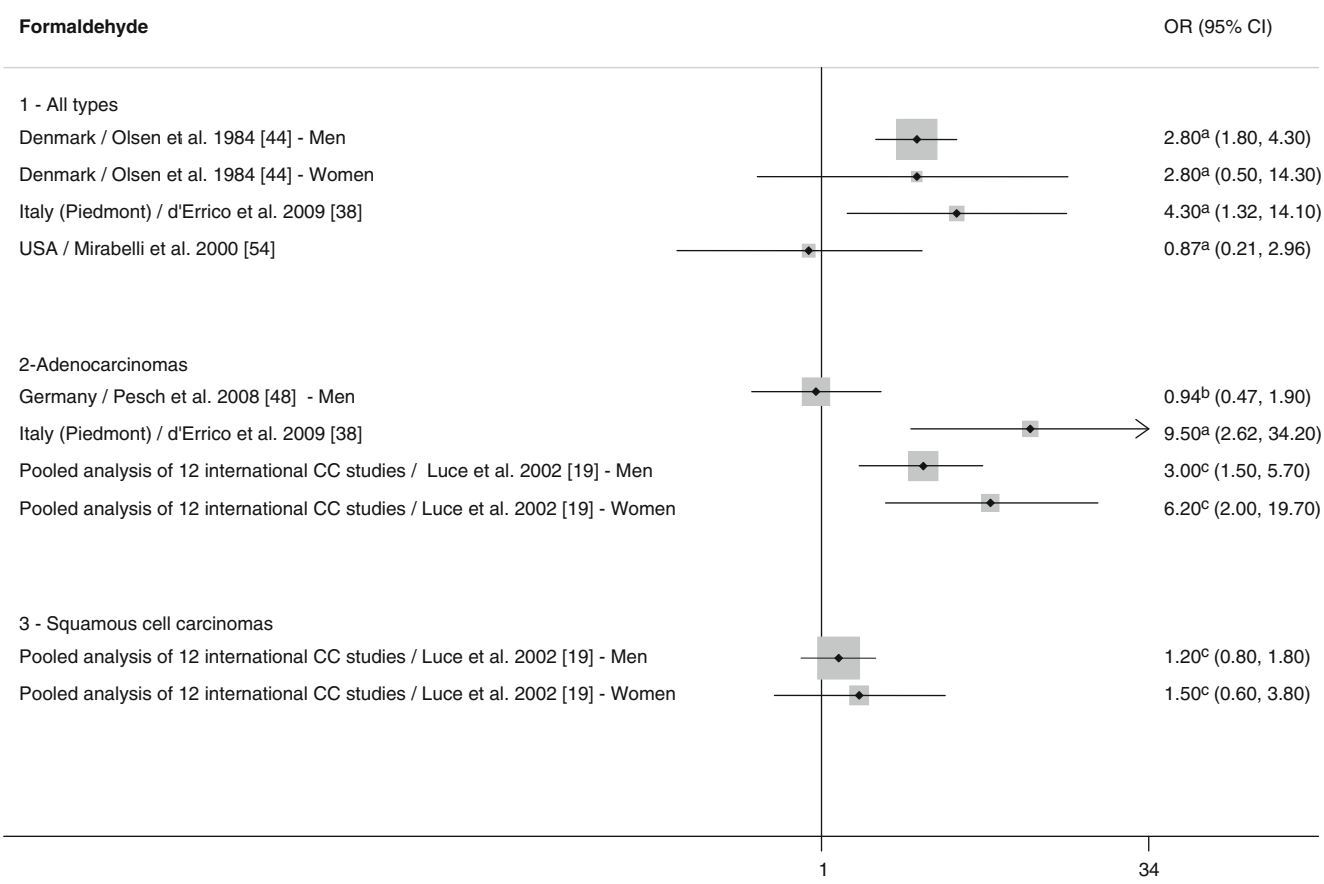


Fig. 7.6 Exposure to formaldehyde. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

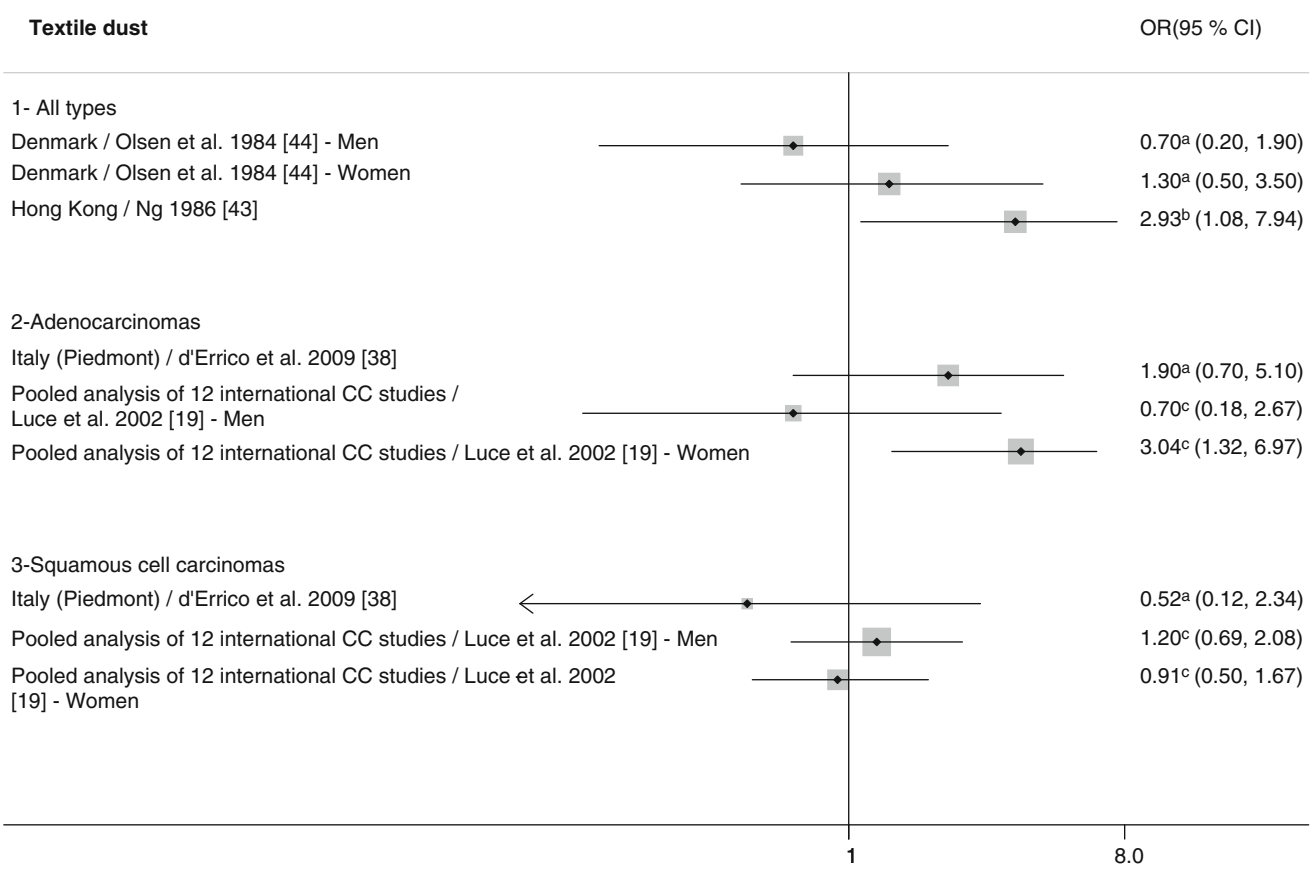
preparation (OR 5.1; 95 % CI 1.3–19.2) or finishing of textile products (OR 3.0; 95 % CI 1.0–9.1).

The same dataset was also analyzed according to exposure to textile dust, which was considered a plausible causal agent [19]. The risk of adenocarcinoma was associated with cumulative exposure to textile dust only in women, with no clear dose-response relationship: the ORs were 1.7, 3.5, and 2.5 for low, medium, and high levels, respectively. No association with the cumulative level, probability, and duration of exposure to textile dust was found among men for both histological types or among women for squamous cell carcinoma. However, a high risk of squamous cell carcinoma (OR 6.6; 95 % CI 1.4–31.8) was observed among men who had been exposed to more than 0.5 mg/m^3. Textile dust or textile work was also associated with elevated risks of sinonasal cancer in several other case-control studies (Fig. 7.7).

A possible role of exposure to formaldehyde has been proposed to explain the observed elevated risk in the textile industry, but in the pooled analysis, adjustment for formaldehyde exposure did not change markedly the ORs associated with textile dust [19]. The difference between men and women might be explained by exposure to different types of textile fibers. The role of cotton dust was postulated by Brinton et al. [35], who reported a high proportion of cases exposed to cotton. The nature of textile fibers (cotton, wool, synthetic fibers) was available in four studies in the pooled analysis, but when the data were combined, no specific effect of a particular type of textile was found [19].

Other Occupational Exposures

An increased risk of carcinomas of the paranasal sinuses and mastoid process was found in radium watch-dial painters, who ingested radium by "pointing" their brush with their lips. This excess risk was associated with internally



• For each study, when ORs were reported for specific histological types, the OR for the category "All types" is not presented.
• Results from individual studies included in the pooled analysis are not presented.
• Exposure categories: [a]Textile dust [b]Textile workers,[c]Level of cumulative exposure : ≥ medium high (recalculated)

Fig. 7.7 Exposure to textile dust. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

deposited radium-226 [15]. There is also sufficient evidence that the manufacture of isopropyl alcohol by the strong-acid process causes sinonasal cancer. The evidence is inadequate to draw conclusions on the carcinogenicity of isopropyl alcohol, isopropyl oils, or isopropanol produced using other methods [63].

Other occupational exposures have been associated with the risk of sinonasal cancer, such as paints [42], adhesives [24], cutting oils [49, 50], and chlorophenols [33, 54, 55]. In the pooled analysis [19], an increased risk of squamous cell carcinoma was observed among men with a high cumulative exposure to asbestos (OR 1.6; 95 % CI 1.1–2.3). However, no significant association has been found in the few other case-control studies that have evaluated the risk associated with exposure to asbestos [21, 42], but the level of exposure and the histological type were not taken into account. Associations between exposure to arsenic (OR 5.2; 95 % CI 1.20–22.20) and sinonasal squamous cell carcinoma and between exposure to organic solvents and adenocarcinoma (OR 8.2; 95 % CI 4.32–15.72) have also recently been reported [38] and need to be confirmed.

A high risk of sinonasal cancer has been observed in many other occupations. The pooled analysis of 12 case-control studies highlights several associations [18]. Some results have reinforced the plausibility of associations reported in other studies (not included in the pooled analysis): a significantly elevated risk of sinonasal cancer has been observed in farmers, men employed in the food industry, food preservers, cooks, and vehicle drivers. The high risks reported in some studies for coal miners [79], construction [23, 27, 43], or metalworking [28, 47, 79] were not confirmed in the pooled analysis. However, two new associations emerged with respect to sinonasal squamous cell carcinomas: significant ORs were observed for hairdressers (OR 2.87; 95 % CI 1.03–8.02) and rubber workers (OR 3.17; 95 % CI 1.28–7.86).

Other Risk Factors

There is a causal relationship between tobacco smoking and the risk of cancer of the nasal cavity and the paranasal sinuses [80, 81]. One cohort study and nine case-control studies have examined the risk of tobacco smoking and sinonasal cancer. The association is consistently stronger for sinonasal squamous cell carcinomas than for adenocarcinomas [82]. With an average relative risk of 1.5–2.5, the association is significantly less strong than for many other tobacco-associated cancers, e.g., for lung cancer with an estimated relative risk of 15–30 [82].

No other nonoccupational risk factor has been identified for sinonasal cancer. In particular, with regard to biological agents classified as human carcinogens, nasal cavity and sinuses are not among the cancer sites for which there is sufficient or limited evidence in humans. Although Epstein-Barr virus (EBV) infection is associated with sinonasal lymphomas, no relation was reported with sinonasal carcinomas. Similarly, the detection of human papillomavirus (HPV) was reported in sinonasal cancer cases, but there is a lack of evidence from case-control studies to support these data [83, 84].

Summary and Conclusions

Occupational factors have a predominant role in the etiology of sinonasal cancer, and apart from these exposures, only tobacco smoking has been confirmed as a risk factor. Exposures to wood dust and leather dust are predominantly associated with adenocarcinomas, whereas increased risks for tobacco smoking were mainly found in squamous cell carcinomas. Epidemiological data do not allow determining whether other occupational exposures linked to sinonasal cancer are associated with specific histological types. In addition, no epidemiological studies are available differentiating histological subtypes, such as intestinal-type adenocarcinoma. The very high excess risks associated with wood dust exposure, together with the large number of exposed workers, mean that wood dust is a major cause of sinonasal cancer.

Exposure Characteristics

There is a range of exposures where causality to development of sinonasal cancer has been documented (see Section on Epidemiology and Occupational Risk Factors). This section summarizes and discusses exposure characteristics for commonly used substances evaluated by the International Agency for Research on Cancer (IARC) as being carcinogenic to humans and to which there is sufficient evidence for sinonasal cancer in humans [4]. The work-related substances are wood dust, nickel compounds and nickel metal, and "shoe and leather work" (leather dust). Hexavalent chromium is also included, although in the latest IARC evaluation, it is stated that "the epidemiological evidence remains suggestive but inconclusive regarding the effect of chromium VI on nasal and sinonasal cancers" [4]. In addition to these occupational exposures, tobacco smoking is associated with increased risk of sinonasal cancer [81].

The exposure characteristics for each substance are summarized in Table 7.3. Formaldehyde is not included as there is only limited epidemiological evidence that formaldehyde causes sinonasal cancer, as opposed to nasopharyngeal cancer where the association with formaldehyde exposure is well documented [4, 89] (see Section on Epidemiology and Occupational Risk Factors).

All substances, except for "shoe and leather work," are prevalent exposures all around the world. In 2001–2003, approximately 3.6 million workers in the European Union alone were being exposed to wood dust on a regular basis; worldwide the numbers are hundreds of millions [2, 90]). Similarly, several million workers worldwide are exposed to airborne fumes, dusts, and mists containing nickel and nickel compounds; the same is true for exposure to chromium or its compounds [62]. Smoking is still very prevalent in most countries and is practiced by more than 1,000 million people around the world [80, 81, 88].

Wood Dust

Wood dust exposure is present in many industries; the typical high exposure industries or tasks are furniture industry, cabinetmaking, and joineries [2, 4] (see Section on Epidemiology and Occupational Risk Factors). The wood dust exposure levels in various industries in the past and more recently have been fairly well documented; it is known that dust levels above 5 mg/m^3 were previously common, mainly in sanding operations and similar tasks, for example, during furniture and cabinet manufacturing. However, even today many subjects are exposed to levels above 5 mg/m^3 [90, 91]. In epidemiological studies on wood dust exposure and sinonasal cancer, more exposure-response relations have been revealed, and now there is evidence in the literature that high exposure (>1–5 mg/m^3) for several years may be required in order to develop sinonasal cancer [2, 38, 57, 85, 92] (see Section on Epidemiology and Occupational Risk Factors). Although no threshold value exists, it is likely that health effects at exposure levels below 1 mg/m^3 are clearly less significant as opposed to higher exposure levels [92].

Chromium VI

Exposure to hexavalent chromium is prevalent in a range of industries and chromium compounds have been in widespread commercial use for more than 100 years. High exposure to chromium VI occurs during chromate production,

Table 7.3 Exposure characteristics for agents causally related to sinonasal cancer (SNC). Only agents evaluated as carcinogenic to humans by IARC (Group 1) are included

	Histological type of SNC	Industries/job of relevance	Exposure-response patterns, threshold values	Exposure information sources
Wood dust[a]	Adenocarcinoma. Probably squamous cell carcinoma	High exposed wood industries, e.g., furniture industry, cabinet manufacturing, joinery shops	Exposure-response relationships observed in several studies	IARC [2]
			High exposure (>1–5 mg/m^3) for several years. No confirmed risk for exposures below 1 mg/m^3	IARC [85] Demers et al. [57] d'Errico et al. [38] IARC [4]
Chromium VI	Not specified	Chromium production, chromium pigment production, chromium platers	Exposure-response relationships not reported	IARC [62]
			Airborne chromium VI concentrations >1 mg/m^3 found in past studies, lower in recent years	d'Errico et al. [38] Luippold et al. [86] IARC [4]
Nickel compounds	Not specified	Nickel refining industry	No clear exposure-response relationships reported	IARC [62]
		Hydrometallurgy Electrolysis workers Calcining workers	Airborne nickel concentrations >1 mg/m^3 found in earlier studies, lower in recent years	IARC [4]
"Shoe and leather work" (leather dust)	Mainly adenocarcinoma. Possibly other types	Boot and shoe manufacture	Exposure-response relationships observed in five studies ("leather dust years" or exposure intensity)	IARC [87]
		Boot and shoe repair	Increased for both light and heavy exposure, and increased for 5 and 10 years of exposure	Merler et al. [30] d'Errico et al. [38] Straif et al. [14] IARC [4]
Tobacco smoking	Squamous cell carcinoma	–	Exposure-response relationships observed in several studies (duration, intensity)	IARC [88]
			No clear threshold values	't Mannetje et al. [20] IARC [81]

[a]The evaluation is based on studies including workers predominantly exposed to hardwood dust

chrome pigment manufacturing, chrome plating, spray painting, and during welding [4, 62].

IARC's evaluations are based on the excess cases of sinonasal cancer found in workers in chromium and chromium pigment production and among chromium platers, whereas no consistent relationship has been seen among spray painters and welders (see Section on Epidemiology and Occupational Risk Factors). Airborne chromium VI levels above 1 mg/m^3 have been found in earlier studies, but in general the exposure levels have decreased substantially to below 10 µg/m^3 in the chromium production industry [4, 86]. No epidemiological studies on chromate VI and sinonasal cancer have reported exposure-response relationships, and there is no definitive knowledge of the duration and the intensity of the exposure needed to cause sinonasal cancer.

Nickel Compounds and Nickel Metal

Nickel compounds and nickel metal are used in many industries and have also been in widespread commercial use for more than 100 years. High exposure to airborne nickel occurs in nickel refining, nickel alloy production, welding, electroplating, grinding, and cutting operations [4, 62]. IARC's evaluation is based on excess cases of sinonasal cancer found among workers in the nickel refining industry and employees in hydrometallurgy and electrolysis plants, whereas no consistent relation has been seen in other occupations, e.g., welders. Furthermore, IARC's evaluation is based on exposure to nickel compounds like nickel sulfate and the combination of nickel sulfides and oxides [4, 62] (see Section on Epidemiology and Occupational Risk Factors). For example, airborne nickel levels above 1 mg/m^3 have earlier been found during nickel refining and nickel alloy production. The exposure levels have decreased with time, but are still highly variable with measured levels between 4 and 800 µg/m^3 in different industries and with different production methods [4]. The past concentration levels of individual nickel compounds are not known. A range of epidemiological studies included exposure-response analysis, but no clear exposure-response relationships have been revealed. There is no firm knowledge of the duration and the intensity of the exposure needed to cause sinonasal cancer.

Shoe and Leather Work

Working in the "shoe and leather work" industry is causally related to the development of sinonasal cancer. Excess risks have been observed among workers employed in boot and shoe manufacture and in boot and shoe repair [87]. Shoe and leather work involves a wide variety of different work procedures and exposure to many toxic substances, and in the IARC monograph published in 1981, the occupation "shoe and leather work" was stated as the causal agent. In the following year, an increased body of evidence in both case-control studies and cohort studies revealed leather dust to be causally related to sinonasal cancer in a dose-dependent manner, especially adenocarcinoma (see Section on Epidemiology and Occupational Risk Factors). Leather dust is now considered as a human carcinogen by IARC [4, 14], but there is no firm knowledge of the duration and the intensity of the exposure needed to cause sinonasal cancer.

Tobacco Smoking

Smoking is still very prevalent worldwide and has been a common lifestyle-related exposure for at least subgroups of individuals for several decades [80, 81, 88]. Several studies have analyzed exposure-response relations for sinonasal cancer in terms of intensity (cigarettes/day), duration, or pack-years, and most have revealed a positive exposure-response relationship. No clear threshold limit for intensity or duration has been identified. In general, the associations to cancer of the nose and paranasal sinuses were considerably lower than for wood dust exposure [4, 88].

IARC has also evaluated the effect of involuntary smoking, the type of tobacco smoke exposure related to exposure at work, on the development of sinonasal cancer, and the evaluation concluded that the literature was sparse and with conflicting results [4, 88].

Pathology

General

The WHO Classification of Tumours [6] lists a total of 63 primary tumor types occurring in the nasal cavity and paranasal sinuses, 12 of which are malignant epithelial types of tumor (Table 7.4). The other tumor categories are benign epithelial tumors, soft tissue tumors, tumors of the bone and cartilage, hematolymphoid tumors, neuroectodermal tumors, and germ cell tumors. In addition to a linkage to occupational exposure, some sinonasal tumors are associated with viruses [6]. The lymphoepithelial carcinoma is strongly associated with EBV, and HPV can be identified in some cases of squamous cell carcinomas [6].

The most common location of the sinonasal carcinomas is in the maxillary sinus (55–60 %), 19–35 % occur in the nasal cavity, 9–15 % in the ethmoid sinus, and only 1 % in the sphenoid and frontal sinuses [93, 94] (Fig. 7.1). A staging (T) classification for maxillary and ethmoid carcinomas has been adopted [95]. Occupational exposure is predominantly associated with squamous cell carcinomas and adenocarcinomas (Fig. 7.8) with these two tumor types having somewhat different etiologies as indicated by epidemiological studies [2, 4, 6] (see Section on Epidemiology and Occupational Risk Factors).

In several studies, squamous cell carcinomas have constituted approximately 35–70 % of the malignancies in the sinonasal region [6, 94, 96] (see Section on Epidemiology and Occupational Risk Factors). Squamous cell carcinoma of the vestibule is considered to be a carcinoma of the skin rather than carcinoma of the sinonasal mucous epithelium. Adenocarcinomas account for a variable proportion of sinonasal cancers, varying

Table 7.4 Malignant epithelial tumors of the nasal cavity and paranasal sinuses

Histological type	ICD-O	Histological type	ICD-O
Squamous cell carcinoma	8070/3	**Salivary gland-type carcinomas**	
Verrucous carcinoma	8051/3	Adenoid cystic carcinoma	8200/3
Papillary squamous cell carcinoma	8052/3	Acinic cell carcinoma	8550/3
Basaloid squamous cell carcinoma	8083/3	Mucoepidermoid carcinoma	8430/3
Spindle cell carcinoma	8074/3	Epithelial-myoepithelial carcinoma	8562/3
Adenosquamous carcinoma	8560/3	Clear cell carcinoma NOS	8310/3
Acantholytic squamous cell carcinoma	8075/3	Myoepithelial carcinoma	8982/3
		Carcinoma ex pleomorphic adenoma	8941/3
		Polymorphous low-grade adenocarcinoma	8525/3
Adenocarcinomas		**Neuroendocrine tumors**	
Intestinal-type adenocarcinoma	8144/3	Typical carcinoid	8240/3
Non-intestinal-type adenocarcinoma	8140/3	Atypical carcinoid	8249/3
Lymphoepithelial carcinoma	8082/3	Small cell carcinoma, neuroendocrine type	8041/3
Sinonasal undifferentiated carcinoma	8020/3		

Adapted from WHO Classification of Tumours [6]

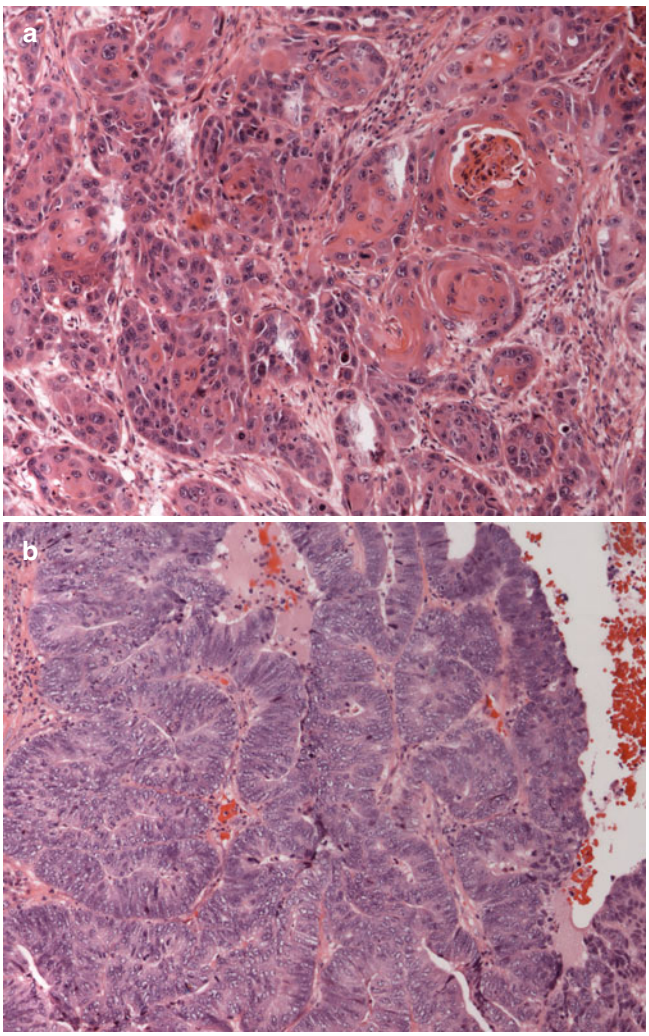


Fig. 7.8 Two main histological types of sinonasal cancer. Squamous cell carcinoma (**a**) and adenocarcinoma (intestinal type) (**b**) are illustrated hematoxylin-eosin staining; 20× objective used

from 10 to 50 %, depending on the country [6] (see Section on Epidemiology and Occupational Risk Factors).

Squamous Cell Carcinoma

Squamous cell carcinomas can be subdivided into distinctive forms including keratinizing, nonkeratinizing, and adenosquamous types (Table 7.4) [6]. An example of a keratinizing squamous cell carcinoma is shown in Fig. 7.8a. The precursor lesions to sinonasal squamous cell carcinomas are poorly known. Sinonasal Schneiderian (inverted) papilloma appears to be a precursor lesion in about 10 % of the cases; the role of squamous metaplasia remains undetermined [6]. There have been no reports describing any specific associations between squamous cell carcinoma subtypes and particular exposures (see Section on Epidemiology and Occupational Risk Factors).

Intestinal-Type Adenocarcinoma

Adenocarcinomas are divided into two groups by WHO, namely, the intestinal-type adenocarcinomas (ITACs) (Figs. 7.8b and 7.9) and the sinonasal non-intestinal type of adenocarcinomas (non-ITACs) [6]. A considerable proportion, 40 % of the sinonasal ITACs, involves the ethmoid sinuses, with the nasal cavities being implicated in 27 % of the cases and the maxillary sinus in 20 % [97, 98]. The distinguishing feature of ITACs is reflected in the name, i.e., they display features of intestinal carcinomas (large intestine or small intestine) morphologically, immunohistochemically, and ultrastructurally. The epidemiological studies on the association between sinonasal cancer and wood dust exposure do not differentiate between adenocarcinoma subtypes. However, the pathology literature associates ITACs with wood dust exposure [6].

Two classifications for ITACs are in use (Table 7.5) [98, 99]. The categories within the classifications are compatible between classifications as shown in the Table 7.5, with the exception that there is no subdivision of mucinous carcinomas in the Barnes classification [6, 98]. In this article, the Barnes classification will be used. Immunohistochemistry for cytokeratin has been routinely used to identify the origin of a tumor; immunostaining for cytokeratin 20 is typically positive in the intestinal epithelium and carcinomas, while cytokeratin 7 is positive in tumors of the respiratory tract. ITACs are usually positive for cytokeratin 20 and less so for cytokeratin 7 (Fig. 7.9b, c). The CDX-2 homeobox gene plays a crucial role in the differentiation of the intestine. CDX-2 is commonly expressed in ITACs (Fig. 7.9d) [100–102].

Precursor lesions to ITACs are of special interest as they could represent a marker which could be used in the early detection and prevention of malignancies in exposed workers. This question has been addressed in three articles [103–105] to some extent. In a cytological study, cuboidal cell metaplasia and goblet cell hyperplasia were observed in wood dust-exposed workers [104]. Histological metaplastic changes have also been associated with wood dust exposure [105]. In a third study examining mucosal lesions adjacent to ITACs, metaplastic and mild dysplastic lesions were found adjacent to the tumors [103]. However, the changes were present whether the patients had been exposed to wood dust or not. Interestingly, in the two later studies, wood dust was associated with increased expression of p53 tumor suppressor protein in epithelial nonmalignant cells.

Non-intestinal-Type Adenocarcinoma

The first description on low-grade sinonasal adenocarcinomas emerged in a study published in early 1980s [106]. In that study, high-grade tumors were also included, and the article

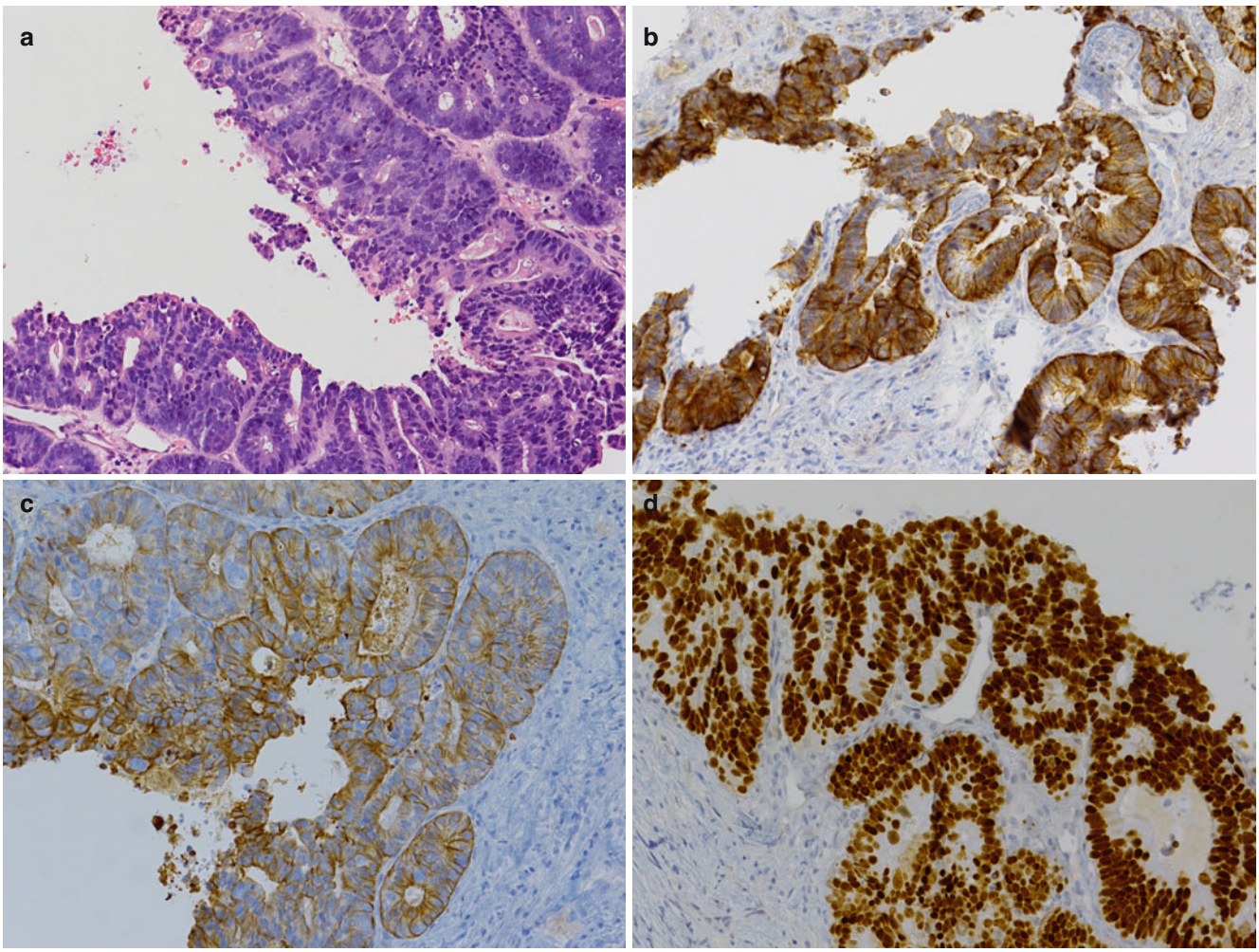


Fig. 7.9 Sinonasal intestinal-type adenocarcinoma (*ITAC*) of colonic type (**a**) hematoxylin-eosin staining, with immunochemistry (**b–d**). Immunohistochemically ITACs are positive for various epithelial markers: positivity for CK20 (**b**), CK7 (**c**), and CDX-2 (**d**) is shown (20× objective used) (Courtesy of Prof. Ilmo Leivo, MD PhD, Dept. Pathology, University of Turku, Turku, Finland)

Table 7.5 Classifications of the sinonasal intestinal-type adenocarcinoma (ITAC). Three-year survival rates from Kleinsasser and Schroeder are also indicated

Barnes and WHO Classification of Tumours [6, 98]	Kleinsasser and Schroeder [99]	3-year cumulative survival [99] (%)
Papillary type	PTCC-I	82
Colonic type	PTCC-II	54
Solid type	PTCC-III	36
Mucinous type	Alveolar goblet	46
	Signet-ring	0
Mixed	Transitional	71

PTCC papillary tubular cylinder cell, *I* well differentiated, *II* moderately differentiated, *III* poorly differentiated

noted that 12 of the 27 high-grade tumors displayed a striking similarity to moderately differentiated colonic adenocarcinomas, with the remainder presumably not exhibiting this feature [106]. The current WHO classification (Table 7.4) recognizes sinonasal non-ITAC tumors as a separate entity which is further divided into low- and high-grade subtypes [5, 6].

The low-grade type is relatively distinctive with numerous fairly uniform small glands or acini arranged in a back-to-back or a coalescent pattern with little or no intervening stroma. The glands are lined by a single layer of various types of fairly bland cells or sometimes by a double layer where the second layer consists of basal/myoepithelial cells. The prognosis of the low-grade non-ITACs is generally good. The high-grade non-ITAC can be described as a high-grade adenocarcinoma with a predominately solid pattern of growth, although glandular or papillary

patterns can be detected [6]. The differential diagnosis between the high-grade non-ITACs and other high-grade adenocarcinomas is challenging [107]. It has been proposed that they form a heterogeneous group of tumors of multiple unknown entities or variants of known entities [107]. The survival rate of subjects with high-grade non-ITACs is dismal; 3-year survival is a mere 20 %.

There is rather limited information available about the immunohistochemistry of non-ITAC tumors. The study of Franchi and coworkers [100] included four low-grade non-ITACs, which in contrast to ITACs did not stain with CDX2 or cytokeratin 20 but stained with cytokeratin 7. In a recent article, high-grade non-ITACS were shown to lack staining for CDX2 and, for the most part, also for cytokeratin 20, whereas cytokeratin 7 staining was relatively common [107].

As mentioned above the epidemiological studies do not differentiate between adenocarcinoma subtypes. In addition, non-ITACs are considered to be rarer than ITACs [107], although there are apparently no studies specifically reporting on the relative frequency of ITACs and non-ITACs. Thus, there is no direct information evaluating the association of non-ITACs to various exposures (see Section on Epidemiology and Occupational Risk Factors).

Summary and Conclusions

The sinonasal area is composed of the centrally located paired nasal cavities surrounded by paired paranasal sinuses (maxillary, frontal, ethmoidal, and sphenoidal). Sinonasal carcinomas are rare. The most important locations of the tumors associated with occupational exposures are the nasal cavity, maxillary sinus, and ethmoid sinus. The two histological types predominantly associated with occupational exposure are adenocarcinoma and squamous cell carcinoma. Squamous cell carcinomas have seven different subtypes; no association has been reported between occupational exposures and the presence of a particular subtype. Adenocarcinomas are divided into intestinal-type adenocarcinomas and non-intestinal-type adenocarcinomas, with some 40 % of the former located in ethmoidal sinuses. The striking feature of the sinonasal ITACs is their close resemblance to adenocarcinomas of the intestine, with similar positivity for various immunohistochemical markers. ITACs presumably represent the majority of sinonasal adenocarcinomas.

There is a strong epidemiological association between wood dust exposure and adenocarcinomas. There is, however, no direct epidemiological information about the association of different adenocarcinoma subtypes to wood dust exposure. In the pathology literature, ITACs are often considered as being associated with occupational exposure to wood dust.

Mechanisms of Carcinogenesis

Relatively little is known about the pathomechanisms involved in the development of sinonasal cancer. However, there is mechanistic information obtained from experimental settings as well as from human biomarker studies on toxicity, inflammatory effects, genotoxicity, and carcinogenicity of wood dust, wood extracts, or chemical constituents of wood. In addition, there are a few studies that have investigated wood dust-related sinonasal cancer in humans providing further molecular and mechanistic data [2, 4].

The mechanisms involved in cancer development have not been investigated to any significant extent for occupational exposures other than wood dust considered to be associated with an increased risk of sinonasal cancer, e.g., exposure to leather dust or textile dusts. However, somewhat more is known about other exposures such as tobacco smoke, nickel and chromium compounds, and formaldehyde, all with evidence for genotoxicity and mechanisms involved [4, 63, 81, 88, 108].

The primary focus of this section will be on reviewing and discussing the data available for cancer mechanisms likely to be involved in the sinonasal cancer related to wood dust exposure. A brief summary of some of the experimental and human evidence published is presented in Table 7.6.

Toxicological Features of Wood Dust Exposure

The chemical composition of wood largely varies according to the species of tree. The wood species used in wood-related industries vary not only from region to region but also by type of product; both hardwoods (gymnosperms, i.e., conifers) and softwoods (angiosperms, i.e., deciduous trees) are widely used. Wood dust, which is generated in processing of wood, is a complex mixture of substances, composed mainly of cellulose (approximately 40–50 %), polyoses and lignin, and a large and variable number of compounds of lower relative molecular masses. The last set of compounds include nonpolar organic extractives (fatty acids, resin acids, waxes, alcohols, terpenes, sterols, steryl esters, and glycerides), polar extractives (tannins, flavonoids, quinones, and lignans), as well as water-soluble extractives. With regard to the inorganic compounds in wood, chromium compounds have been identified although they primarily appear to be present in wood treated with preservatives or stains [2, 4].

A number of biologically active compounds has been identified in both hardwood and softwood species. For example, substances with biological activity belonging to many organic groups have been characterized in wood. These include terpenes, phenols, tannins, flavonoids, quinones, lignans, and stilbenes; wood also contains some alkaloids and

furocoumarins [2]. The various mechanisms through which wood dust may exert its biological activity are not well characterized but are likely to be complex [2, 4].

Some of the compounds identified in wood have been found to exert cellular toxicity (for instance, abeitic acid, plicatic acid) or mutagenicity (Δ^3-carene, quercetin). Furthermore, quinones, present primarily in hardwood species but some also in softwood [2], are recognized as redox-active chemicals that can generate radical oxygen species (ROS) and, ultimately, evoke a toxic response [130]. Wood, nevertheless, also contains compounds that may counteract such toxic effects (e.g., flavonoids and phenolic compounds with antioxidant capacity) [2]. Further adding to the complexity, some compounds or groups of compounds found in wood may exhibit both types of activities, depending on the chemical structure or

Table 7.6 Summary of various molecular mechanisms suggested to be involved in wood dust-related sinonasal carcinogenesis

Mechanism studied/aim	Assay/test system	Exposure/treatment/work environment	Main findings	Reference
Carcinogenicity in animals	Rodent carcinogenicity studies (rats; hamsters; mice)	Beech wood dust by inhalation or intratracheal injection Beech dust extract (solvent) by skin application Oakwood dust (with or without wood preservatives) by inhalation	Inconsistent or inconclusive results from the small number of studies carried out	Reviewed in IARC [2, 4]
Mutagenicity and DNA damage in vitro	Bacterial mutagenicity (*Salmonella*) assay	Solvent or water extracts of beech, oak, and some other woods	Weak mutagenicity for a number of wood species Consistent positive mutagenicity for beech wood extract	Reviewed in detail in IARC [2]
	Comet assay for DNA damage in human cell line	Dusts from beech, birch, oak, pine, spruce, teak, and oak-coated MDF	DNA damage detected for hardwood (beech, teak) and softwood (pine) species, and for oak-coated MDF	Bornholdt et al. [109]
Inflammatory response in experimental systems	Cytokine and chemokine expression (mRNA, protein) in rodent macrophages in vitro	Dusts from hardwood (oak, beech, birch, teak) and softwood (pine, spruce), and oak-coated MDF	Increased expression of various proinflammatory mediators (cytokines and chemokines) following exposure to hardwood and softwood dusts. Generation of ROS by rat alveolar macrophages in response to pine dust	Long et al. [110], Määttä et al. [111, 112], Bornholdt et al. [109]
	A nonallergic in vivo mouse model for pulmonary inflammation	Repeated intranasal instillation of fine (>99 % of particles ≤5 μm) dusts from oak and birch	Elicitation of proinflammatory response (several cytokines and chemokines) by oak and birch dusts in the lungs of the exposed mice	Määttä et al. [113]
	An allergic (ovalbumin sensitized) in vivo mouse model for pulmonary inflammation	Repeated intranasal instillation of fine (>99 % of particles ≤5 μm) dust from oak	Modulation of pulmonary inflammation assessed by cytokine and chemokine expressions (and of asthmatic response) in allergic mice compared to nonallergic mice)	Määttä et al. [114]
Genotoxicity in exposed workers	DNA damage in peripheral blood lymphocytes or WBC DNA by alkaline single-strand breakage or the Comet assay	Wooden furniture manufacturing plant	Elevated DNA damage in exposed versus control workers (both smokers and nonsmokers)	Palus et al. [115], Palus et al. [116]
	Micronuclei in buccal epithelial cells	Furniture workers from a woodworking shop	Increased frequency of micronuclei and other nuclear changes in woodworkers versus controls (both smokers and nonsmokers)	Çelik and Kanik [117]

Table 7.6 (continued)

Mechanism studied/aim	Assay/test system	Exposure/treatment/work environment	Main findings	Reference
Genetic and epigenetic changes in human sinonasal cancer tissue	Various genetic alterations (e.g., chromosomal imbalance [copy number changes], LOH, gene amplification)[a]	Tumor tissue from human SNC Mainly AD, with ITACs examined in many studies	Relatively high frequencies of many of the various types of genetic alterations examined; changes in gene expression	Several studies (reviewed in IARC [4]. E.g., Perrone et al. [131], Korinth et al. [132], Llorente et al. [122], Franchi et al. [133], Perez-Escuredo et al. [135]
	Mutations in *KRAS* gene[a]	Tumor tissue from human SNC (*n* cases = 28 AD). Data available on occupational wood dust and leather dust exposures	*KRAS* mutations observed in 14 % of AD cases, and 9 % of the ITAC cases. A few mutation positive AD cases with occupational exposure to wood dust. Certain types of mutations seen	Saber et al. [130]
		Tumor tissue from human SNC (*n* = 20 ITACs)		Frattini et al. [124]
		Tumor tissue from human SNC (*n* cases = 58 AD, 109 SQ, 7 other carcinomas) from incident cases collected in three European countries. Data available on wood dust and other occupational exposures		Bornholdt et al. [125]
	Mutations in *TP53* tumor suppressor gene[a]	Tumor tissue from human SNC (almost exclusively AD studied). Some studies with tumor tissue from cases with ITAC histology, from compensated cases, or from cases without exposure details	*TP53* mutations found with variable frequencies, ranging between appr. 20 and 60 %	Several studies; e.g., Perrone et al. [118], Perez-Escuredo et al. [122]
		Tumor tissue from human SNC (*n* = 122 AD, 213 SQ, 23 other carcinomas) from incident cases collected in three European countries. Data available on wood dust and other occupational exposures	In the largest single study, high frequency (77 %) of *TP53* mutations in SNC. Risk of mutation increased in association with wood dust exposure at work. Increased risk of mutation associated with long duration of occupational exposure or cumulative level of wood dust exposure	Holmila et al. [127, 128]
	Epigenetic changes[a]	Tumor tissue from human SNC (*n* = 21 ITACs)	High frequency of promoter hypermethylation in tumor suppressor genes *p14ARF* and *p16INK4a*	Perrone et al. [118]
		Inverted sinonasal papillomas (*n* cases = 7); a panel of 35 genes studied	Suggestive data for aberrant methylation	Stephen et al. [145]

WBC white blood cells, *MDF* medium-density fiberboard, *SNC* sinonasal cancer, *AD* adenocarcinoma, *SQ* squamous cell carcinoma, *ITAC* intestinal-type adenocarcinoma, *LOH* loss of heterozygosity
[a]See text for more detail

metabolism in human tissues. One such example is quercetin, as mentioned above, classified as one of the mutagenic compounds [2] but also as a flavonoid known to function as a dietary antioxidant [131].

An essential characteristic of wood dust, in common with many other exposures with a known or putative capacity to increase risk of sinonasal cancer (e.g., leather dust, tobacco smoking, textile dust, welding fumes containing nickel or

chromium; see Sections on Epidemiology and Occupational Risk Factors and Exposure Characterization), is that, in addition to a multitude of various chemical substances, it also contains particulate matter [2]. In wood dust, concentrations and types of particles present in the dust generated largely depend on the type of wood being processed and the methods used in the processing (sawing, sanding, etc.) [2, 4].

Related to its complex nature, wood dust exposure may exert human toxicity at many levels, e.g., through affecting particle deposition in and clearance from the upper respiratory tract. There are many characteristics such as breathing patterns, airflow, and airway epithelium condition of which are known to influence particle deposition in the respiratory tract [4, 132, 133]. Furthermore, there are a multitude of various cellular and molecular mechanisms involved in particle-induced toxicity, including the capacity to evoke DNA damage due to the generation of radical oxygen species (primary genotoxicity) or as a consequence of the inflammatory response elicited (secondary genotoxicity), known or at least suspected to occur in humans [4, 132–134]. It is likely that several of those contribute to wood dust-related toxicity in the epithelia of the nose, sinuses, and other parts of the respiratory tract. It has been suggested that impaired clearance of wood dust leads to prolonged exposure of the upper respiratory epithelium [3, 4].

Finally, in occupational environments where wood is being processed, there may be exposure to other chemicals or agents, such as glues, lacquers, paints, solvents, formaldehyde, wood preservatives, and fungal spores [2, 4].

Animal Carcinogenicity Studies on Wood Dust

Studies with experimental animals exposed to wood dust have so far provided little clarification for processes involved in wood dust-related sinonasal carcinogenesis. The few published studies on rodents (rats or hamsters), conducted mainly in the 1980s and 1990s, utilized inhalation or intratracheal injection as the routes of exposure to investigate carcinogenicity of beech or oakwood dusts. The results obtained from such studies have largely been negative or inconclusive [2, 4], at least partially due to many shortcomings in design and reporting [2, 4]. In addition to testing wood dusts as such in the experiments, the mutagenic fraction of beech dust solvent extract has also been studied for skin cancer (exposure by skin application) in mice. Similarly to the carcinogenicity studies on wood dust, the results reported for beech solvent extracts were somewhat variable [2, 4].

A more recent study on rats investigated the carcinogenicity of oakwood dust administered by inhalation, and in addition to pure oakwood dust, the carcinogenic effects of dust from oakwood treated with preservatives or a chromium-containing stain were examined. The results obtained were, however, inconclusive to some extent [135].

In the most recent evaluation by IARC [4], the evidence for the carcinogenicity of wood dust in experimental animals remained inadequate as few studies additional to those evaluated in the earlier monograph [2] had been published in the interim.

DNA Damage Induced by Wood Dust *In Vitro*

DNA damage following exposure to wood dust has been investigated in a few genotoxicity studies, with some positive results reported. Early work pointed to mainly weak bacterial mutagenicity for solvent or water extracts of oak, ash, obeche, walnut, and limba wood (also particle board) [2]. Consistent mutagenicity in the *Salmonella* assay was observed for beech wood extract (reviewed in detail in [2]). Wood extracts have also been studied in some other experimental systems for their ability to damage DNA, with positive findings [2, 4].

Apart from wood extracts, also dusts from hardwood and softwood species have been studied for their ability to cause DNA damage. Fine dusts from six commonly used wood species, including beech, birch, oak, teak, pine, spruce, plus dust from oak-coated medium-density fiberboard (MDF), were studied for DNA damage in a human lung cell line in a widely used genotoxicity assay (the Comet assay) [109]. The study found that hardwood (beech, teak) and softwood (pine) dusts, plus the MDF dust, induced genotoxicity. Importantly, it was reported that the DNA damage observed was not secondary to the cytokine response [109], pointing to primary genotoxicity.

Inflammatory Response to Wood Dusts Exposure in Experimental Studies

Recent studies have indicated that exposure to wood dust, both hardwood and softwood dusts, has the capacity to trigger a proinflammatory process by modulating the expression of macrophage-derived cytokines and chemokines. A series of *in vitro* studies revealed that fine dusts from hardwood species (oak, beech, birch, and teak) and softwood species (pine and spruce) modulate inflammatory response in rat alveolar macrophages [110], in a mouse macrophage cell line [111, 112], and in a human lung cell line [109]. In these *in vitro* experiments, hardwoods and softwoods have induced the expression of several cytokines (e.g., TNF-α, IL-6, and IL-8) and chemokines [109–112], with some quantitative differences being observed between some of the species [111, 112]. It is likely that the induction of an inflammatory response by wood dusts involves at least in part mechanisms mediated by ROS; reactive nitrogen species are also known to be generated in the inflammatory process [109, 110, 136]. As mentioned above, the timing of DNA damage induction

in human A549 lung cells by hardwood and softwood dusts indicates that inflammatory response is not necessary for genotoxicity of wood dust [109].

The inflammatory effects of wood dust in the lungs were further studied utilizing *in vivo* mouse models. Repeated intranasal instillation of fine dust (particle size of ≤5 μm for >99 % of the particles) from two hardwood species, oak and birch, induced the influx of inflammatory cells (macrophages, neutrophils, lymphocytes, and eosinophils) into the lungs of nonallergic mice [113]. An enhancement of lymphocytes and neutrophils was observed after oak dust exposure, whereas a greater infiltration of eosinophils followed exposure to birch dust. The infiltration of inflammatory cells was associated with an increased level of expression of several cytokines, chemokines, and chemokine receptors in the lung tissue. Overall, oak dust appeared to be a more potent inducer of these inflammatory mediators than birch dust [113]. Finally, findings from an allergic (ovalbumin sensitized) *in vivo* mouse model have indicated that repeated airway exposure to fine oak dust can modulate pulmonary inflammation (and also asthmatic response) [114].

Inflammation has also been postulated to play a role in the development of sinonasal cancer in humans [2, 120]. Recently, increased expression of COX-2, an enzyme involved in prostaglandin synthesis and upregulated by many inflammatory factors, was described in sinonasal adenocarcinoma [137]. COX-2 expression showed a significant association to occupational wood dust exposure, whereas tobacco smoking was not linked with COX-2 expression [137].

Genotoxicity in Wood Dust-Exposed Workers

There are a limited number of studies that have investigated genomic damage in workers occupationally exposed to wood dust. The level of DNA damage (DNA single-strand breaks) in peripheral blood lymphocytes was about twice as high among wooden furniture workers who were smokers, when compared to nonexposed smoking controls [115]. Further, the study also observed significant induction of DNA repair in the exposed workers, both smokers and nonsmokers, working in a wooden furniture plant in Poland [115]. Another study by the same group assessed DNA damage in white blood cells (WBC) from another group of workers from the same wooden furniture manufacture plant. Increased levels of DNA damage were detected by the Comet assay in WBC of these woodworkers, as compared to controls, in both smokers and nonsmokers [116]. The two studies indicated that the elevated DNA damage reflected the genotoxic effects of wood dust exposure; however, the possibility that they may have been at least partially related to other exposures present in the work environment of furniture making could not be totally ruled out [115, 116].

A more recent study observed significantly higher frequencies of micronuclei and other nuclear changes in buccal mucosa cells of furniture workers exposed to high concentrations of mixed hardwood and softwood dust in a woodworking shop, as compared to controls. Smokers had higher micronucleus frequencies in both groups, with the wood-dust-exposed smokers exhibiting the highest frequencies [117].

Genetic and Other Alterations in Human Sinonasal Cancer

Studies on the molecular mechanisms involved in human sinonasal cancer, even though somewhat limited in number due to the rare occurrence of the malignancy, demonstrate a variety of genetic and other molecular alterations in sinonasal tumors, as described in more detail in the following section (see also Section on Molecular Markers). Many of these studies have investigated sinonasal cancer cases with occupational exposure to wood dust. However, very few studies have investigated larger series of cancers and provided detailed data on the exposure characteristics [125, 127]. Some of the molecular alterations, the tumor suppressor gene *TP53* mutations in particular, show association to wood dust exposure [127, 128]. In some studies, adenocarcinomas (typically ITACs) from cases occupationally exposed to wood or leather dust have been investigated, with genetic and other molecular alterations being reported [118, 119, 121–124, 126, 138] (see Section on Molecular Markers) for detail).

Other alterations include a reduction of mucociliary transport and neoplastic lesions (epithelial hyperplasia, metaplasia, and dysplasia) proposed to play a role in the development of wood dust-related sinonasal cancer [2, 4]. It is noteworthy that wood dust particulate matter, as well as the chemical constituents present in wood, is believed either to directly participate in such processes or to be able to enhance them [2, 4, 132].

There are also data suggesting that viral factors (HPV or EBV) and some host factors, such as nasal polyps, sinusitis, or rhinitis, may be involved in sinonasal tumorigenesis but the evidence and suggested contributions have remained open [2–4, 132].

Summary and Conclusions

Experimental *in vitro* and *in vivo* studies on wood dust have described a wide variety of adverse biological effects and molecular changes, including cytotoxicity, oxidative DNA damage, genotoxicity, inflammatory response, and increased cell proliferation. It is believed that particulates, chemical substances, and their combinations present in complex mixture exposures, such as wood dust exposure, are the primary players in evoking these harmful effects

likely acting in concert in the biological and molecular pathways leading to development of sinonasal cancer.

There are also reports, although somewhat limited in number, pointing to the occurrence of wood dust-related genotoxic effects in exposed workers, in line with findings of the DNA damaging capacity of wood dusts as reported in various *in vitro* test systems. Studies carried out on human sinonasal cancer, perhaps not as plentiful as they could be if the cancer type were not so rare, have observed multiple genetic and other molecular alterations in the tumor tissue. These findings are also in good agreement with the experimental data and findings from exposed workers.

Collectively, the various sets of data point to a central role for genomic damage, in particular *TP53* mutations, in the development of sinonasal cancer. The frequent occurrence of *TP53* mutations fit well with data from other human cancers which involve regular, long term-exposure to carcinogens, including head and neck cancer. Inflammation is likely to also play a role in the carcinogenesis process. Much less is, however, known about how cancer susceptibility, other host-related factors, or viruses may contribute to tumorigenesis.

Finally, it appears justified to speculate that similar cancer mechanisms as described in the literature for wood dust-related sinonasal cancer may be involved, at least to some extent, in the sinonasal carcinogenesis associated with some other occupational exposures. There is, however, virtually no data available on mechanisms leading to cancer development in association with occupational exposures other than wood dust.

Molecular Markers

Literature on molecular markers in human sinonasal cancer is limited, as partially summarized and discussed in the previous section (see Section on Mechanisms of Carcinogenesis). Overall, the published findings have mainly been based on a relatively small number of cases, mostly involving adenocarcinomas. The studies published have, for example, described high frequencies of DNA copy number changes as detected by comparative genomic hybridization [119, 129, 139], while the mutation rates reported for the *KRAS* gene [123–126, 140–142] and the *TP53* tumor suppressor gene [118, 122, 127, 143, 144] in general have been lower or variable. Furthermore, a few studies have indicated that epigenetic changes (mainly promoter hypermethylation of certain tumor suppressor genes) play a role in sinonasal cancer as in many other types of human cancer [118, 145].

TP53 and *KRAS* Gene Mutations in Human Sinonasal Cancer

Most of the studies exploring the tumor suppressor gene *TP53* mutations, a hallmark genetic change in human cancer [146, 147] or investigating accumulation of the p53 protein in the cell have focused on intestinal-type adenocarcinomas, and there have been limited numbers of cases. In general, the accumulation of p53 often reflects a *TP53* mutation, but other reasons for p53 accumulation are also known; furthermore, not all mutations induce nuclear accumulation of p53 [148, 149]. The results reported for sinonasal cancer indicate that p53 accumulation is a common feature in the adenocarcinomas, with immunopositivity ranging between 20 and 100 % [118, 122, 141, 142, 150, 151]. In the studies analyzing the *TP53* mutations, a variable occurrence has been reported (18–60 %) [118, 122, 141, 143, 144]. *TP53* gene mutations were investigated in a large series of sinonasal cancers collected in three European countries (Denmark, Finland, and France; $n = 358$ cases), with both adenocarcinoma and squamous cell carcinoma histological types being included [127]. All histological tumor diagnoses were reviewed in consensus by a pathology panel, and data on occupational exposure to wood dust were obtained by interview and assessed by industrial hygienists [127]. The study detected a significantly elevated risk of adenocarcinoma histology as opposed to squamous cell carcinoma among the wood dust exposed cases. Furthermore, an overall high frequency of *TP53* mutations (77 %) was found among all sinonasal cancers. The risk of *TP53* mutations was higher among the adenocarcinomas as compared to the squamous cell carcinomas, but there was no difference between ITACs (86 %, 76 of 88 studied) and non-ITACs (85 %, 29 of 34 studied) [127].

The multicenter study further found that *TP53* mutations increased along with increased duration of occupational wood dust exposure, with a fivefold increased risk seen in association with ≥24 years of exposure (OR 5.1; 95 % CI 1.5–17.1), in comparison to nonexposed cases [127]. In addition, an elevated risk of mutation was significantly related to an average level of wood dust exposure of >2 mg/m^3 (OR 3.6, 95 % CI 1.2–10.8) and to a cumulative level of exposure of 30 mg/m^3 × years (OR 3.5, 95 % CI 1.2–10.7). Neither tobacco smoking nor formaldehyde exposure affected these findings significantly [127]. In a further investigation, some differences between the wood dust-exposed and the nonexposed cases in the *TP53* mutation profiles were discovered (Fig. 7.10) [128].

In a series of 44 sinonasal ITACs from Spain, mostly from cases occupationally exposed to wood dust, *TP53* mutations were also commonly detected (41 %), and they were exclusively found in cases with occupational wood dust exposure [122]. From smokers, only 20 % exhibited *TP53* mutation. The profile of mutations discovered in the study exhibited characteristics supporting wood dust-related etiology [122]. Based on the mutation profiles observed (50 % G to A transitions, almost exclusively detected in nonsmokers; all G to T transversions detected in smokers), the authors proposed that reactive nitrogen species generated via chronic inflammatory

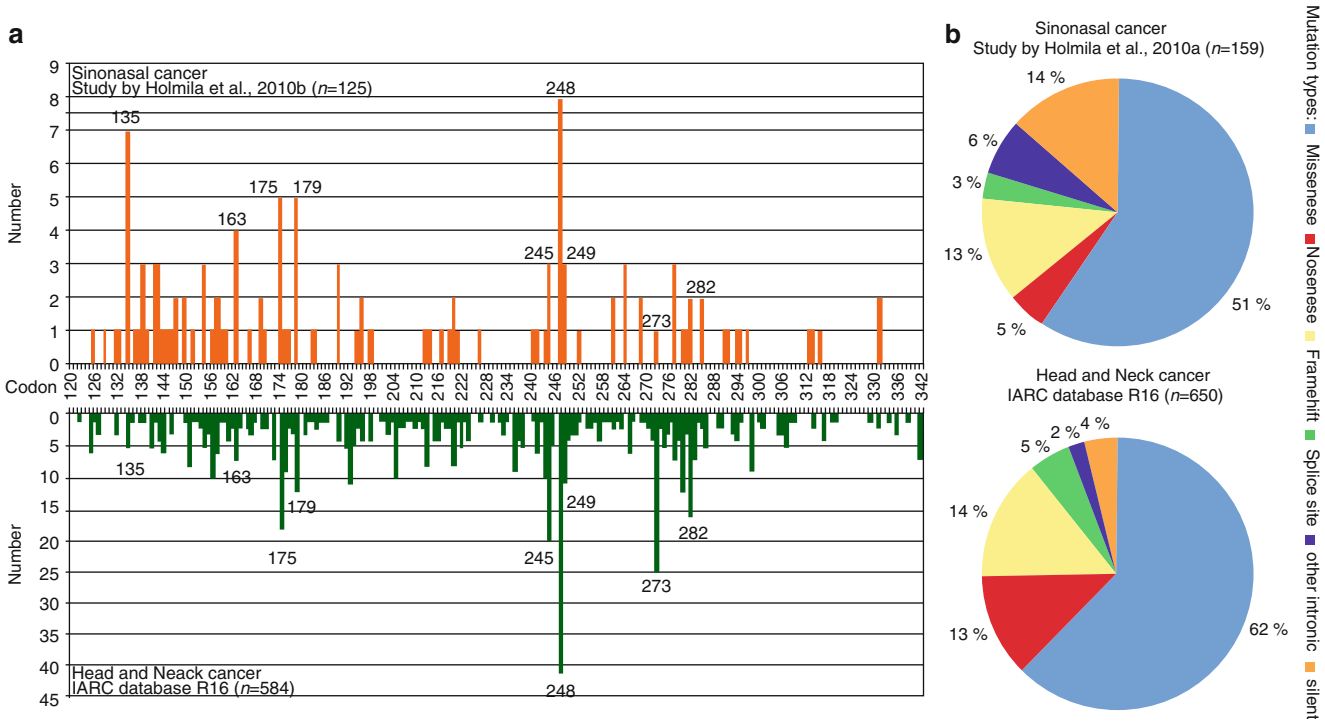


Fig. 7.10 Profile of tumor suppressor gene TP53 mutations in sinonasal cancer and in comparison to head and neck cancer. (**a**) Mutations presented by location (codon number in TP53 gene) in a series of sinonasal cancers studied in a European multicenter study by Holmila et al. [127] (*top*) as compared to similar data for head and neck cancers in IARC mutation database (IARC TP53 Mutation Database, version R16, 2012) (*bottom*). (**b**) Types of mutations detected in the multicenter study by Holmila et al. [128] (*top*) as compared to those included in the IARC mutation database (IARC TP53 Mutation Database, version R16, 2012) (*bottom*). The data for head and neck cancer from IARC database do not include sinonasal cancer cases. Numbers of cancer cases included in the analyses and the various classes of mutations are indicated

process contributed to the *TP53* gene mutagenesis in the exposed cases [122].

Initially, also *KRAS* and *HRAS* mutations were reported to be relatively frequent in sinonasal cancer, with implications for histogenetic and prognostic significance [118, 123, 124, 140–142]. In the large multicenter study of Bornholdt and coworkers [125], the frequency of *KRAS* mutations in adenocarcinoma histology (13 %) was similar to that found in earlier studies. Furthermore, the *KRAS* mutations were found almost exclusively in adenocarcinomas (of which two were ITACs) [125]. The most common type of mutations was G to A substitution; this was also the case among the few wood dust exposed cases [125]. A case series of sinonasal cancers from Spain (57 squamous cell carcinomas and 58 ITACs) were examined for *KRAS* and *BRAF* gene mutations. From these, seven cases (12 %), all ITACs and woodworkers, were positive for *KRAS* mutations but no *BRAF* gene mutations were found [126].

Other Genetic Features

In addition to mutations found in the central cancer-related genes, chromosomal imbalances, loss of heterozygosity (i.e., loss of one of the two alleles or the target gene region due to genetic alterations), gene amplifications, as well as altered gene expression have been discovered in human sinonasal cancer (reviewed in [2, 4, 120]). The pattern of chromosomal abnormalities found in sinonasal adenocarcinomas appears to be different from that of the other tumors of the head and neck region but displays similarities with gastric and colonic adenocarcinomas [121]. On the other hand, DNA copy number analyses and microarray comparative genome hybridization in sinonasal squamous cell carcinoma have shown gene amplifications and similarities with genetic changes found in head and neck squamous cell carcinomas (HNSCC) [152, 153]. In ITACs, comparative genomic hybridization analysis conducted on a limited number of tumors suggests copy number gains and loss throughout the whole genome [120]. In a study reporting on a series of almost 100 ITACs from Spain, *EGFR* (epidermal growth factor receptor) gene copy number changes were detected in 46 % of the cases [138]. All cases were, nevertheless, negative for *EGFR* mutations, while 31 % were positive in immunohistochemistry for EGFR expression [138].

It is well known that even though environmental factors predominantly contribute to the development of most common cancers, heritable factors are also involved [154]. In addition to somatic alterations as reviewed above for sinonasal cancer, genetic susceptibility plays a role in tumorigenesis

[155]. However, only very limited data are available regarding genetic susceptibility in sinonasal cancer. A study of 30 cases of ethmoidal ITAC and 79 noncancer controls suggested an overrepresentation of a certain *CYP1A1* genotype (heterozygotes for codon 46 Thr/Asn) as well as of the combination of this genotype and the deletion (null) genotype of *GSTM1* gene among ITAC cases [156].

Other Molecular and Cellular Changes

The molecular alterations reported for sinonasal cancer have included changes in protein expression as mentioned earlier (see Section on Pathology). Expression of Annexin A1, a member of the annexin family known to be implicated in a broad range of cellular processes, e.g., maintenance of the cytoskeleton, extracellular matrix integrity, tissue growth, and differentiation, was found to be frequently lost in all types of ITACs compared to nonmalignant tissue [157]. The expression of another member of the annexin family, Annexin A2, was also reduced in ITACs; however, this loss was restricted to the less differentiated histopathological types [157]. Another study examined 62 cases of ITACs (most with a history of employment in leather or wood industry) using tissue microarray [158]. Expression of p53 and p16 was the most common alteration observed in ITACs, with mucinous ITACs exhibiting a molecular profile distinct from that of non-mucinous ITACs [158]. Earlier, a difference in the expression pattern of the cell cycle regulators p21, p27, and p53 has been identified between adenocarcinomas and other tumor types of paranasal sinuses, especially the adenoid cystic carcinomas [152].

The expression of COX-2, an enzyme involved in inflammation, has been found to be associated with adenocarcinoma type of tumors, wood dust exposure, and nonsmoking [137]. In another study, EGFR expression was increased among ITAC type of tumors from workers exposed to wood dust [159]. Furthermore, profiling of gene expression in sinonasal adenocarcinomas has led to the identification of the two differentially expressed proteins LGALS4 and CLU [160].

Other types of changes include impaired mucociliary clearance and mucosal alterations that have consistently been reported in sinonasal cancer and associated with chronic wood dust exposure [2]. Mucosal alterations include dysplasia and metaplasia of the columnar epithelium and, to a lesser extent, changes in the squamous epithelium [2, 4, 104].

Summary and Conclusions

Sinonasal cancer exhibits an array of molecular changes, such as DNA copy number changes, allelic imbalance or loss of heterozygosity, gene amplifications, epigenetic changes, and altered gene expression, some of which it apparently shares with head and neck cancer. Mutations of the *TP53* gene frequently occur in sinonasal cancer, and *TP53* mutations have been associated with one of the main occupational risk factors, wood dust exposure. *KRAS* mutations also occur but are clearly less frequent compared to *TP53* mutations. Changes in protein expression profile have also been reported. However, since a distinctive feature of sinonasal cancer is its rare occurrence, more data on molecular markers central to this cancer type are likely to accumulate in the future.

Acknowledgements We thank all our colleagues who participated in the research collaboration in connection with the EU 5 FW project WOODRISK (QLK-2000-00573) and afterwards. Dr. Ewen MacDonald, University of Eastern Finland, Kuopio, is thanked for language revision and Ms. Ritva Järnström, Finnish Institute of Occupational Health, Helsinki, for technical assistance.

References

1. International Agency for Research on Cancer (IARC), Curado MP, Edwards B, Shin HR, et al., editors. Cancer incidence in five continents, IX. IARC Scientific Publications No160. Lyon: IARC; 2007. p. v-897.
2. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Wood dust and formaldehyde, vol. 62. Lyon: IARC; 1995. p. 1–405.
3. Littman AJ, Vaughan TL. Cancers of the nasal cavity and paranasal sinuses. In: Schottenfield D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006. p. 603–19.
4. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: arsenic, metals, fibres, and dusts, vol. 100C. Lyon: IARC; 2012. p. v-499.
5. Gnepp DR. Diagnostic surgical pathology of the head and neck. Philadelphia: Saunders Elsevier; 2009.
6. WHO (World Health Oranization). Classification of tumours. Pathology and genetics of head and neck tumours. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. WHO classification of tumours, vol. 9. 3rd ed. Lyon: International Agency for Research on Cancer (IARC); 2005. p. 12–42.
7. International Agency for Research on Cancer (IARC), Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, editors. Cancer incidence in five continents, VII. IARC Scientific Publications No 143. Lyon: IARC; 1997. p. v-1274.
8. Bhattacharyya N. Cancer of the nasal cavity: survival and factors influencing prognosis. Arch Otolaryngol Head Neck Surg. 2002;128:1079–83.
9. Hansen J, Olsen JH. Survival of Danish cancer patients 1943–1987. Respiratory system. APMIS Suppl. 1993;33:77–98.
10. Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J, editors. SEER survival monograph: cancer survival among adults: U.S. SEER program, 1988–2001, patient and tumor characteristics. 2007 National Cancer Institute, SEER Program. NIH Pub. No. 07-6215. Bethesda: NIH; 2007.
11. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients

diagnosed in 1995–1999. Results and commentary. Eur J Cancer. 2009;45:931–91.
12. Thorup C, Sebbesen L, Dano H, et al. Carcinoma of the nasal cavity and paranasal sinuses in Denmark 1995–2004. Acta Oncol. 2010;49:389–94.
13. Baan R, Grosse Y, Straif K, et al. A review of human carcinogens–Part F: chemical agents and related occupations. Lancet Oncol. 2009;10:1143–4.
14. Straif K, Benbrahim-Tallaa L, Baan R, et al. A review of human carcinogens–Part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 2009;10:453–4.
15. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: radiation, vol. 100D. Lyon: IARC; 2012. p. v-341.
16. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Some flame retardants and textile chemicals, and exposure in the manufacturing industry, vol. 48. Lyon: IARC; 1990. p. v-345.
17. Demers PA, Kogevinas M, Boffetta P, et al. Wood dust and sinonasal cancer: pooled reanalysis of twelve case-control studies. Am J Ind Med. 1995;28:151–66.
18. Leclerc A, Luce D, Demers PA, et al. Sinonasal cancer and occupation. Results from the reanalysis of twelve case-control studies. Am J Ind Med. 1997;31:153–65.
19. Luce D, Leclerc A, Begin D, et al. Sinonasal cancer and occupational exposures: a pooled analysis of 12 case-control studies. Cancer Causes Control. 2002;13:147–57.
20. 't Mannetje A, Kogevinas M, Luce D, et al. Sinonasal cancer, occupation, and tobacco smoking in European women and men. Am J Ind Med. 1999;36:101–7.
21. Zheng W, McLaughlin JK, Chow WH, Chien HT, Blot WJ. Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. Am J Epidemiol. 1993;138: 965–72.
22. Leclerc A, Martinez CM, Gerin M, Luce D, Brugere J. Sinonasal cancer and wood dust exposure: results from a case-control study. Am J Epidemiol. 1994;140:340–9.
23. Luce D, Leclerc A, Morcet JF, et al. Occupational risk factors for sinonasal cancer: a case-control study in France. Am J Ind Med. 1992;21:163–75.
24. Luce D, Gerin M, Leclerc A, Morcet JF, Brugere J, Goldberg M. Sinonasal cancer and occupational exposure to formaldehyde and other substances. Int J Cancer. 1993;53:224–31.
25. Luce D, Gerin M, Morcet JF, Leclerc A. Sinonasal cancer and occupational exposure to textile dust. Am J Ind Med. 1997;32:205–10.
26. Bolm-Audorff U, Vogel C, Woitowitz H. Occupation and smoking as risk factors of nasal and nasopharyngeal cancer. In: Sakurai H, editor. Occupational epidemiology. New York: Elsevier Science Publishers; 1990. p. 71–4.
27. Comba P, Battista G, Belli S, et al. A case-control study of cancer of the nose and paranasal sinuses and occupational exposures. Am J Ind Med. 1992;22:511–20.
28. Comba P, Barbieri PG, Battista G, et al. Cancer of the nose and paranasal sinuses in the metal industry: a case-control study. Br J Ind Med. 1992;49:193–6.
29. Magnani C, Comba P, Ferraris F, Ivaldi C, Meneghin M, Terracini B. A case-control study of carcinomas of the nose and paranasal sinuses in the woolen textile manufacturing industry. Arch Environ Health. 1993;48:94–7.
30. Merler E, Baldasseroni A, Laria R, et al. On the causal association between exposure to leather dust and nasal cancer: further evidence from a case-control study. Br J Ind Med. 1986;43:91–5.
31. Hayes RB, Gerin M, Raatgever JW, de Bruyn A. Wood-related occupations, wood dust exposure, and sinonasal cancer. Am J Epidemiol. 1986;124:569–77.
32. Hayes RB, Raatgever JW, de Bruyn A, Gerin M. Cancer of the nasal cavity and paranasal sinuses, and formaldehyde exposure. Int J Cancer. 1986;37:487–92.
33. Hardell L, Johansson B, Axelson O. Epidemiological study of nasal and nasopharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. Am J Ind Med. 1982;3:247–57.
34. Brinton LA, Blot WJ, Becker JA, et al. A case-control study of cancers of the nasal cavity and paranasal sinuses. Am J Epidemiol. 1984;119:896–906.
35. Brinton LA, Blot WJ, Fraumeni Jr JF. Nasal cancer in the textile and clothing industries. Br J Ind Med. 1985;42:469–74.
36. Vaughan TL, Davis S. Wood dust exposure and squamous cell cancers of the upper respiratory tract. Am J Epidemiol. 1991;133:560–4.
37. Battista G, Cavallucci F, Comba P, Quercia A, Vindigni C, Sartorelli E. A case-referent study on nasal cancer and exposure to wood dust in the province of Siena, Italy. Scand J Work Environ Health. 1983;9:25–9.
38. d'Errico A, Pasian S, Baratti A, et al. A case-control study on occupational risk factors for sino-nasal cancer. Occup Environ Med. 2009;66:448–55.
39. Elwood JM. Wood exposure and smoking: association with cancer of the nasal cavity and paranasal sinuses in British Columbia. Can Med Assoc J. 1981;124:1573–7.
40. Fukuda K, Shibata A. A case-control study of past history of nasal diseases and maxillary sinus cancer in Hokkaido, Japan. Cancer Res. 1988;48:1651–2.
41. Fukuda K, Kojiro M, Hirano M, Hyams VJ, Heffner D. Predominance of squamous cell carcinoma and rarity of adenocarcinoma of maxillary sinus among Japanese. Kurume Med J. 1989;36:1–6.
42. Hernberg S, Westerholm P, Schultz-Larsen K, et al. Nasal and sinonasal cancer. Connection with occupational exposures in Denmark, Finland and Sweden. Scand J Work Environ Health. 1983;9:315–26.
43. Ng TP. A case-referent study of cancer of the nasal cavity and sinuses in Hong Kong. Int J Epidemiol. 1986;15:171–5.
44. Olsen JH, Jensen SP, Hink M, Faurbo K, Breum NO, Jensen OM. Occupational formaldehyde exposure and increased nasal cancer risk in man. Int J Cancer. 1984;34:639–44.
45. Olsen JH, Jensen OM. Nasal cancer and chlorophenols. Lancet. 1984;2:47–8.
46. Olsen JH, Asnaes S. Formaldehyde and the risk of squamous cell carcinoma of the sinonasal cavities. Br J Ind Med. 1986;43:769–74.
47. Olsen JH. Occupational risks of sinonasal cancer in Denmark. Br J Ind Med. 1988;45:329–35.
48. Pesch B, Pierl CB, Gebel M, et al. Occupational risks for adenocarcinoma of the nasal cavity and paranasal sinuses in the German wood industry. Occup Environ Med. 2008;65:191–6.
49. Roush GC, Meigs JW, Kelly JA, Flannery JT, Burdo H. Sinonasal cancer and occupation: a case-control study. Am J Epidemiol. 1980;111:183–93.
50. Roush GC, Walrath J, Stayner LT, Kaplan SA, Flannery JT, Blair A. Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: a case-control study. J Natl Cancer Inst. 1987;79:1221–4.
51. Shimizu H, Hozawa J, Saito H, et al. Chronic sinusitis and woodworking as risk factors for cancer of the maxillary sinus in Northeast Japan. Laryngoscope. 1989;99:58–61.
52. Takasaka T, Kawamoto K, Nakamura K. A case-control study of nasal cancers. An occupational survey. Acta Otolaryngol. 1987;435(Suppl):136–42.
53. Caplan LS, Hall HI, Levine RS, Zhu K. Preventable risk factors for nasal cancer. Ann Epidemiol. 2000;10:186–91.
54. Mirabelli MC, Hoppin JA, Tolbert PE, Herrick RF, Gnepp DR, Brann EA. Occupational exposure to chlorophenol and the risk of

nasal and nasopharyngeal cancers among U.S. men aged 30 to 60. Am J Ind Med. 2000;37:532–41.
55. Zhu K, Levine RS, Brann EA, Hall HI, Caplan LS, Gnepp DR. Case-control study evaluating the homogeneity and heterogeneity of risk factors between sinonasal and nasopharyngeal cancers. Int J Cancer. 2002;99:119–23.
56. Demers PA, Boffetta P, Kogevinas M, et al. Pooled reanalysis of cancer mortality among five cohorts of workers in wood-related industries. Scand J Work Environ Health. 1995;21:179–90.
57. Demers PA, Teschke K, Kennedy SM. What to do about softwood? A review of respiratory effects and recommendations regarding exposure limits. Am J Ind Med. 1997;31:385–98.
58. Acheson ED, Pippard EC, Winter PD. Nasal cancer in the Northamptonshire boot and shoe industry: is it declining? Br J Cancer. 1982;46:940–6.
59. Pippard EC, Acheson ED. The mortality of boot and shoe makers, with special reference to cancer. Scand J Work Environ Health. 1985;11:249–55.
60. Andersen A, Barlow L, Engeland A, Kjaerheim K, Lynge E, Pukkala E. Work-related cancer in the Nordic countries. Scand J Work Environ Health. 1999;25 Suppl 2:1–116.
61. Cecchi F, Buiatti E, Kriebel D, Nastasi L, Santucci M. Adenocarcinoma of the nose and paranasal sinuses in shoemakers and woodworkers in the province of Florence, Italy (1963–77). Br J Ind Med. 1980;37:222–5.
62. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Chromium, nickel and welding, vol. 49. Lyon: IARC; 1990. p. v-648.
63. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: chemical agents and related occupations, vol. 100F. Lyon: IARC; 2012. p. v-499.
64. Swenberg JA, Kerns WD, Mitchell RI, Gralla EJ, Pavkov KL. Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res. 1980;40:3398–402.
65. Bertazzi PA, Pesatori AC, Radice L, Zocchetti C, Vai T. Exposure to formaldehyde and cancer mortality in a cohort of workers producing resins. Scand J Work Environ Health. 1986;12:461–8.
66. Edling C, Jarvholm B, Andersson L, Axelson O. Mortality and cancer incidence among workers in an abrasive manufacturing industry. Br J Ind Med. 1987;44:57–9.
67. Bertazzi PA, Pesatori A, Guercilena S, Consonni D, Zocchetti C. Carcinogenic risk for resin producers exposed to formaldehyde: extension of follow-up. Med Lav. 1989;80:111–22.
68. Andjelkovich DA, Janszen DB, Brown MH, Richardson RB, Miller FJ. Mortality of iron foundry workers: IV. Analysis of a subcohort exposed to formaldehyde. J Occup Environ Med. 1995;37: 826–37.
69. Hansen J, Olsen JH. Formaldehyde and cancer morbidity among male employees in Denmark. Cancer Causes Control. 1995;6:354–60.
70. Hansen J, Olsen JH. Occupational exposure to formaldehyde and risk of cancer. Ugeskr Laeger. 1996;158:4191–4.
71. Coggon D, Harris EC, Poole J, Palmer KT. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. J Natl Cancer Inst. 2003;95:1608–15.
72. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from solid cancers among workers in formaldehyde industries. Am J Epidemiol. 2004;159:1117–30.
73. Pinkerton LE, Hein MJ, Stayner LT. Mortality among a cohort of garment workers exposed to formaldehyde: an update. Occup Environ Med. 2004;61:193–200.
74. Walrath J, Fraumeni Jr JF. Mortality patterns among embalmers. Int J Cancer. 1983;31:407–11.
75. Walrath J, Fraumeni Jr JF. Cancer and other causes of death among embalmers. Cancer Res. 1984;44:4638–41.
76. Levine RJ, Andjelkovich DA, Shaw LK. The mortality of Ontario undertakers and a review of formaldehyde-related mortality studies. J Occup Med. 1984;26:740–6.
77. Stroup NE, Blair A, Erikson GE. Brain cancer and other causes of death in anatomists. J Natl Cancer Inst. 1986;77:1217–24.
78. Hayes RB, Blair A, Stewart PA, Herrick RF, Mahar H. Mortality of U.S. embalmers and funeral directors. Am J Ind Med. 1990;18:641–52.
79. Acheson ED, Cowdell RH, Rang EH. Nasal cancer in England and Wales: an occupational survey. Br J Ind Med. 1981;38:218–24.
80. Secretan B, Straif K, Baan R, et al. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009;10:1033–4.
81. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: personal habits and indoor combustions, vol. 100E. Lyon: IARC; 2012. p. v-579.
82. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer. 2004;45 Suppl 2:S3–9.
83. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens–Part B: biological agents. Lancet Oncol. 1990;10:321–2.
84. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: biological agents, vol. 100B. Lyon: IARC; 2012. p. v-475.
85. International Agency for Research on Cancer (IARC), Demers PA, Boffetta P, editors. Cancer risk from occupational exposure to wood dust, A pooled analysis of epidemiological studies. IARC Technical report No. 30. Lyon: IARC; 1998. p. i-97.
86. Luippold RS, Mundt KA, Dell LD, Birk T. Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. J Occup Environ Med. 2005;47:381–5.
87. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Wood, leather and some associated industries, vol. 25. Lyon: IARC; 1981. p. v-421.
88. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Tobacco smoke and involuntary smoking, vol. 83. Lyon: IARC; 2004. p. v-1452.
89. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Formaldehyde, 2-Butoxyethanol and 1- tert-Butoxypropan-2-ol, vol. 88. Lyon: IARC; 2006. p. v-478.
90. Kauppinen T, Vincent R, Liukkonen T, et al. Occupational exposure to inhalable wood dust in the member states of the European Union. Ann Occup Hyg. 2006;50(6):549–61.
91. Rongo LM, Msamanga GI, Burstyn I, Barten F, Dolmans WM, Heederik D. Exposure to wood dust and endotoxin in small-scale wood industries in Tanzania. J Expo Anal Environ Epidemiol. 2004;14(7):544–50.
92. Scientific Committee group on Occupational Exposure Limits (SCOEL). Wood dust. Luxembourg: European Commission; 2003. SCOEL/INF/576.
93. Roush GC. Epidemiology of cancer of the nose and paranasal sinuses: current concepts. Head Neck Surg. 1979;2:3–11.
94. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. Clin Otolaryngol Allied Sci. 1979;4:431–56.
95. Sobin L, Wittekind C, editors. TNM classification of malignant tumours. 6th ed. New York: Wiley; 2002.
96. Muir C, Weiland L. Upper aerodigestive tract cancers. Cancer. 1995;75:147–53.

97. Klintenberg C, Olofsson J, Hellquist H, Sokjer H. Adenocarcinoma of the ethmoid sinuses. A review of 28 cases with special reference to wood dust exposure. Cancer. 1984;54:482–8.
98. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Am J Surg Pathol. 1986;10:192–202.
99. Kleinsasser O, Schroeder HG. Adenocarcinomas of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behavior in 79 cases. Arch Otorhinolaryngol. 1988;245:1–15.
100. Franchi A, Massi D, Palomba A, Biancalani M, Santucci M. CDX-2, cytokeratin 7 and cytokeratin 20 immunohistochemical expression in the differential diagnosis of primary adenocarcinomas of the sinonasal tract. Virchows Arch. 2004;445:63–7.
101. Kennedy MT, Jordan RC, Berean KW, Perez-Ordonez B. Expression pattern of CK7, CK20, CDX-2, and villin in intestinal-type sinonasal adenocarcinoma. J Clin Pathol. 2004;57:932–7.
102. Resto VA, Krane JF, Faquin WC, Lin DT. Immunohistochemical distinction of intestinal-type sinonasal adenocarcinoma from metastatic adenocarcinoma of intestinal origin. Ann Otol Rhinol Laryngol. 2006;115:59–64.
103. Vivanco B, Llorente JL, Perez-Escuredo J, Alvarez Marcos C, Fresno MF, Hermsen MA. Benign lesions in mucosa adjacent to intestinal-type sinonasal adenocarcinoma. Patholog Res Int. 2011:Article ID 230147; 8 pages. doi:10.4061/2011/230147.
104. Wilhelmsson B, Lundh B. Nasal epithelium in woodworkers in the furniture industry. A histological and cytological study. Acta Otolaryngol. 1984;98:321–34.
105. Valente G, Ferrari L, Kerim S, et al. Evidence of p53 immunohistochemical overexpression in ethmoidal mucosa of woodworkers. Cancer Detect Prev. 2004;28:99–106.
106. Heffner DK, Hyams VJ, Hauck KW, Lingeman C. Low-grade adenocarcinoma of the nasal cavity and paranasal sinuses. Cancer. 1982;50:312–22.
107. Stelow EB, Jo VY, Mills SE, Carlson DL. A histologic and immunohistochemical study describing the diversity of tumors classified as sinonasal high-grade nonintestinal adenocarcinomas. Am J Surg Pathol. 2011;35:971–80.
108. Sunderman FW. Nasal toxicity, carcinogenicity, and olfactory uptake of metals. Ann Clin Lab Sci. 2001;31:3–24.
109. Bornholdt J, Saber AT, Sharma AK, Savolainen K, Vogel U, Wallin H. Inflammatory response and genotoxicity of seven wood dusts in the human epithelial cell line A549. Mutat Res. 2007;632:78–88.
110. Long H, Shi T, Borm PJ, et al. ROS-mediated TNF-α and MIP-2 gene expression in alveolar macrophages exposed to pine dust. Part Fibre Toxicol. 2004;1:3. doi:10.1186/1743-8977-1-3.
111. Määttä J, Majuri M-L, Luukkonen R, et al. Characterization of oak and birch dust-induced expression of cytokines and chemokines in mouse macrophage RAW 264.7 cells. Toxicology. 2005;215:25–36.
112. Määttä J, Luukkonen R, Husgafvel-Pursiainen K, Alenius H, Savolainen K. Comparison of hardwood and softwood dust-induced expression of cytokines and chemokines in mouse macrophage RAW 264.7 cells. Toxicology. 2006;218:13–21.
113. Määttä J, Lehto M, Leino M, et al. Mechanisms of particle-induced pulmonary inflammation in a mouse model: exposure to wood dust. Toxicol Sci. 2006;93:96–104.
114. Määttä J, Haapakoski R, Leino M, et al. Immunomodulatory effects of oak dust exposure in a murine model of allergic asthma. Toxicol Sci. 2007;99:260–6.
115. Palus J, Dziubaltowska E, Rydzynski K. DNA single-strand breaks and DNA repair in the lymphocytes of wooden furniture workers. Mutat Res. 1998;408:91–101.
116. Palus J, Dziubaltowska E, Rydzynski K. DNA damage detected by the comet assay in the white blood cell of workers in a wooden furniture plant. Mutat Res. 1999;444:61–74.
117. Çelik A, Kanik A. Genotoxicity and occupational exposure to wood dust: micronucleus frequency and nuclear changes in exfoliated buccal mucosa cells. Environ Mol Mutagen. 2006;47:693–8.
118. Perrone F, Oggionni M, Birindelli S, et al. TP53, p14ARF, p16INK4a and H-ras gene molecular analysis in intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Int J Cancer. 2003;105(2):196–203.
119. Korinth D, Pacyna-Gengelbach M, Deutschmann N, et al. Chromosomal imbalances in wood dust-related adenocarcinomas of the inner nose and their associations with pathological parameters. J Pathol. 2005;207(2):207–15.
120. Llorente JL, Perez-Escuredo J, Alvarez-Marcos C, Suarez C, Hermsen M. Genetic and clinical aspects of wood dust related intestinal-type sinonasal adenocarcinoma: a review. Eur Arch Otorhinolaryngol. 2009;266:1–7.
121. Franchi A, Miligi L, Palomba A, Giovannetti L, Santucci M. Sinonasal carcinomas: recent advances in molecular and phenotypic characterization and their clinical implications. Crit Rev Oncol Hematol. 2011;79(3):265–77.
122. Pérez-Escuredo J, Martinez JG, Vivanco B, et al. Wood dust-related mutational profile of TP53 mutations in intestinal-type sinonasal adenocarcinoma. Hum Pathol. 2012;43:1894–901.
123. Saber AT, Nielsen LR, Dictor M, Hagmar L, Mikoczy Z, Wallin H. K-ras mutations in sinonasal adenocarcinomas in patients occupationally exposed to wood or leather dust. Cancer Lett. 1998;126(1):59–65.
124. Frattini M, Perrone F, Suardi S, et al. Phenotype-genotype correlation: challenge of intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Head Neck. 2006;28(10):909–15.
125. Bornholdt J, Hansen J, Steiniche T, et al. K-ras mutations in sinonasal cancers in relation to wood dust exposure. BMC Cancer. 2008;8:53.
126. López F, García Inlcán C, Pérez-Escuredo J, et al. *KRAS* and *BRAF* mutations in sinonasal cancer. Oral Oncol. 2012;48:629–97.
127. Holmila R, Bornholdt J, Heikkila P, et al. Mutations in TP53 tumor suppressor gene in wood dust-related sinonasal cancer. Int J Cancer. 2010;127:578–88.
128. Holmila R, Bornholdt J, Suitiala T, et al. Profile of TP53 gene mutations in sinonasal cancer. Mutat Res. 2010;686:9–14.
129. Hermsen MA, Llorente JL, Perez-Escuredo J, et al. Genome-wide analysis of genetic changes in intestinal-type sinonasal adenocarcinoma. Head Neck. 2009;31(3):290–7.
130. Monks TJ, Jones DC. The metabolism and toxicity of quinones, quinonimines, quinone methides, quinone-thioethers. Curr Drug Metab. 2002;3:425–38.
131. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol. 2008;585:325–37.
132. Feron VJ, Arts JHE, Kuper CF, Slootweg PJ, Woutersen RA. Health risks associated with inhaled nasal toxicants. Crit Rev Toxicol. 2001;31:313–47.
133. Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. 2005;113:823–39.
134. Kuper CF, Woutersen RA, Slootweg PJ, Feron VJ. Carcinogenic response of the nasal cavity to inhaled chemical mixtures. Mutat Res. 1997;380:19–26.
135. Klein RG, Schmezer P, Amelung F, Schroeder H-G, Woeste W, Wolf J. Carcinogenicity assays of wood dust and wood additives in rats exposed by long-term inhalation. Int Arch Occup Environ Health. 2001;74:109–18.
136. Naarala J, Kasanen J-P, Pasanen P, et al. The effects of wood dusts on the redox status and cell death in mouse macrophages (RAW 264.7) and human leukocytes in vitro. J Toxicol Environ Health. 2003;66(A):1221–35.
137. Holmila R, Cyr D, Luce D, et al. COX-2 and p53 in human sinonasal cancer: COX-2 expression is associated with adenocarcinoma

histology and wood-dust exposure. Int J Cancer. 2008;122: 2154–9.
138. Gárcia-Inclán C, López F, Pérez-Escuredo J, et al. *EGFR* status and *KRAS/BRAF* mutations in intestinal type sinonasal adenocarcinomas. Cell Oncol. 2012;35:443–50.
139. Ariza M, Llorente JL, Alvarez-Marcas C, et al. Comparative genomic hybridization in primary sinonasal adenocarcinomas. Cancer. 2004;100(2):335–41.
140. Perez P, Dominguez O, Gonzalez S, Trivino A, Suarez C. Ras gene mutations in ethmoid sinus adenocarcinoma: prognostic implications. Cancer. 1999;86(2):255–64.
141. Wu TT, Barnes L, Bakker A, Swalsky PA, Finkelstein SD. K-ras-2 and p53 genotyping of intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Mod Pathol. 1996;9(3): 199–204.
142. Yom SS, Rashid A, Rosenthal DI, et al. Genetic analysis of sinonasal adenocarcinoma phenotypes: distinct alterations of histogenetic significance. Mod Pathol. 2005;18(3):315–9.
143. Bandoh N, Hayashi T, Kishibe K, et al. Prognostic value of p53 mutations, bax, and spontaneous apoptosis in maxillary sinus squamous cell carcinoma. Cancer. 2002;94(7):1968–80.
144. Licitra L, Suardi S, Bossi P, et al. Prediction of TP53 status for primary cisplatin, fluorouracil, and leucovorin chemotherapy in ethmoid sinus intestinal-type adenocarcinoma. J Clin Oncol. 2004;22(24):4901–6.
145. Stephen JK, Vaught LE, Chen KM, et al. Epigenetic events underlie the pathogenesis of sinonasal papillomas. Mod Pathol. 2007;20(10):1019–27.
146. Levine AJ, Oren M. The first 30 years of p53: growing ever more complex. Nat Rev Cancer. 2009;9:749–58.
147. Vousden KH, Prives C. Blinded by the light: the growing complexity of p53. Cell. 2009;137(3):413–31.
148. Partridge M, Costea DE, Huang X. The changing face of p53 in head and neck cancer. Int J Oral Maxillofac Surg. 2007;36(12):1123–38.
149. Goh AM, Coffill CR, Lane DP. The role of mutant p53 in human cancer. J Pathol. 2011;223(2):116–26.
150. Bashir AA, Robinson RA, Benda JA, Smith RB. Sinonasal adenocarcinoma: immunohistochemical marking and expression of oncoproteins. Head Neck. 2003;25(9):763–71.
151. Affolter A, Helmbrecht S, Finger S, Hormann K, Gotte K. Altered expression of cell cycle regulators p21, p27, and p53 in tumors of salivary glands and paranasal sinuses. Oncol Rep. 2005;13(6):1089–94.
152. Lopez F, Llorente JL, Garcia-Inclan C, et al. Genomic profiling of sinonasal squamous cell carcinoma. Head Neck. 2011;33(2): 145–53.
153. Lopez F, Llorente JL, Oviedo CM, et al. Gene amplification and protein overexpression of EGFR and ERBB2 in sinonasal squamous cell carcinoma. Cancer. 2012;118:1818–26.
154. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343(2):78–85.
155. Fletcher O, Houlston RS. Architecture of inherited susceptibility to common cancer. Nat Rev Cancer. 2010;10(5):353–61.
156. Pastore E, Perrone F, Orsenigo M, et al. Polymorphisms of metabolizing enzymes and susceptibility to ethmoid intestinal-type adenocarcinoma in professionally exposed patients. Transl Oncol. 2009;2(2):84–8.
157. Rodrigo JP, Garcia-Pedrero JM, Llorente JL, et al. Down-regulation of annexin A1 and A2 protein expression in intestinal-type sinonasal adenocarcinomas. Hum Pathol. 2011;42(1):88–94.
158. Franchi A, Palomba A, Fondi C, et al. Immunohistochemical investigation of tumorigenic pathways in sinonasal intestinal-type adenocarcinoma. A tissue array of 62 cases. Histopathology. 2011;59:98–105.
159. Franchi A, Fondi C, Paglierani M, Pepi M, Gallo O, Santucci M. Epidermal growth factor receptor expression and gene copy number in sinonasal intestinal type adenocarcinoma. Oral Oncol. 2009;45(9):835–8.
160. Tripodi D, Quemener S, Renaudin K, et al. Gene expression profiling in sinonasal adenocarcinoma. BMC Med Genomics. 2009;2:65.

Laryngeal Cancer

8

Paolo Boffetta

Keywords
Laryngeal cancer • Asbestos • Squamous cell carcinomas • Supraglottic tumors • Strong inorganic acid mists • Respiratory carcinogens

Introduction

More than 90 % of cancers of the larynx are squamous cell carcinomas, and the majority originates from the supraglottic and glottic regions of the organs. The incidence in men is high (10/100,000 or more) in Southern and Central Europe and South America, while the lowest rates (<1/100,000) are recorded in Southeast Asia and Central Africa. The incidence in women is below 1/100,000 in most populations [29]. In the USA, Blacks have 50–70 % higher incidence than Whites. In most high-income countries, rates have declined in men over the last two decades. An estimated 157,000 new cases occurred worldwide in 2012, of which 138,000 are men [25]. The estimated global number of deaths was 83,000.

Up to 80 % of cases of laryngeal cancer in high-income countries are attributable to tobacco smoking, alcohol drinking, and the interaction between the two factors [60]. The effect of tobacco, with risks in smokers in the order of ten relative to nonsmokers, seems to be stronger for glottic than supraglottic neoplasms. Studies in several populations have shown a dose-response relationship and a beneficial effect of quitting smoking. Smoking black-tobacco cigarettes entails a stronger risk than smoking blond-tobacco cigarettes. The effect of alcohol is stronger for supraglottic tumors than for tumors at other sites: it is not clear, however, whether different alcoholic beverages exert a different carcinogenic effect.

There are suggestions of a protective effect exerted by high intake of fruits and vegetables, although the evidence is not conclusive and the data regarding specific micronutrients, such as carotenoids and vitamin C, are inadequate [86]. Data concerning a possible effect of other foods are not consistent.

An etiological role of HPV infection has been suggested by the association of this infection with oropharyngeal cancer and by the observation that laryngeal papillomatosis, a condition characterized by multiple benign papillomas caused by infection with HPV types 6 and 11, entails an increased risk of laryngeal cancer. However, studies aimed at assessing the presence of HPV DNA have provided contrasting results [47].

There are no recognized strong genetic factors in laryngeal carcinogenesis; however, polymorphism for enzymes implicated in the metabolism of alcohol might represent susceptibility factors [54].

Survival from laryngeal cancer is relatively good (5-year survival rates are in the order of 60 % in high-income countries [18]). These patients are at very high risk of developing a second primary tumor in the oral cavity, pharynx, and lung. While shared risk factors are likely to play an important role, it is plausible that host factors are also partially responsible.

Occupational Risk Factors of Laryngeal Cancer

There are two established occupational risk factors of laryngeal cancer: asbestos and strong inorganic acid mists. In addition, workers in occupations entailing an increased consumption of alcohol and tobacco, such as waiters and cooks, are at increased

P. Boffetta, MD, MPH
Institute for Translational Epidemiology,
Icahn School of Medicine at Mount Sinai,
One Gustave L. Levy Place, New York, NY 10029, USA
e-mail: paolo.boffetta@mssm.edu

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_8, © Springer-Verlag London 2014

risk of the disease. An increased risk has been also reported in a few additional occupations and exposure circumstances, but the evidence is not conclusive at present.

Asbestos

Results on incidence or mortality from laryngeal cancer has been reported in more than 30 occupational cohorts and a number of community-based case-control studies. Detailed reviews are available [42].

Table 8.1 reports the design and results of cohort studies of workers exposed to asbestos. In general, these results are consistent in showing an increased mortality (or incidence) of laryngeal cancer among workers exposed to asbestos. The magnitude of the excess risk, however, is rather modest: as shown in Table 8.2, a meta-analysis of the results reported in Table 8.1 results in a summary RR of 1.51 (95 % CI 1.31–1.74). The results in Table 8.1 are not adjusted for tobacco smoking and alcohol drinking, the two main risk factors of laryngeal cancer. Based on the formula proposed by [4] for indirect adjustment of confounding, an RR of 1.5 for laryngeal cancer would be explained by tobacco smoking or alcohol drinking confounding only under rather extreme assumptions of the distribution of these risk factors in the exposed groups. For example, under the assumption of a proportion of current and former smokers in the reference population equal to 25, 45, and 30 % and RR for current and former smoking equal to 7.0 and 4.7 [30], an RR of 1.5 would be explained by a distribution among exposed of 75 % current smokers, 20 % former smokers, and 5 % never smokers, which seems implausible.

In 16/32 of the available studies, either not enough information is provided to characterize the type of fibers to which workers were exposed or exposure was defined as "mixed fiber

Table 8.1 Results of cohort studies of laryngeal cancer in workers exposed to asbestos

Reference	Industry	Asbestos type	Country	Period of employment	Sex	No. workers	No. deaths	SMR	95 % CI
Peto et al. [63]	Textile product manufacture	P Ch	UK	1933–1974	M	3,211	4	1.55	*0.42–3.97*
Gardner et al. [31]	Cement workers	Ch	UK	1941–1983	MF	2,090	1	0.91	*0.02–5.06*
Hughes et al. [41]	Cement workers	P Ch	USA	1937–1970	M	5,492	3	0.56	*0.11–1.62*
Enterline et al. [24]	Mixed	Mix	USA	1941–1967	M	1,074	2	1.14	*0.14–4.13*
Armstrong et al. [3]	Crocidolite miners	Cr	Australia	1943–1966	PM	6,505	2	0.68	0.17–2.74
Tola et al. [84]	Shipyard workers	Mix	Finland	1945–1960	M	7,775	24[d]	1.20	0.77–1.79
Raffn et al. [69]	Cement workers	Mix	Denmark	1928–1984	M	7,996	14[d]	1.66	0.91–2.78
Finkelstein [26]	Automotive part manufacture	Ch	Canada	1950–1980	M	224[c]	8	8.54	*1.76–25.0*
Piolatto et al. [64]	Miners	Ch	Italy	1946–1987	M	1,058	8	2.67	*1.15–5.25*
Parnes [61]	Brake lining manufacture	Ch	USA	1937–1980	M	2,057	3	4.03	*0.80–11.4*
Selikoff and Seidman [73]	Insulation workers	Mix	USA	1967	M	17,800	18	1.70	*1.01–2.69*
Botta et al. [12]	Cement workers	Mix	Italy	1950–1980	M	2,608	5	0.70	0.23–1.64
Sluis-Cremer et al. [76]	Miners	Am, Cr	S Africa	1945–1981	M	7,317	5	1.86	0.60–4.34
Giaroli et al. [33]	Cement workers	P Ch	Italy	1952–1987	NA	3,341	2	0.82	0.15–2.59
Meurman et al. [56]	Miners	Antho	Finland	1953–1967	M	736	4[d]	1.75	0.48–4.47
Berry [7]	Friction material manufacture	P Ch	UK	1941–1979	M	9,104[c]	6	0.64	0.23–1.39
Liddell et al. [48]	Miners	Ch	Canada	1902–1971	M	8,923	36	1.11	*0.79–1.55*
Levin et al. [46]	Insulation material manufacture	Am	USA	1954–1972	M	753	1	2.21	0.06–12.3
Germani et al. [32]	Asbestosis patients	Mix	Italy	1979[a]	F	631	1	8.09	0.21–45.1

Table 8.1 (continued)

Reference	Industry	Asbestos type	Country	Period of employment	Sex	No. workers	No. deaths	SMR	95 % CI
Karjalainen et al. [45]	Asbestosis patients	Mix	Finland	1964–1995[a]	MF	1,376	5[b]	*3.88*	*1.26–9.05*
Battista et al. [5]	Railroad carriage manufacture and repair	Mix	Italy	1945–1969	M	734	5	2.40	0.95–5.05
Berry et al. [8]	Textile, other products; insulators	Mix	UK	1933–1964	M	~3,000	3	2.05	*0.42–6.01*
Puntoni et al. [68]	Shipyard workers	NA	Italy	1960–1981	M	3,984	32	1.64	1.12–2.32
Szeszenia-Dabrowska et al. [82]	Asbestosis patients	Mix	Poland	1970–1997[a]	M	902	1	0.43	*0.01–2.40*
Smailyte et al. [77]	Cement workers	Ch	Lithuania	1956–1985	M	1,285	7[d]	1.4	0.7–2.9
Reid et al. [70]	Crocidolite miners millers	Cr	Australia	1943–1966	PM	5,685	19[d]	1.82	1.16–2.85
Finkelstein and Verma [27]	Plumbers, pipe–sprinkler fitters	Mix	Canada	1949–1980	M	14,408	*18*	1.38	*0.82–2.18*
Pira et al. [65]	Textile product manufacture	Mix	Italy	1946–1984	MF	1,966	7	2.38	0.95–4.90
Hein et al. [37]	Textile product manufacture	Ch	USA	1940–1965	MF	3,072	6	1.68	0.61–3.66
Loomis et al. [49]	Textile product manufacture	P Ch	USA	1950–1973	PM	5,770	6	1.15	0.42–2.51
Harding et al. [36]	Mixed	Mix	UK	1983–1987[b]	PM	98,117	49	1.48	1.09–1.95
Menegozzo et al. [55]	Cement workers	Mix	Italy	1950–1986	M	1,247	5	0.97	0.31–2.26

When multiple reports have been published for the same cohort, only the most recent one is summarized in the table
Results in italics were calculated based on raw data
Small groups of female workers were included in the studies by Berry et al. [8], Botta et al. [12], and Peto et al. [63]. No cases/deaths from laryngeal cancer were observed in these populations
P Ch predominantly chrysotile, *Ch* chrysotile, *Cr* crocidolite, *Am* amosite, *Mix* mixed exposure, *Tre* tremolite, *Act* actymolite, *Antho* anthophyllite, *M* males, *MF*, males and females, *PM* predominantly males, *NA* not available
[a]Period of diagnosis
[b]Period of enrolment in the survey
[c]10+ years since first employment
[d]Incident cases (results are expressed as SIR)

Table 8.2 Meta-analysis of risk of laryngeal cancer in cohort studies of workers exposed to asbestos

	N studies	N deaths	RR	95 % CI	*p* het.
All studies	32	310	1.51	1.31–1.74	0.22
Type of fibers					
Pure/predominant chrysotile	11	82	1.29	0.97–1.71	0.29
Amphiboles[a]	5	31	1.70	1.18–2.46	0.77
Mixed, unknown	16	197	1.61	1.33–1.95	0.18
Country					
UK	5	63	1.39	1.07–1.81	0.48
USA	7	39	1.55	1.10–2.19	0.54
Canada	3	62	1.73	0.86–3.49	0.01
Finland	3	33	1.82	0.89–3.75	0.09
Italy	8	65	1.68	1.19–2.37	0.23
Australia	3	21	1.40	0.59–3.29	0.19

Studies listed in Table 8.1
[a]Pure/predominant amphiboles or mixed chrysotile and amphiboles

types" (see Table 8.1 for details). Among the remaining studies, chrysotile was either the only or the predominant type of asbestos fiber in 11, while in the remaining five studies, workers were exposed only or predominantly to amphiboles. The results of the meta-analysis stratified by asbestos fiber type provided some evidence of an increased risk of laryngeal cancer among workers exposed to amphiboles (or to unspecified/mixed fibers, which presumably contained amphiboles) than among workers exposed to chrysotile (Table 8.2). Caution should be applied in interpreting these results, because of the crude classification of exposure and the potential residual confounding by other characteristics, including background incidence of laryngeal cancer, as well as time since first exposure, duration of exposure, and level of asbestos exposure. In Table 8.2 the results of the meta-analysis are also stratified by country: the higher risk estimates in studies from Italy, a country with relatively high incidence of laryngeal cancer, compared to the RR in the UK and the USA, two low-risk countries, are worth noticing; results from studies from Canada and Finland, also low-risk countries, were heterogeneous. Given the relatively small number of studies, it is difficult to reciprocally adjust the results by fiber type and countries, but the meta-analysis of the seven studies of chrysotile workers from the UK and the USA, which presumably are closer to the risk pattern experienced nowadays by most (former) asbestos workers, resulted in a summary risk estimate of 1.21 (95 % CI 0.76–1.92).

Information on dose-response is available in a small number of cohort studies, which mainly reported results according to duration of employment. These results are summarized in Table 8.3: they are limited by the small number of events in the groups with longer duration or higher exposure, but do not consistently suggest a dose-response relation.

Table 8.3 Dose-response analyses of risk of laryngeal cancer in cohort studies of workers exposed to asbestos

Reference	Exposure category	No. deaths	SMR	95 % CI
Peto et al. [63]	Duration <10 years; TSFE <20 years	0	0	*0–4.24*
	20+ years	4	3.70	*1.01–9.48*
	Duration 10+ years; TSFE <20 years	0	0	*0–19.4*
	20+ years	0	0	*0–8.2*
Raffn et al. [69]	TSFE 15+ years; duration 1–4 years	2	0.81	0.09–2.94
	5+ years	6	2.27	0.83–4.95
Finkelstein [26]	Duration 1–19 years	0	0	*0–36.3*
	20+ years	3	11.9	*2.46–34.8*
Piolatto et al. [64]	Cum. exposure <100 fb-years	1	1.43	*0.04–7.96*
	100–400 fb-years	2	2.22	*0.27–8.02*
	>400 fb-years	5	3.85	*1.25–8.98*
Parnes [61]	Duration 1–4 years	2	6.64	*0.76–22.7*
	5+ years	1	2.24	*0.06–12.4*
Meurman et al. [56]	Moderate exposure	1	1.33	0.03–7.40
	Heavy exposure	3	1.95	0.40–5.69
	Heavy exposure; duration >5 years	2	3.60	0.44–13.0
Liddell et al. [48]	Cum. exp. <300 mpcf-years	24	1.03	*0.66–1.53*
	300+ mpcf-years	6	1.08	*0.40–2.35*
Berry et al. [8]	Low/moderate exp.	0	0	*0–5.27*
	Severe exp.; duration <2 years	2	4.65	*0.56–16.8*
	>2 years[a]	1	3.03	*0.08–26.4*
Puntoni et al. [68]	Duration 1–14 years	6	1.14	*0.42–2.48*
	15–24 years	8	1.59	*0.69–3.13*
	25+ years	18	1.96	*1.16–3.10*
Smailyte et al. [77]	Duration <1 years	2	0	*0–4.1*
	1–4 years	3	1.6	0.5–4.8
	5–9 years	2	3.0	0.8–12.5
	10+ years	2	1.3	0.4–5.7
Pira et al. [65]	Duration <1 years	1	1.05	*0.03–5.87*
	1–4 years	3	3.98	*0.82–11.6*
	5–9 years	2	3.90	*0.47–14.1*
	10+ years	1	1.38	*0.03–7.67*

See Table 8.1 for details of the cohort studies
TSFE time since first exposure, *exp* expected deaths
[a]Only male factory workers

Table 8.4 Results of case-control studies of laryngeal cancer and occupational exposure to asbestos

Reference	Country	N ca/co	Source co	Sex	Exposure assessment	No. exp ca	OR	95 % CI	Comments
Stell and McGill [81]	UK	100/100	Hospital	M	NA	31	*14.5*	*4.3–49.4*	
Shettigara and Morgan [75]	Canada	43/43	Hospital	M	Self-reports	10	∞	NA	0 exposed controls; $p = 0.001$
Hinds et al. [39]	USA	47/NA	Residential	M	Self-report	25	1.75	NA	$p = 0.2$
Burch et al. [14]	Canada	204/204	Residential	M	Self-report	36	1.6	NA	$p = 0.07$
					Job titles	14	2.3	NA	$p = 0.05$
Olsen and Sabroe [59]	Denmark	276/971	Residential	M	Self-report	17	1.8	1.0–3.4	
Zagraniski et al. [88]	USA	92/181	Hospital	M	Job titles	11	1.1	0.4–2.9	
Brown et al. [13]	USA	183/250	Residential	M	Job titles classified by IH	88	1.5	1.0–2.2	No dose-response
Ahrens et al. [2]	Germany	100/100	Hospital	M	Self-report	NA	1.1	0.5–2.4	Prevalent cases
Muscat and Wynder [58]	USA	194/184	Hospital	M	Self-report	66	1.1	0.7–1.9	
Wortley et al. [87]	USA	235/547	RDD	MW	JEM	90	*1.2*	*0.9–1.7*	Weak dose-response
Zheng et al. [90]	China	177/269	Residential	M	Self-report	26	2.0	1.0–4.3	
Gustavsson et al. [35]	Sweden	157/641	Residential	M	Occ. history assessed by IH	62	*1.44*	*1.02–2.05*	Positive dose-response
De Stefani et al. [19]	Uruguay	112/509	Hospital (cancer)	M	Self-report	23	1.8	0.9–3.2	
Marchand et al. [51]	France	296/295	Hospital	M	JEM	216	1.24	0.83–1.90	Positive dose-response
Elci et al. [23]	Turkey	940/1519	Hospital (cancer)	M	JEM	150	1.0	0.8–1.3	No dose-response
Berrino et al. [6]	3 European countries	1070/2176	Residential	M	JEM	<55 – 215	1.5	1.0–2.4	Weak dose-response <55; no dose-response 55+
						55+ – 347	1.0	0.8–1.4	
Dietz et al. [20]	Germany	257/769	Residential	PM	Self-reports, JEM	59	1.3	0.8–2.1	
Shangina et al. [74]	4 European countries	316/728	Hospital	M	Occ. history assessed by IH	65	0.86	0.51–1.45	

MW men and women, *M* men, *PM* predominantly men, *IH* industrial hygienist, *JEM* job-exposure matrix, *AL* acids/lye, *SA* sulfuric acid, *AM* acid mists, *OR* odds ratio, *CI* confidence interval, *NA* not available

Community-based studies of laryngeal cancer that reported studies on exposure to asbestos are summarized in Table 8.4. Most of these studies reported an association, although in most instances the results were not statistically significant. Results on duration or level of exposure were reported in a few studies, which provided limited evidence of dose-response. Because of the problems in exposure misclassification inherent in community-based studies, however, it is not surprising that the evidence from community-based studies is weaker than that from industry-based studies.

Overall, the results of cohort and case-control studies are relatively consistent in showing a carcinogenic effect of asbestos on the larynx and indicate a relative risk in the range of 1.5–2.0 for ever exposure. The small number of events in most studies, the lack of strong evidence of dose-response, and the presence of potential residual confounding in occupational cohort studies are all limitations of the available dataset. In addition, there are no strong data showing accumulation and persistence of asbestos fibers in the larynx; two studies reported either asbestos bodies [71] of fibers [44] in

Table 8.5 Results of cohort studies of laryngeal cancer in workers exposed to strong inorganic acid mists

Reference	Industry (exposure to SA)	Country	Period of employment[a]	Sex	No. workers	Exposure	No. deaths	SMR	95 % CI
Weil et al. [85]	Isopropyl alcohol manufacture (H)	USA	1928–1950	M	182	Any	1	NA	NA
Hueper [40]	Isopropyl alcohol manufacture (H)	USA	1927–1950	M	779	Any	2	NA	NA
Lynch et al. [50]	Chemical work, isopropyl alcohol jobs (H)	USA	1950–1976	PM	741	Any	7	3.2	*1.5–6.7*
Ahlborg et al. [1]	Stainless steel pickling house (H)	Sweden	1951–1979	M	181	Any	3[a]	50	16–155
Cooper et al. [17]	Battery manufacture (L)	USA	1947–1970	M	4,519	Any	6	1.28	0.47–2.8
						20+ years	4	1.41	*0.38–3.61*
Forastiere et al. [28]	Soap manufacture (I)	Italy	1964–1972	M	361	Any	5[a]	*6.94*	*2.26–16.2*
Block et al. [9]	Phosphate fertilizer manufacture (I)	USA	1950–1979	M	2,610[b]	Any	2	1.91	*0.23–6.90*
Steenland and Beaumont [80]	Steelworkers in pickling jobs (H)	USA	1940–1965	PM	1,165	Any	14	2.19	1.2–3.7
						SA daily	10	2.5	1.7–4.7
Teta et al. [83]	Isopropyl/ethyl alcohol manufacture (H)[c]	USA	1928–1968	M	538	Any	1	*1.43*	0–8.0
Teta et al. [83]	Isopropyl/ethyl alcohol manufacture (H)	USA	1941–1992	M	493	Any	1	*3.3*	0.1–19
Coggon et al. [15]	Battery manufacture and steel works with acid mist exp.(L)	UK	1950–1990	M	2,678	Any	1	0.48	0.01–2.7
Moulin et al. [57]	Stainless steel, metal alloy manufacture (I)	France	1968–1991	M	4,288	Any	17	1.47	0.9–2.4
Sorahan and Esmen [78]	Ni–Cd battery manufacture (L)	UK	1947–1975	M	926	Any	2	1.95	0.24–7.06
Pesatori et al. [62]	Sulfuric acid manufacture (H)	Italy	1962–1997	M	1,372	Any	4	1.30	0.35–3.33

SA sulfuric acid, *L* low, *I* intermediate, *H* high, *M* men, *PM* predominantly men, *NA* not available
[a]Incident cases
[b]White men; no deaths in a separate cohort of 841 black men
[c]Including weak acid unit

this area, but contamination from other tissues could not be ruled out. In addition, inhalation studies in rats and hamsters, which were positive for mesothelioma, did not show chronic inflammation or cancer of the larynx [38, 52, 53].

Strong Inorganic Acid Mists

Mists of strong inorganic acids are potential carcinogens for the upper respiratory tract, with sulfuric acid being the most prevalent exposure. Exposure to sulfuric acid is highest in metal pickling, sulfuric acid production, and isopropanol production, while it is present, albeit at lower level, in soap production, nitric acid and ethanol production, copper and zinc refining, phosphate fertilizer production, and lead battery production [72]. Cohort studies were conducted in these industries, which reported results on risk of laryngeal cancer: they are summarized in Table 8.5. Although the results of individual studies were limited by the small number of deaths (or cases) or laryngeal cancer, they were consistent in showing an increased risk of the disease, in particular when workers at high exposure to sulfuric acid were studied. In none of these studies was the potential confounding effect of tobacco smoking and alcohol drinking adjusted for, but the risk estimates, in particular those in studies of workers at high exposure in isopropanol production and metal pickling, are sufficiently high to reduce the plausibility of residual confounding. Data on dose-response are limited (Table 8.5), yet they are compatible with a carcinogenic effect of the exposure.

Case-control studies of laryngeal cancer with assessment of exposure to sulfuric acid mist, acid mists in general, or related exposure were conducted in Canada, the USA, Uruguay, and various European countries. Relevant results are summarized in Table 8.6: they are less consistent than those of cohort studies in showing an increased risk; this can reflect a lower specificity

Table 8.6 Results of case-control studies of laryngeal cancer and exposure to strong inorganic acid mists

Reference	Country	N ca/co	Source co	Sex	Exposure assessment	Exposure	No. exp ca	OR	95 % CI	Comments
Olsen and Sabroe [59]	Denmark	326/1134	Residential	MW	Self-report	AL	43	1.3	0.9–1.9	
Cookfair et al. [16]	USA	352/1050	Hospital	M	Review of job titles	SA <20 years	NA	2.05	NA	
						20+ years		2.43		
Zemla et al. [89]	Poland	328/656	Hospital	M	Unclear	AM	11	4.27	NA	
Brown et al. [13]	USA	183/250	Residential	M	Job titles classified by IH	SA	22	0.76	0.42–1.35	
Soskolne et al. [79]	Canada	204/204	Neighborhood	PM	JEM	SA ≤ 10 years	6	3.57	1.19–10.7	'Substantial' exposure
						>10 years	19	5.57	2.0–15.5	
Eisen et al. [21]	USA	108/538	Cohort	PM	Measurements, JEM	AM 1+ years	NA	0.90	0.66–1.22	Nested in cohort of auto workers
De Stefani et al. [19]	Uruguay	112/509	Hospital (cancer)	M	Self-report	SA any	46	1.6	0.9–2.6	
						≥20 years	12	1.2	0.6–2.5	
						20+ years	34	1.8	1.1–3.1	
Shangina et al. [74]	4 European countries	316/728	Hospital	M	Occ history assessed by IH	AM	37	0.94	0.6–1.5	Includes hypopharyngeal cancer

MW men and women, *M* men, *PM* predominantly men, *IH* industrial hygienist, *JEM* job-exposure matrix, *AL* acids/lye, *SA* sulfuric acid, *AM* acid mists, *OR* odds ratio, *CI* confidence interval, *NA* not available

(and possibly sensitivity) of exposure assessment in some of the studies, as the number of subjects employed in high-exposure industries in these studies was low. Dose-response results were reported in a few studies: as in the case of cohort studies, these were consistent with a carcinogenic effect.

The evidence from epidemiologic studies of an increased risk of laryngeal among workers exposed to strong inorganic acid mists (mainly from sulfuric acid) is supported by mechanistic data showing that reduced pH may lead to increased DNA damage and decreased DNA repair (reviewed in [43]).

Other Occupational Agents

Other occupational exposures associated with laryngeal cancer in some studies include mixtures of polycyclic aromatic hydrocarbons [10, 22], diesel engine exhaust [22, 13], formaldehyde [74, 87], organic solvents [6, 74], mineral oil [2], and wood dust [11]. Most of these agents exert a carcinogenic effect on other respiratory organs, including the nasal cavity, the nasopharynx, and the lung: a similar effect on the larynx is therefore plausible. For none of agents, however, the clinical or epidemiological evidence is sufficiently consistent to conclude in favor of a causal association.

Employment in Specific Industries and Occupations

Several studies reported an increased risk of laryngeal cancer among workers employed in specific industries and occupations, including construction workers [11], butchers [11, 19], welders [35], transport workers [34, 66], textile workers [22], and bartenders [88]. The interpretation of these associations is complicated by the possibility of selective reporting of positive results, heterogeneity in the definition of occupational groups, and lack of power in individual studies. Large-scale systematic analyses of occupational groups address these limitations: the results of a pooled analysis of over 7.4 million men from five Nordic countries, whose job title was based on the information recorded at national censuses from 1961 onwards [67]; during an average 25-year follow-up, 18,488 cases of laryngeal cancer were identified through linkage with the data from the national cancer registries. In Table 8.7, results are presented for occupational groups with more than ten observed cases: a statistically significant (at $\alpha = 0.05$) increase in laryngeal cancer incidence was found for 22 out of 50 occupational groups (excluding economically inactive men) and a statistically significant decrease

Table 8.7 Standardized incidence ratio of laryngeal cancer in selected occupations. Results of NOCCA study [67]

Occupation	N cases	SIR	95 % CI
Technical workers	899	0.74	0.69–0.79
Laboratory workers	11	0.53	0.27–0.96
Physicians	47	0.59	0.43–0.78
Dentists	26	0.85	0.55–1.24
Assistant	21	1.04	0.65–1.60
Other health workers	52	0.84	0.63–1.10
Teachers	253	0.55	0.48–0.62
Religious workers	184	0.70	0.61–0.81
Artistic workers	92	1.11	0.89–1.36
Journalists	50	1.27	0.95–1.68
Administrators	847	0.97	0.91–1.04
Clerical workers	573	0.93	0.86–1.01
Sales agents	839	1.19	1.12–1.28
Shop workers	580	1.02	0.94–1.10
Farmers	1,052	0.46	0.44–0.49
Gardeners	291	0.58	0.51–0.65
Fishermen	241	1.20	1.05–1.36
Forestry workers	255	0.73	0.64–0.82
Miners and quarry workers	80	0.96	0.76–1.20
Seamen	378	1.85	1.67–2.04
Transport workers	313	0.98	0.88–1.10
Drivers	1,226	1.37	1.29–1.45
Postal workers	172	0.99	0.85–1.15
Textile workers	182	1.08	0.94–1.25
Shoe and leather workers	87	1.40	1.12–1.73
Smelting workers	374	1.29	1.17–1.43
Mechanics	1,356	1.12	1.06–1.18
Plumbers	149	1.04	0.89–1.22

Table 8.7 (continued)

Occupation	N cases	SIR	95 % CI
Welders	146	1.14	0.97–1.34
Electrical workers	477	1.13	1.03–1.23
Wood workers	819	0.82	0.77–0.88
Painters	303	1.22	1.09–1.36
Other construction workers	751	1.23	1.15–1.32
Bricklayers	167	1.05	0.90–1.23
Printers	173	1.21	1.04–1.41
Chemical process workers	247	1.16	1.02–1.31
Food workers	379	1.26	1.14–1.39
Beverage workers	59	2.65	2.02–3.42
Glass makers	284	1.22	1.08–1.37
Packers	536	1.32	1.21–1.43
Engine operators	435	1.20	1.09–1.32
Public safety workers	233	0.97	0.85–1.10
Cooks and stewards	96	2.27	1.84–2.77
Waiters	102	3.52	2.90–4.27
Building caretakers	255	1.28	1.13–1.45
Chimney sweeps	13	1.05	0.56–1.80
Hairdressers	66	1.55	1.20–1.97
Launderers	25	0.96	0.62–1.42
Military personnel	130	0.96	0.81–1.14
Other workers	*840*	*1.27*	*1.21–1.36*
Economically inactive	1,322	1.42	1.35–1.50

Results in italics were calculated based on raw data
N number of cases, *SIR* standardized incidence ratio, *CI* confidence interval

in nine occupations. While several occupations at increased or decreased risk might reflect high (e.g., cooks and waiters) or low (e.g., religious workers) consumption of tobacco and alcohol, and other associations might reflect exposure to known carcinogens (e.g., plumbers exposed to asbestos), a number of positive findings provide supportive evidence for possible exposure to carcinogenic agents, including seamen, drivers, shoe and leather workers, packers, and hairdressers.

Conclusion

The fact that the laryngeal mucosa is directly exposed to inhaled agents makes this organ a target for respiratory carcinogens. However, the evidence of an association is strong only for asbestos and strong inorganic acid mists. For several other occupational agents, including established carcinogens for other respiratory organs, the evidence of a role in laryngeal carcinogenesis is not fully established. From a practical viewpoint, the lack of conclusive evidence in favor of a causal association is of limited importance because preventive actions which are justified on the basis of the evidence available for other types of cancer would also reduce the risk, if any, of occupational cancer of the larynx. An increased risk of laryngeal cancer has been reported, albeit inconsistently, in several occupations and industries: the relatively rarity of the disease, the possibility of confounding by tobacco smoking and alcohol drinking, and of reporting bias complicate the identification of additional occupational laryngeal carcinogens.

Control of tobacco smoking and excessive alcohol drinking and the main actions which would lead to the prevention of laryngeal cancer, avoiding exposure to known carcinogens, would contribute to the prevention of a relatively small number of cases, which concentrate in some occupational groups. Available results contribute to identify avenues of research aimed at clarifying the role of suspected carcinogens.

References

1. Ahlborg Jr G, Hogstedt C, Sundell L, Aman CG. Laryngeal cancer and pickling house vapors. Scand J Work Environ Health. 1981;7:239–40.
2. Ahrens W, Jockel K, Patzak W, Elsner G. Alcohol, smoking, and occupational factors in cancer of the larynx: a case-control study. Am J Ind Med. 1991;20:477–93.
3. Armstrong BK, de Klerk NH, Musk AW, Hobbs MS. Mortality in miners and millers of crocidolite in Western Australia. Br J Ind Med. 1988;45:5–13.
4. Axelson O, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med. 1988;13:105–18.

5. Battista G, Belli S, Comba P, et al. Mortality due to asbestos-related causes among railway carriage construction and repair workers. Occup Med. 1999;49:536–9.
6. Berrino F, Richiardi L, Boffetta P, et al. Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case control study in France, Italy, Spain and Switzerland. Cancer Causes Control. 2003;14:213–23.
7. Berry G. Mortality and cancer incidence of workers exposed to chrysotile asbestos in the friction-products industry. Ann Occup Hyg. 1994;38:539–46.
8. Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in East London 1933–1980. Occup Environ Med. 2000;57:782–5.
9. Block G, Matanoski GM, Seltser R, Mitchell T. Cancer morbidity and mortality in phosphate workers. Cancer Res. 1988;48:7298–303.
10. Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control. 1997;8:444–72.
11. Boffetta P, Richiardi L, Berrino F, et al. Occupation and larynx and hypopharynx cancer: an international case-control study in France, Italy, Spain, and Switzerland. Cancer Causes Control. 2003;14:203–12.
12. Botta M, Magnani C, Terracini B, et al. Mortality from respiratory and digestive cancers among asbestos cement workers in Italy. Cancer Detect Prev. 1991;15:445–7.
13. Brown LM, Mason TJ, Pickle LW, et al. Occupational risk factors for laryngeal cancer on the Texas Gulf Coast. Cancer Res. 1988;48:1960–4.
14. Burch JD, Howe GR, Miller AB, Semenciw R. Tobacco, alcohol, asbestos, and nickel in the etiology of cancer of the larynx: a case-control study. J Natl Cancer Inst. 1982;67:1219–24.
15. Coggon D, Pannett B, Wield G. Upper aerodigestive cancer in battery manufacturers and steel workers exposed to mineral acid mists. Occup Environ Med. 1996;53:445–9.
16. Cookfair D, Wende K, Michalek A, Vena J. A case-control study of laryngeal cancer among workers exposed to sulfuric acid. Am J Epidemiol. 1985;122:521.
17. Cooper WC, Wong O, Kheifets L. Mortality among employees of lead battery plants and lead-producing plants, 1947–1980. Scand J Work Environ Health. 1985;11:331–45.
18. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5-a population-based study. Lancet Oncol. 2014;15:23–34.
19. De Stefani E, Boffetta P, Oreggia F, Ronco A, Kogevinas M, Mendilaharsu M. Occupation and the risk of laryngeal cancer in Uruguay. Am J Ind Med. 1998;33:537–42.
20. Dietz A, Ramroth H, Urban T, Ahrens W, Becher H. Exposure to cement dust, related occupational groups and laryngeal cancer risk: results of a population based case-control study. Int J Cancer. 2004;108:907–11.
21. Eisen EA, Tolbert PE, Hallock MF, et al. Mortality studies of machining fluid exposure in the automobile industry. III: a case-control study of larynx cancer. Am J Ind Med. 1994;26:185–202.
22. Elci OC, Dosemeci M, Blair A. Occupation and the risk of laryngeal cancer in Turkey. Scand J Work Environ Health. 2001;27:233–9.
23. Elci OC, Akpinar-Elci M, Blair A, Dosemeci M. Occupational dust exposure and the risk of laryngeal cancer in Turkey. Scand J Work Environ Health. 2002;28:278–84.
24. Enterline PE, Hartley J, Henderson V. Asbestos and cancer: a cohort followed up to death. Br J Ind Med. 1987;44:396–401.
25. Ferlay J, Soerjomataram I, Ervik M, et al. Globocan 2012 v1.0, Cancer incidence and mortality worldwide: IARC cancer base no. 11. Lyon: International Agency for Research on Cancer; 2013.
26. Finkelstein MM. Mortality rates among employees potentially exposed to chrysotile asbestos at two automotive parts factories. CMAJ. 1989;141:125–30.
27. Finkelstein MM, Verma DK. A cohort study of mortality among Ontario pipe trades workers. Occup Environ Med. 2004;61:736–42.
28. Forastiere F, Valesini S, Salimei E, et al. Respiratory cancer among soap production workers. Scand J Work Environ Health. 1987;13:258–60.
29. Forman D, Bray F, Brewster DH, Gombe Mbalawa C, et al. Cancer incidence in five continents, vol. X. Lyon: IARC; 2013.
30. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer. 2008;122:155–64.
31. Gardner MJ, Winter PD, Pannett B, Powell CA. Follow up study of workers manufacturing chrysotile asbestos cement products. Br J Ind Med. 1986;43:726–32.
32. Germani D, Belli S, Bruno C, Grignoli M, Nesti M, Pirastu R, et al. Cohort mortality study of women compensated for asbestosis in Italy. Am J Ind Med. 1999;36:129–34.
33. Giaroli C, Belli S, Bruno C, Candela S, Grignoli M, Minisci S, et al. Mortality study of asbestos cement workers. Int Arch Occup Environ Health. 1994;66:7–11.
34. Goldberg P, Leclerc A, Luce D, Morcet JF, Brugère J. Laryngeal and hypopharyngeal cancer and occupation: results of a case control-study. Occup Environ Med. 1997;54:477–82.
35. Gustavsson P, Jakobsson R, Johansson H, Lewin F, Norell S, Rutkvist LE. Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden. Occup Environ Med. 1998;55:393–400.
36. Harding AH, Darnton A, Wegerdt J, McElvenny D. Mortality among British asbestos workers undergoing regular medical examinations (1971–2005). Occup Environ Med. 2009;66:487–95.
37. Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. Occup Environ Med. 2007;64:616–25.
38. Hesterberg TW, Miller WC, McConnell EE, et al. Chronic inhalation toxicity of size-separated glass fibres in Fischer 344 rats. Fundam Appl Toxicol. 1993;20:464–76.
39. Hinds MW, Thomas DB, O'Reilly HP. Asbestos, dental X-rays, tobacco, and alcohol in the epidemiology of laryngeal cancer. Cancer. 1979;44:1114–20.
40. Hueper WC. Occupational and environmental cancers of the respiratory system. Berlin: Springer; 1966.
41. Hughes JM, Weill H, Hammad YY. Mortality of workers employed in two asbestos cement manufacturing plants. Br J Ind Med. 1987;44:161–74.
42. Institute of Medicine of the National Academies. Asbestos: selected cancers. Washington, DC: National Academy Press; 2006.
43. International Agency for Research on Cancer. Occupational exposures to mists and vapours from strong inorganic acids and other industrial chemicals. IARC Monogr Eval Carcinog Risks Hum. 1992;54:1–310.
44. Kambic V, Radsel Z, Gale N. Alterations in the laryngeal mucosa after exposure to asbestos. Br J Ind Med. 1989;46:717–23.
45. Karjalainen A, Pukkala E, Kauppinen T, Partanen T. Incidence of cancer among Finnish patients with asbestos-related pulmonary or pleural fibrosis. Cancer Causes Control. 1999;10:51–7.
46. Levin J, McLarty J, Hurst GA, Smith A, Frank AL. Tyler asbestos workers: mortality experience in a cohort exposed to amosite. Occup Environ Med. 1998;55:155–60.
47. Li X, Gao L, Li H, et al. Human papillomavirus infection and laryngeal cancer risk: a systematic review and meta-analysis. J Infect Dis. 2013;207:479–88.
48. Liddell FD, McDonald AD, McDonald JC. The 1891–1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. Ann Occup Hyg. 1997;41:13–36.
49. Loomis D, Dement JM, Wolf SH, Richardson DB. Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers. Occup Environ Med. 2009;66:535–42.

50. Lynch J, Hanis NM, Bird MG, et al. An association of upper respiratory cancer with exposure to diethyl sulfate. J Occup Med. 1979;21:333–41.
51. Marchand JL, Luce D, Leclerc A, et al. Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibers: results of a case-control study. Am J Ind Med. 2000;37:581–9.
52. McConnell EE, Kamstrup O, Musselman R, et al. Chronic inhalation study of size-separated rock and slag wool insulation fibres in Fischer 344/N rats. Inhal Toxicol. 1994;6:571–614.
53. McConnell EE, Axten C, Hesterberg TW, et al. Studies on the inhalation toxicology of two fibreglasses and amosite asbestos in the Syrian golden hamster. Part II. Results of chronic exposure. Inhal Toxicol. 1999;11:785–835.
54. McKay JD, Truong T, Gaborieau V, et al. A genome-wide association study of upper aerodigestive tract cancers conducted within the INHANCE consortium. PLoS Genet. 2011;7:e1001333.
55. Menegozzo S, Comba P, Ferrante D, De Santis M, Gorini G, Izzo F, et al. Mortality study in an asbestos cement factory in Naples, Italy. Ann Ist Super Sanita. 2011;47:296–304.
56. Meurman LO, Pukkala E, Hakama M. Incidence of cancer among anthophyllite asbestos miners in Finland. Occup Environ Med. 1994;51:421–5.
57. Moulin JJ, Clavel T, Roy D, et al. Risk of lung cancer in workers producing stainless steel and metallic alloys. Int Arch Occup Environ Health. 2000;73:171–80.
58. Muscat J, Wynder E. Tobacco, alcohol, asbestos, and occupational risk factors for laryngeal cancer. Cancer. 1992;69:2244–51.
59. Olsen J, Sabroe S. Occupational causes of laryngeal cancer. J Epidemiol Community Health. 1984;38:117–21.
60. Olshan FA. Cancer of the larynx. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 2006. p. 627–37.
61. Parnes SM. Asbestos and cancer of the larynx: is there a relationship? Laryngoscope 1990;100:254–61.
62. Pesatori AC, Consonni D, Rubagotti M, et al. Mortality study in a cohort of workers employed in a plant producing sulphuric acid. Med Lav. 2006;97:735–48.
63. Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann Occup Hyg. 1985; 29:305–55.
64. Piolatto G, Negri E, La Vecchia C, Pira E, Decarli A, Peto J. An update of cancer mortality among chrysotile asbestos miners in Balangero, Northern Italy. Br J Ind Med. 1990;47:810–4.
65. Pira E, Pelucchi C, Buffoni L, Palmas A, Turbiglio M, Negri E, et al. Cancer mortality in a cohort of asbestos textile workers. Br J Cancer. 2005;92:580–6.
66. Pollán M, López-Abente G. Wood-related occupations and laryngeal cancer. Cancer Detect Prev. 1995;19:250–7.
67. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48:5,646–790.
68. Puntoni R, Merlo F, Borsa L, Reggiardo G, Garrone E, Ceppi M. A historical cohort mortality study among shipyard workers in Genoa, Italy. Am J Ind Med. 2001;40:363–70.
69. Raffn E, Lynge E, Juel K, Korsgaard B. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. Br J Ind Med. 1989;46:90–6.
70. Reid A, Ambrosini G, de Klerk N, Fritschi L, Musk B. Aerodigestive and gastrointestinal tract cancers and exposure to crocidolite (blue asbestos): incidence and mortality among former crocidolite workers. Int J Cancer. 2004;111:757–61.
71. Roggli VL, Greenberg SD, McLarty JL, Hurst GA, Spivey CG, Heiger LR. Asbestos body content of the larynx in asbestos workers: a study of five cases. Arch Otolaryngol. 1980;106: 533–5.
72. Sathiakumar N, Delzell E, Amoateng-Adjepong Y, et al. Epidemiologic evidence on the relationship between mists containing sulfuric acid and respiratory tract cancer. Crit Rev Toxicol. 1997;27:233–51.
73. Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987. Ann N Y Acad Sci. 1991;643:1–14.
74. Shangina O, Brennan P, Szeszenia-Dabrowska N, et al. Occupational exposure and laryngeal and hypopharyngeal cancer risk in central and eastern Europe. Am J Epidemiol. 2006;164:367–75.
75. Shettigara PT, Morgan RW. Asbestos, smoking, and laryngeal carcinoma. Arch Environ Health. 1975;30:517–9.
76. Sluis-Cremer GK, Liddell FD, Logan WP, Bezuidenhout BN. The mortality of amphibole miners in South Africa, 1946–80. Br J Ind Med. 1992;49:566–75.
77. Smailyte G, Kurtinaitis J, Andersen A. Cancer mortality and morbidity among Lithuanian asbestos-cement producing workers. Scand J Work Environ Health. 2004;30:64–70.
78. Sorahan T, Esmen NA. Lung cancer mortality in UK nickel-cadmium battery workers, 1947–2000. Occup Environ Med. 2004; 61:108–16.
79. Soskolne CL, Jhangri GS, Siemiatycki J, et al. Occupational exposure to sulfuric acid in southern Ontario, Canada, in association with laryngeal cancer. Scand J Work Environ Health. 1992;18: 225–32.
80. Steenland K, Beaumont J. Further follow-up and adjustment for smoking in a study of lung cancer and acid mists. Am J Ind Med. 1989;16:347–54.
81. Stell P, McGill T. Asbestos and laryngeal carcinoma. Lancet. 1973;Ii:416–7.
82. Szeszenia-Dabrowska N, Urszula W, Szymczak W, Strzelecka A. Mortality study of workers compensated for asbestosis in Poland, 1970–1997. Int J Occup Med Environ Health. 2002;15:267–78.
83. Teta MJ, Perlman GD, Ott MG. Mortality study of ethanol and isopropanol production workers at two facilities. Scand J Work Environ Health. 1992;18:90–6.
84. Tola S, Kalliomaki PL, Pukkala E, Asp S, Korkala ML. Incidence of cancer among welders, platers, machinists, and pipe fitters in shipyards and machine shops. Br J Ind Med. 1988;45:209–18.
85. Weil CS, Smyth Jr HF, Nale TW. Quest for a suspected industrial carcinogen. Arch Ind Hyg Occup Med. 1952;5:535–47.
86. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2006.
87. Wortley P, Vaughan TL, Davis S, Morgan MS, Thomas DB. A case-control study of occupational risk factors for laryngeal cancer. Br J Ind Med. 1992;49:837–44.
88. Zagraniski RT, Kelsey JL, Walter SD. Occupational risk factors for laryngeal carcinoma: Connecticut, 1975–1980. Am J Epidemiol. 1986;124:67–76.
89. Zemla B, Day N, Swiatnicka J, Banasik R. Larynx cancer risk factors. Neoplasma. 1987;34:223–33.
90. Zheng W, Blot WJ, Shu XO, et al. Diet and other risk factors for laryngeal cancer in Shanghai, China. Am J Epidemiol. 1992;136: 178–91.

Lung Cancer (Exposure Assessment, Pathology, and Epidemiology)

9

Elizabeth N. Pavlisko, Paolo Boffetta, and Victor L. Roggli

Keywords
Occupational lung cancer • Epidemiology • Asbestos • Pulmonary asbestos analysis • Arsenic • Silica • Chromium • Nickel • Polyaromatic hydrocarbons

Introduction

Lung cancer is the most common malignancy worldwide and the most common cause of a cancer-related death. Tobacco smoking is the most important cause of lung cancer in most populations although occupational exposures cause an increased risk of lung cancer more than any other malignancy [1]. This chapter will review the histomorphology and classification of carcinoma of the lung and the evidence for specific occupational exposures reported to cause lung cancer.

Histopathology of Lung Carcinoma

The 2004 WHO classification of carcinoma of the lung includes four major histomorphologic patterns: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma. Some major patterns are divided into types due to differences in prognosis/progression/survival. Table 9.1 outlines the major patterns and their "subtypes."

E.N. Pavlisko, MD (✉) • V.L. Roggli, MD
Department of Pathology, Duke University Medical Center, Durham, NC, USA
e-mail: elizabeth.pavlisko@duke.edu

P. Boffetta, MD, MPH
Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA
e-mail: paolo.boffetta@mssm.edu

Adenocarcinoma

Adenocarcinoma is the most common histologic pattern of carcinoma in the lung in most populations. Broadly, adenocarcinomas are epithelial tumors with mucin production or glandular differentiation. Morphologic variants include carcinoma in situ, mucinous, acinar, papillary, micropapillary, and solid (Fig. 9.1). Adenocarcinomas are most often peripherally located stellate masses, less than 4 cm, and rarely cavitary [2]. Peripherally located tumors frequently abut and may pucker the overlying visceral pleura. Radiographic identification of these peripherally located tumors has improved with technologic advances and increased use of computed tomography (CT) of the thorax.

Tumors are graded as well differentiated (grade 1), moderately differentiated (grade 2), or poorly differentiated (grade 3). Histologic variants generally align with the degree of differentiation as seen in Table 9.2 [2]. Involvement of hilar lymph nodes is less frequent than with other histologic patterns of lung cancer, yet spread is usually via the lymphovasculature. In the in situ type, aerogenous dissemination can occur, leading to involvement of the same lobe or a different lobe in the ipsilateral or contralateral lung [2]. The staging of adenocarcinoma is the same as for other carcinomas of the lung and follows the 2010 AJCC TNM system (Table 9.3) [3].

Since the 2004 edition of the WHO's classification of tumors of the lung, there has been a burst of growth specifically regarding adenocarcinoma of the lung. The non-mucinous or mucinous bronchioloalveolar cell carcinoma (BAC) terminology has fallen out of favor, and adenocarcinoma in situ has been proposed as a replacement for only the non-mucinous variant. The proposed reclassification for

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_9, © Springer-Verlag London 2014

Table 9.1 Histologic classification of lung cancer

Squamous cell carcinoma
Papillary
Clear cell
Small cell
Basaloid
Small cell carcinoma
Combined small cell carcinoma
Adenocarcinoma
Minimally invasive adenocarcinoma – defined as ≤3 cm lepidic predominant tumor with ≤5 mm invasive component
Invasive adenocarcinoma
Patterns of invasive adenocarcinoma
Lepidic predominant – defined as former non-mucinous bronchioloalveolar carcinoma (BAC) with >5 mm invasion
Acinar
Papillary
Micropapillary
Solid with mucin
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal
Enteric
Large cell carcinoma
Large cell neuroendocrine
Basaloid carcinoma
Lymphoepithelioma-like carcinoma
Clear cell carcinoma
Large cell carcinoma with rhabdoid phenotype
Adenosquamous
Sarcomatoid carcinoma
Pleomorphic carcinoma
Spindle cell carcinoma
Giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma
Carcinoid tumor
Typical carcinoid
Atypical carcinoid
Carcinomas of salivary gland type
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Epimyoepithelial carcinoma

Modified from Travis [174], Copyright 2011, with permission from Elsevier

mucinous BAC is mucinous adenocarcinoma as virtually all have an invasive component [4].

Immunohistochemistry can be helpful when the tumor histomorphology does not allow for classification. Common immunohistochemical (IHC) antibodies used in the distinction between primary adenocarcinoma of the lung versus squamous cell carcinoma versus common metastatic tumors and mesothelioma can be seen in Table 9.4 [5].

Squamous Cell Carcinoma

Squamous cell carcinoma is a malignant epithelial tumor composed of cells forming keratin or intercellular bridges (Fig. 9.2). Histologic variants of squamous cell carcinoma include papillary, clear cell, small cell, and basaloid [2]. Immunohistochemical stains helpful in determining squamous differentiation include p63, CK903 (34βE12), and CK5/6 (Table 9.4). The small cell variant may express chromogranin, synaptophysin, and/or CD56.

Greater than 90 % of squamous cell carcinomas occur in cigarette smokers, although occupational exposures have also been implicated in the development of squamous cell carcinoma. This histologic pattern of lung cancer tends to arise centrally from the bronchial epithelium and may protrude into the bronchial lumen causing obstructive symptoms. It is the most common tumor to form a cavitary, encapsulated mass. Centrally located tumors spread via intraepithelial growth along bronchioles and bronchi with or without extension/invasion into submucosal tissue or may protrude with intraluminal polypoid growth. Squamous cell carcinomas are more often locally aggressive with direct extension into adjacent structures, including lymph nodes [2]. Metastasis to distant organs is less common versus adenocarcinoma, and local recurrence is more common following resection than in other histologic types of lung cancer. Squamous cell carcinoma is staged using the same TNM system as that for adenocarcinoma.

Small Cell Carcinoma

Small cell carcinoma is a malignant epithelial tumor composed of round to oval or spindled cells with scant cytoplasm surrounding a nucleus with finely dispersed euchromatin-lacking nucleoli (Fig. 9.3). The sole histologic variant is combined small cell carcinoma which includes any component of non-small cell carcinoma intermixed with small cell histology [2]. Immunohistochemical stains helpful in distinguishing small cell carcinoma include cytokeratin with a thin rim and dot-like staining of the cytoplasm and Golgi apparatus, respectively. As small cell carcinoma falls within a larger class of tumors of neuroendocrine differentiation, staining for chromogranin, synaptophysin, and/or CD56 is often positive. Tumor cells express TTF-1 in the majority of cases (Fig. 9.3).

Like squamous cell carcinoma, small cell carcinomas are usually located centrally as a hilar or perihilar mass with hilar/mediastinal lymphadenopathy. Clinical symptoms can include pneumonia, hoarseness, and vocal cord paralysis but more often reflect dissemination to distant organs (liver, bone marrow, or brain) due to its propensity to spread quickly and present late. Paraneoplastic syndromes are also associated with small cell carcinoma and are discussed below

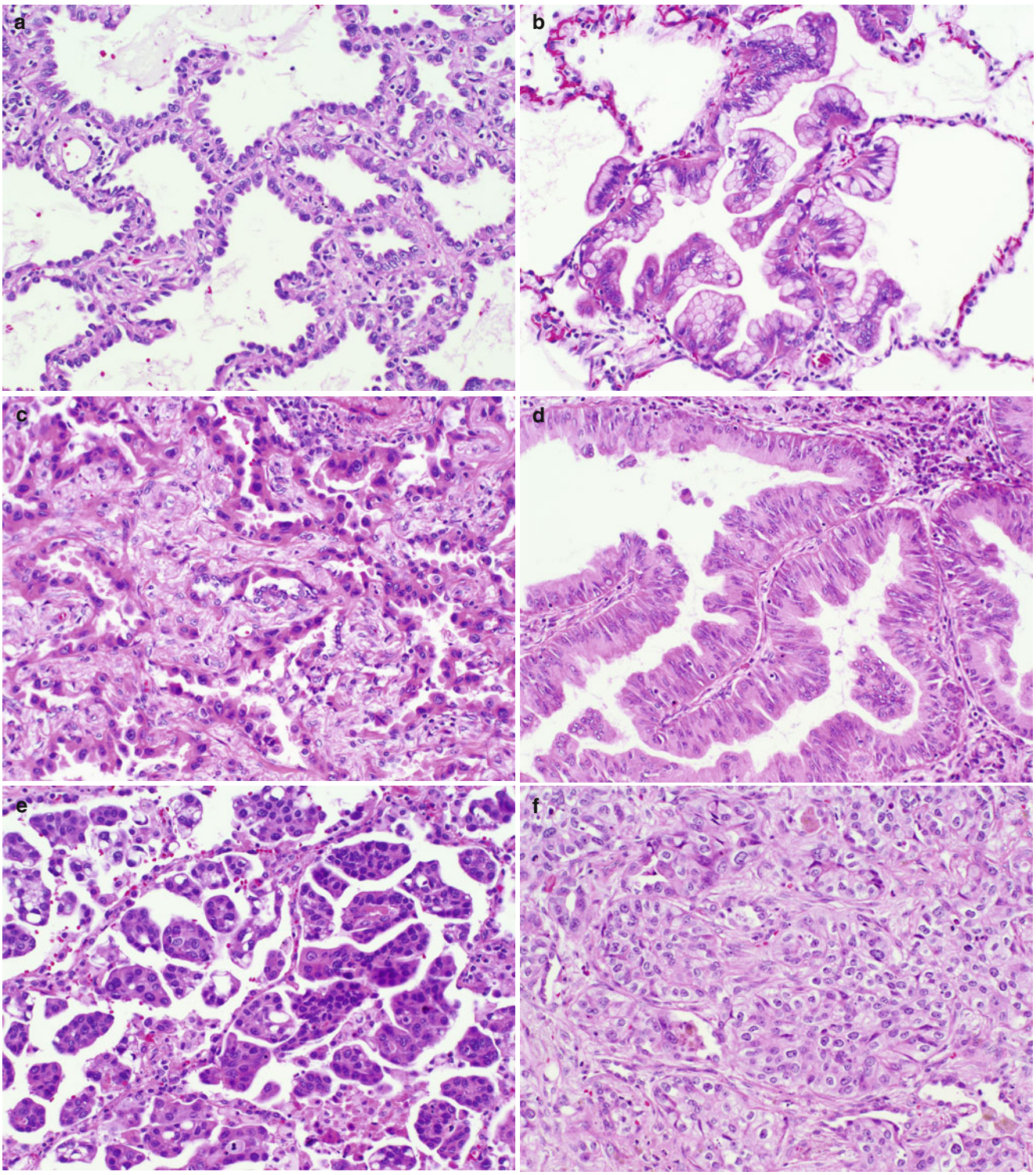


Fig. 9.1 Morphologic variants of adenocarcinoma: (**a**) adenocarcinoma in situ, (**b**) mucinous, (**c**) acinar, (**d**) papillary, (**e**) micropapillary and (**f** solid [hematoxylin and eosin (H&E), original magnification ×200]

Table 9.2 Histologic variants of adenocarcinoma and degree of differentiation

Adenocarcinoma in situ	Well differentiated (G1)
Acinar	Moderately or poorly differentiated (G2 or G3)
Papillary	Moderately or poorly differentiated (G2 or G3)
Solid	Poorly differentiated (G3)
Micropapillary	Poorly differentiated (G3)

Data from Travis et al. [2]

Table 9.3 2010 AJCC staging for carcinoma of the lung

Primary lung tumor (T)	
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	≤3 cm in greatest dimension
T1a	≤2 cm
T1b	>2 cm but ≤3 cm
T2	>3 cm but ≤7 cm
T2a	>3 cm but ≤5 cm
T2b	>5 cm but ≤7 cm
T3	>7 cm or directly invades parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, pericardium, or tumor in the main bronchus without involvement of the carina
T4	Any size tumor with invasion of mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, ipsilateral lobe
Regional lymph nodes (N)	
NX	Lymph node status cannot be assessed
N0	No lymph node metastasis
N1	Metastasis to a level 10 lymph node or higher
N2	Metastasis to an ipsilateral level 9 lymph node or lower
N3	Metastasis to a contralateral level 9 lymph node or lower or to a supraclavicular lymph node
Metastatic disease (M)	
MX	Metastasis cannot be assessed
M0	No metastasis
M1	Distant metastasis
M1a	Separate tumor in contralateral lobe, pleural tumor nodules, or malignant effusion
M1b	Distant metastasis

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the *AJCC Cancer Staging Manual*, 7th edn (2010) published by Springer Science and Business Media LLC, www.springer.com

Table 9.4 Immunohistochemical panels

Panel for lung adenocarcinoma versus squamous cell carcinoma

Immunohistochemical stain/antibody	Primary lung adenocarcinoma	Squamous cell carcinoma
Cytokeratin 7	+	+/–
TTF-1 (nuclear)	+	–
Napsin-A	+	–
p63	+/–	+
Cytokeratin 5/6	–	+
Cytokeratin 903/34βE12	+/–	+

Panel for lung adenocarcinoma versus metastatic breast cancer

Immunohistochemical stain/antibody	Primary lung adenocarcinoma	Squamous cell carcinoma
Cytokeratin 7	+	+
TTF-1 (nuclear)	+	–
Napsin-A	+	–
Mammaglobin	–	+
BRST-2 (GCDFP)	–	+

Panel for lung adenocarcinoma versus metastatic colorectal cancer

Immunohistochemical stain/antibody	Primary lung adenocarcinoma	Squamous cell carcinoma
Cytokeratin 7	+	+/–
TTF-1 (nuclear)	+	–
Napsin-A	+	–
Cytokeratin 20	–	+
CDX-2	–	+

Panel for lung adenocarcinoma versus mesothelioma

Immunohistochemical stain/antibody	Primary lung adenocarcinoma	Squamous cell carcinoma
TTF-1 (nuclear)	+	–
Carcinoembryonic antigen (CEA) polyclonal	+	–
B72.3	+	–
MOC-31	+	–
Ber-EP4	+	–
Calretinin	–	+
Cytokeratin 5/6	–	+
WT-1	+/–	+
D2-40 (podoplanin)	–	+

+Positive staining in majority of cases
–Negative staining in majority of cases
+/–Usually negative but positive staining in 20–30 % of cases

under *Clinical Symptoms*. Staging is categorized as limited or extensive disease rather than using the TNM system.

Large Cell Carcinoma

Large cell carcinomas account for less than 10 % of all lung cancers and are poorly differentiated, falling in the non-small cell category and lacking squamous or glandular differentiation (Fig. 9.4). Histologic variants include large cell neuroendocrine, combined large cell neuroendocrine, basaloid, lymphoepithelioma-like, clear cell, and large cell carcinomas with rhabdoid phenotype. Large cell carcinomas are most often peripherally located large masses and commonly invade pleura and adjacent structures including chest wall. Spread occurs to hilar and/or mediastinal lymph nodes followed by metastasis to distant organs. Specific variants of large cell carcinoma differ in their pattern of spread and response to treatment. Basaloid,

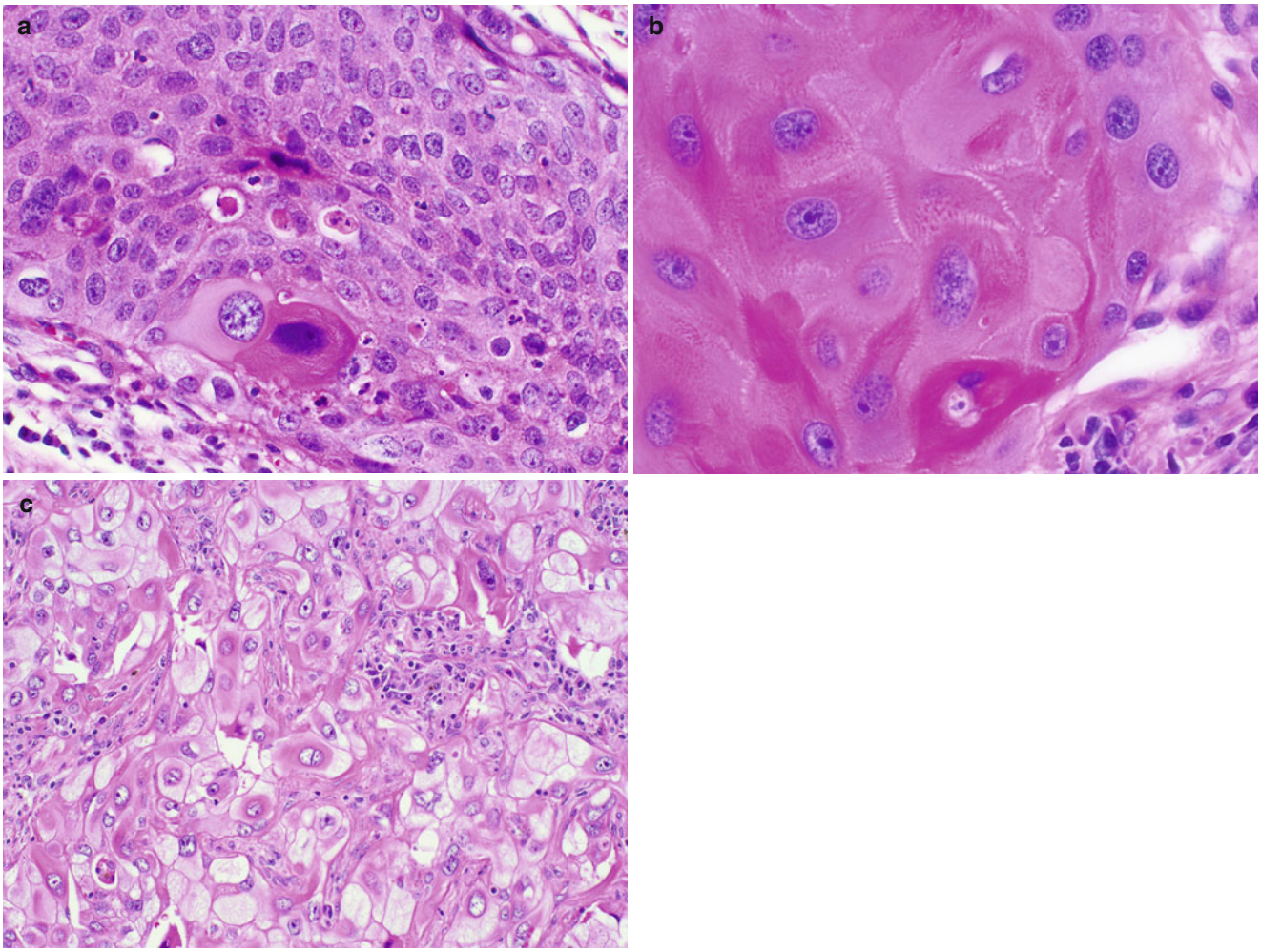


Fig. 9.2 Squamous cell carcinoma: **(a)** H&E stain demonstrates a large keratinizing squamous cell carcinoma [original magnification × 400], **(b)** intercellular bridges can be seen between cells [original magnification × 600], **(c)** clear cell histology in a squamous cell carcinoma [original magnification ×200]

combined large cell neuroendocrine, and large cell carcinomas with rhabdoid phenotype have a worse prognosis versus classic large cell carcinoma, and lymphoepithelioma-like carcinoma has a better prognosis [2]. Previously, giant cell carcinoma (Fig. 9.5) was included as a histologic variant of large cell carcinoma; however, in the current WHO classification, it is classified under sarcomatoid carcinoma along with pleomorphic carcinoma, spindle cell carcinoma, and carcinosarcoma. Staging for large cell carcinoma is the same as for the previously mentioned non-small cell histologic types.

Clinical Symptoms

Clinical symptoms of lung cancer include constitutional symptoms such as malaise, anorexia, and weight loss but otherwise depend largely on the location of the tumor as well as tumor burden. For centrally located non-small cell carcinomas, additional symptoms can include cough, dyspnea, sputum production, hemoptysis, or pneumonia secondary to airway obstruction. Similarly, peripherally located tumors may lead to cough and dyspnea and can also produce pain. Regional spread within the thorax may produce innumerable symptoms/findings including pleural effusion, Horner syndrome (meiosis, partial ptosis, and anhidrosis), Pancoast syndrome (severe shoulder region pain, atrophy of hand and arm muscles, Horner syndrome, and vascular compression with edema), and superior vena cava (SVC) syndrome (compression/obstruction of the SVC causing congestion/swelling of the upper extremities and head, headache, dyspnea, etc.), hoarseness from involvement of the left recurrent laryngeal nerve, or an elevated hemidiaphragm from phrenic nerve involvement. Paraneoplastic

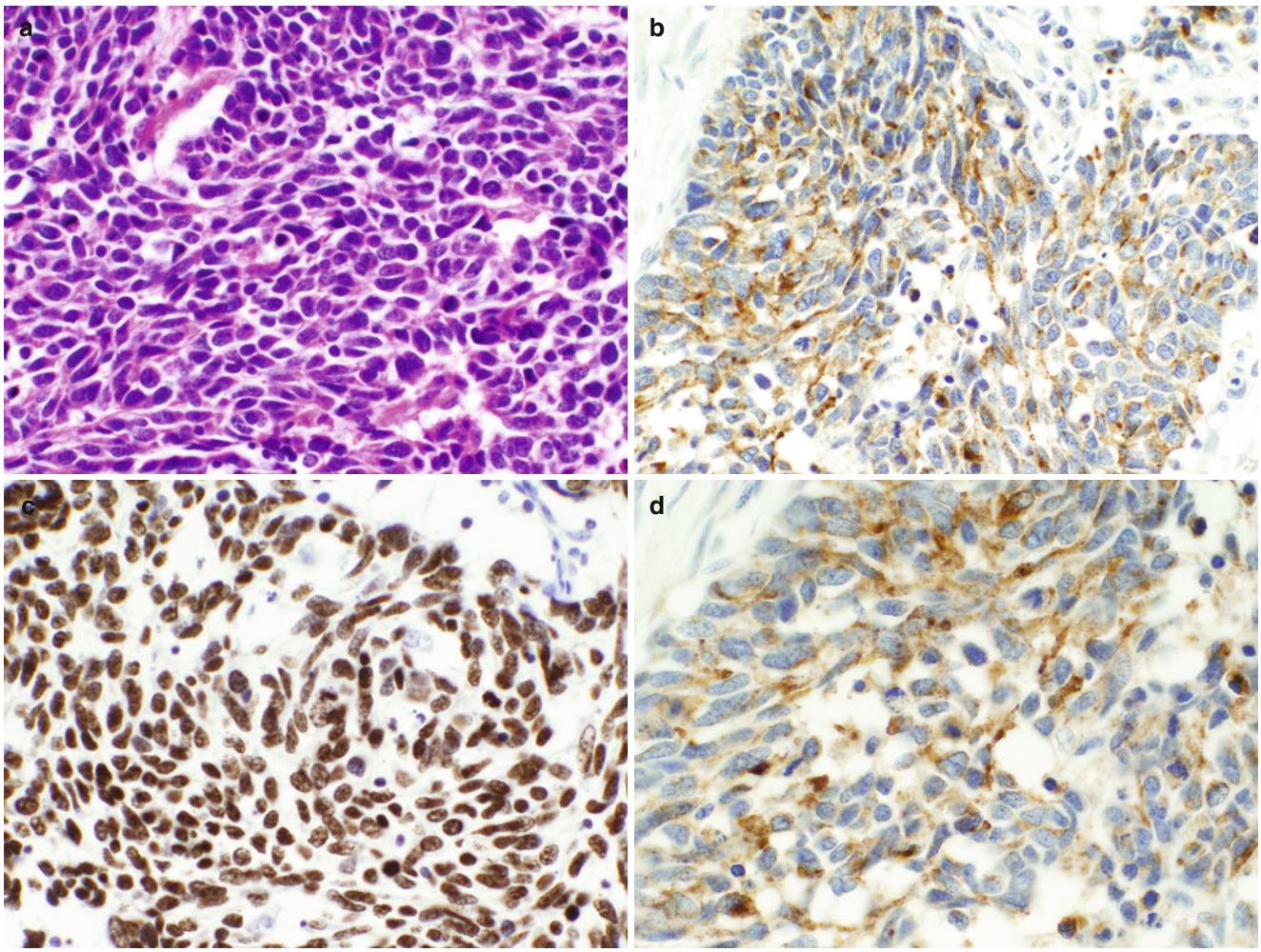


Fig. 9.3 Small cell carcinoma: **(a)** H&E stain demonstrates cells with scant cytoplasm surrounding a nucleus with finely dispersed chromatin, **(b)** cytokeratin immunohistochemical stain with positive cytoplasmic staining, **(c)** TTF-1 immunohistochemical stain with positive nuclear staining, **(d)** chromogranin immunohistochemical stain with positive cytoplasmic staining [original magnification ×400]

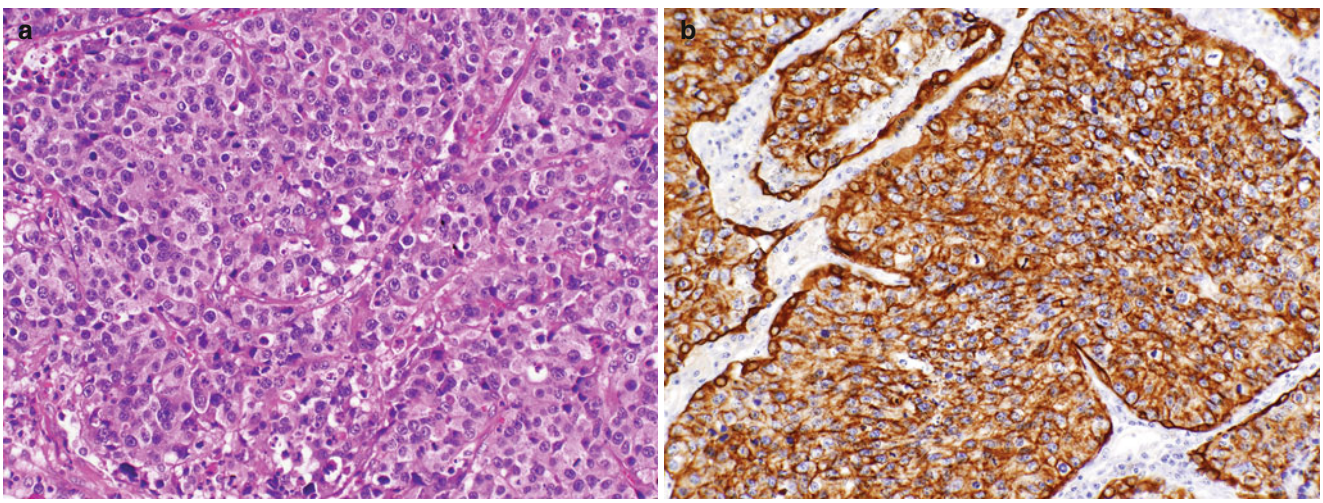


Fig. 9.4 Large cell carcinoma: **(a)** H&E stain showing pleomorphic tumor cells with no histologic evidence of glandular or squamous differentiation, **(b)** cytokeratin 7 (CK7) immunohistochemical stain with positive cytoplasmic staining [original magnification ×200]

syndromes occur secondary to elaboration of hormones by the tumor and may produce a variety of metabolic derangements (Table 9.5) [6, 7].

Radiographic Imaging

Radiographic studies of the chest performed for pulmonary symptoms or for other reasons are often the first look at a patient's undiagnosed lung cancer and/or lung disease. As there is increasing use of and continual advances in imaging technology, it is likely that asymptomatic, incidental pulmonary nodules will be identified with increasing frequency. Plain film chest roentgenograms (chest x-rays) are rarely able to identify lung cancer unless the lesion is greater than 1 cm. However, due to better contrast resolution, computed tomography of the chest (chest CT) can detect much smaller lesions [8]. Peripheral lung cancer often appears as a solitary pulmonary nodule with irregular or spiculated borders yet well delineated in density from the surrounding lung parenchyma. One exception to this is adenocarcinoma in situ (formerly bronchioloalveolar cell carcinoma) in which ground glass opacities are seen in the region of disease. A dense nodule surrounded by "ground glass" may represent a central core of invasive adenocarcinoma with surrounding in situ growth [4]. Centrally located lung cancer can obstruct the bronchi, causing collapse of a lobe or the appearance of a lobar pneumonia. Cavitating lesions, most often seen with squamous cell carcinoma, can be seen on both plain film and CT imaging studies. Contrast-enhanced chest CT and magnetic resonance imaging (MRI) can be useful in distinguishing neoplastic from nonneoplastic lung tissue. Positron-emission tomography (PET) studies are useful in determining the extent/stage of disease prior to treatment as well as in following progression or recurrence [8].

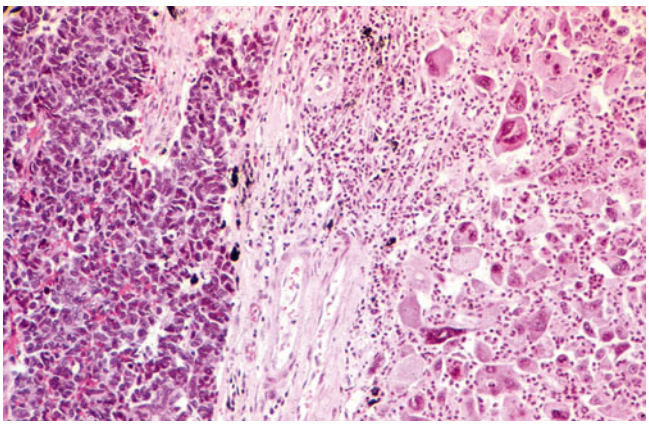


Fig. 9.5 Giant cell carcinoma (*right*) with concurrent small cell carcinoma (*left*) histology [H&E stain, original magnification × 200]

Acquiring Tissue for a Diagnosis

Centrally located tumors may be sampled via sputum cytology and/or bronchoscopic brushing, washing, fine needle aspiration, or biopsy. Image assistance using endobronchial ultrasound (EBUS) is also an option. Peripherally located tumors are more challenging and often require percutaneous biopsy, such as transthoracic needle aspiration or biopsy, with the guidance of fluoroscopic or CT imaging. A more invasive procedure is often necessary if the aforementioned fails to produce a diagnosis, and video-assisted thoracoscopic surgery (VATS) biopsy is usually the next choice. VATS is also the preferred method for tumor resection, which usually follows a biopsy or cyto-

Table 9.5 Paraneoplastic syndromes

Clinical symptom	Mechanism	Common carcinoma type
Endocrine		
Hypercalcemia	Parathyroid hormone-related protein (PTHRP), TGF-a, TNF, IL-1	Squamous cell carcinoma
Hyponatremia/SIADH	Antidiuretic hormone (ADH) or atrial natriuretic hormones	Small cell carcinoma
Cushing syndrome	Adrenocorticotrophic (ACTH) or ACTH-like substance	Small cell carcinoma
Neuromuscular		
Myasthenia	Immune mediated	Bronchogenic carcinoma
Lambert–Eaton syndrome	Immune mediated	Small cell carcinoma
Dermatologic		
Acanthosis nigricans	Immunologic secretion of epidermal growth factor	Lung carcinoma
Dermatomyositis	Immune mediated	Bronchogenic carcinoma
Cardiovascular		
Nonbacterial thrombotic endocarditis	Hypercoagulable state/unknown mechanism	Adenocarcinoma

Modified from *Neoplasia*. Kumar et al. [6]. Copyright Elsevier 2005

logic diagnosis. For those tumors not amenable to less invasive diagnostic procedures, diagnosis and tumor resection can occur simultaneously with the assistance of a frozen section diagnosis while the patient is under anesthesia. Surgical resection may yield a wedge biopsy, lobectomy, or pneumonectomy depending on the location and extent of disease.

Confounding Effects of Other Causes of Lung Cancer

Tobacco Smoking

There is a clear and strong relationship between the development of lung cancer and tobacco smoking with no discrimination of histologic type. Aside from lung cancer, tobacco smoke causes other pathologic processes in the lung, and it is important for the pathologist not to overlook secondary diagnoses such as centrilobular emphysema, chronic bronchitis, and small airways disease when diagnosing and staging lung cancer. Occupational exposure history is often difficult to document as it is frequently retrospective. In some circumstances, recreation of the occupational setting by industrial hygienists with models and estimations of exposure levels to a particular substance may be useful. Because tobacco smoke is such a potent cause of lung cancer, one must take into consideration the confounding effects of tobacco when evaluating an individual for occupational lung cancer. For some exposures, tobacco smoke has a synergistic effect in the causation of lung cancer. It is important for clinicians to distinguish between never smokers, ex-smokers, and current smokers as the risk for an ex-smoker never declines back to that of a never smoker but approaches that risk after two or three decades. Radiographic manifestations of an occupational exposure may be distorted or obscured by the effects of smoking, or smoking may lead to opacities seen on chest radiographs which can mimic an occupational exposure.

Other Causes of Lung Cancer

In addition to tobacco smoking, other causes of lung cancer have been identified, including indoor exposure to radon decay products, secondhand smoke, and, in particular in poorly ventilated settings in low- and middle-income countries, outdoor air pollution, cooking and heating emissions, as well as chronic lung infections from tuberculosis and other agents. Although these causes are less potent than tobacco smoking, they should be taken into account as potential cofactors of the disease in exposed workers, in particular in never smokers and long-term quitters.

Occupational Exposure and Lung Cancer

In this section, we review the role of known occupational carcinogens in causing lung cancer, including some chronic occupational lung diseases which have been causally associated with lung cancer. Since a large number of investigations have been conducted on known and suspected occupational causes of lung cancer, we did not aim to list them all (systematic reviews are available in the recent IARC Monographs Volume 100 series [9]); rather, we mentioned for each agent the most significant studies. In Table 9.6, we summarized the estimates of the number of lung cancers attributable to specific occupational agents, based on the IARC evaluations, made in two recent studies from the United Kingdom [10] and France [1]. While asbestos remains the most important occupational lung carcinogen, there are important differences in the results on silica, radon, heavy metals, and PAHs, stressing the need to interpret these results with caution.

Table 9.6 Number of cases of lung cancers attributable to specific occupational exposures in the United Kingdom and France

Agent	UK [10]	France [1]
Sufficient evidence of carcinogenicity[a]		
Asbestos	2,223	1,428
Silica	907	111
SHTS	284	132
Painters	282	134
Radon	209	26
Arsenic	129	NA
Chromium VI	67	579
Steel founding	29	[b]
PAHs	4	710
Nickel	10	145
Cadmium	9	9
Beryllium	7	NA
Ionizing radiation	2	NA
Limited evidence of carcinogenicity[c]		
Diesel exhaust	695	–
Mineral oils	470	–
Dioxin	215	–
Welding	175	–
Strong inorganic acid mists	76	–
Cobalt	73	–
Inorganic lead	42	–
Tin mining	2	–

NA not available

[a]Agents classified by IARC as established lung carcinogens when the studies were conducted

[b]Included under PAHs

[c]Agents classified by IARC as suspected lung carcinogens when the UK and the French studies were conducted (agents may be established carcinogens for other organs or may have been reevaluated as established carcinogens after the studies were conducted). The French study was restricted to established carcinogens

Arsenic

Arsenic, a semimetallic element, is rarely found pure in nature. More often arsenic occurs in compounds with other elements such as copper, nickel, iron, cobalt, and lead. Occupational exposure to arsenic is primarily inhalational and through dermal contact, and occupations with exposure to arsenic include mining, nonferrous smelting (extraction of metal from its metal ore state via heat plus a reducing agent), electronic semiconductor production, wood preservation, the production or application of pesticides, and sheep dip manufacturing [11]. Wood preservation accounts for a majority of the arsenic consumption in the United States. It is also worth noting that ingestion of arsenic via contaminated food or drinking water can also be a source of arsenic exposure. Clinical signs and symptoms of acute arsenic poisoning include headache, nausea/vomiting, diarrhea, abdominal pain, renal failure, encephalopathy, and cardiac arrhythmia. Death can occur from massive fluid loss resulting in dehydration. Chronic exposure has been associated with skin pigmentation irregularities on the trunk and neck, hyperkeratosis of the palms and soles, Mees lines (white transverse lines across the nails), cirrhosis, hypertension, neuritis, and malignancy. Acute arsenic exposure can be assessed through urinary arsenic content, and long-term exposure is better detected by measuring the arsenic content in hair and nails [11].

In 1980, arsenic was classified as "known to be carcinogenic in humans" by the IARC, and since that time studies have provided evidence consistent with this designation. With respect to arsenic's causal relationship to lung cancer, the supporting studies primarily came from miners and smelters who inhaled high levels of inorganic arsenic dust. Lee-Feldstein observed mortality among 8,045 male smelters in the United States from 1938 to 1977. Arsenic exposure was estimated for each worker based on industrial hygiene data in the smelter, and mortality from lung cancer was analyzed based on maximum lifetime exposure to arsenic and time period of first employment. The author concluded that for workers first employed prior to 1925, mortality from lung cancer was two to nine times the expected rate and mortality increased with increasing cumulative exposure. For those after 1925, a linear exposure–response relationship was also noted. Smoking was not addressed as a possible confounder [12].

In 1987, Enterline and colleagues set out to account for possible effects of sulfur dioxide (SO_2) and cigarette smoking among smelters. They reported data from 6,078 men who were exposed for at least 3 years between 1946 and 1976 among eight US copper smelters. They found a dose–response relationship between arsenic exposure and lung cancer. A nested case–control analysis was performed and only tobacco smoking and arsenic were significant in their relation to lung cancer while SO_2, dust, nickel, cadmium, and lead were not. They further note that the causal relationship between arsenic and lung cancer was confirmed in a single smelter with high exposure [13]. Jarup et al. reported data from a Swedish cohort of 3,916 male smelters who were exposed to arsenic for at least 3 months between 1928 and 1967. Mortality was followed through 1981, and a positive exposure–response relationship between cumulative arsenic exposure and lung cancer was identified. The authors also noted that lung cancer mortality was related to the intensity of arsenic exposure but not duration [14]. Their findings are further supported by Lubin et al. who found that the relative risk of lung cancer was greater when a set dose was delivered at a higher concentration with shorter duration versus a lower concentration over a longer period of time [15].

In 1995, Enterline set to update a previously published cohort from one of the largest copper smelters in the United States [16]. The cohort consisted of 2,080 men who worked for at least 1 year from 1940 to 1964 and the 10 additional years of mortality data took follow-up to 1986. There were 182 malignant neoplasms of the bronchus, trachea, and lung, of which only 85 were expected. Of the 182 cases, 17 occurred in less than 20 years since first exposure and 165 occurred more than 20 years since first exposure. In cases where the worker was hired prior to 1940, cumulative exposure to arsenic was greater than for those hired after 1940. They estimated exposure based on data from the smelter's departments on airborne arsenic as well as from urinary arsenic from the workers. Their data show a clear dose–response relationship between respiratory cancer and inhaled arsenic.

Regarding tobacco smoke as a possible confounder in the reported causal relationship between arsenic exposure and lung cancer, several studies have shown a higher mortality from lung cancer in workers who smoked and were exposed to arsenic versus those with exposure to either alone suggesting a synergistic effect [11]. Lundstrom noted that most smelters in the aforementioned cohorts, as well as others not described here, had multifactorial exposure and that in many cases smoking data were lacking. He set to determine whether occupational exposure to arsenic, lead, and/or smoking led to the development of lung cancer and found that cumulative arsenic exposure and tobacco smoking were risk factors for the development of lung cancer. Exposure to lead was not a risk factor [17]. Epidemiological studies are conclusive that arsenic exposure is associated with an increased risk of lung cancer, although it is likely that cumulative exposures encountered today are on a smaller scale than those of the past secondary to improved working environments.

Asbestos

In 1935, with Lynch and Smith's case report of an asbestos worker who developed carcinoma of the lung, the association

between asbestos exposure and lung cancer began to come to light [18]. In 1955, Sir Richard Doll concluded, following a combined epidemiological and pathologic study of lung cancer in asbestos workers, that carcinoma of the lung was a "specific industrial hazard" of asbestos workers [19]. The synergistic effect of cigarette smoking and asbestos exposure in the development of lung cancer was first suggested by Selikoff in 1968 [20]. Most carcinomas of the lung secondary to asbestos exposure occur in the setting of asbestosis. There is debate as to whether asbestosis must be present to relate lung carcinoma to asbestos exposure or whether it is the dose/tissue asbestos fiber content that is the determining factor [21–24]. Within the literature, three hypotheses exist: (1) asbestosis (interstitial fibrosis) is a prerequisite for asbestos-related lung cancer, (2) a lung fiber burden level in the asbestosis range is a prerequisite for asbestos-associated lung cancer, and (3) any level of asbestos exposure increases the risk of lung cancer [23]. Regardless, most agree that asbestos exposure causation/attribution in the development of lung cancer requires a higher lung asbestos fiber burden in comparison to the development of mesothelioma or parietal pleural plaques and develops following a long latency period, typically measured in decades. In 1993, Churg concluded that asbestosis must be present for causation/attribution of lung cancer to asbestos exposure and that histologic type of tumor was not helpful [25]. Roggli et al. responded noting that the incidence of lung cancer in cases of interstitial fibrosis is less than that seen in cases of asbestosis [26]. The authors also cite a study by Hillerdal [27] in which a large group of workers with increased lung cancer risk were found to have radiographic pleural plaques without evidence of asbestosis. In 2004, Henderson et al. reviewed studies from 1997 to 2004 with emphasis on the relationship between asbestos exposure and lung cancer. The authors review supportive and contradictory evidence for each of the three aforementioned hypotheses and concluded that the weight of evidence supported a cumulative exposure model by which the lung fiber burden level in the range of asbestosis is sufficient for causation in the absence of asbestosis; however, greater cumulative exposure is required for chrysotile versus amphibole exposure [24].

Asbestos Exposure

Exposure to asbestos is commonly occupational but rarely may be environmental or through a household contact. Table 9.7 demonstrates occupations of 419 lung cancer cases with asbestos fiber analysis from the authors' series and notes the presence of pleural plaques and/or asbestosis. Table 9.8 shows the histologic types of lung cancer seen in the 410 cases. Occupations associated with heavy asbestos exposure include asbestos miners and millers, persons involved in manufacturing products composed of asbestos (textiles and insulation products), and those in construction trades (insulators, boiler makers, etc.) or working in shipyards. Household contacts infrequently sustain exposure levels needed to generate asbestosis and/or lung cancer. A history of past or current cigarette smoking imposes confounding issues. A synergistic effect has been described such that the risk for the development of lung cancer in smokers with asbestos exposure is higher versus those with the same exposure who are nonsmokers (see also Chap. 20). Table 9.9 shows the relative risk of dying from lung cancer [28]. It is important to note that the asbestos-exposed individuals in this cohort were insulators, whereas in individuals with less asbestos exposure, the relative risk would be less. For insulators, a multiplicative model has long been accepted for the interaction between smoking and asbestos. The net effect of these two carcinogens may range from additive to supramultiplicative, and there has been debate over which model, if any, fits best. Henderson et al. cite Lee [29] who found a multiplicative model to best fit as well as others [30, 31] who have found fault with both additive and multiplicative models. Henderson concludes by noting that "the combined effect of cigarette smoke and asbestos involves an interactive effect whereby the joint effect is greater than the sum of the two separate effects" [24]. There are several hypotheses with regard to the mechanism of lung cancer in asbestos-exposed individuals including the following: (1) smoking imparts impaired clearance of asbestos fibers, (2) asbestos fibers absorb carcinogenic compounds from the cigarette smoke, (3) smoking may facilitate asbestos fiber penetration into bronchial walls, and (4) tobacco may assist in translocation of iron across cell membranes resulting in enhanced susceptibility to oxidant stress (see also Chap. 20 for further discussion of cocarcinogenesis) [23].

Despite the fact that asbestos use has been banned in many countries and strongly regulated in those still allowing it, exposure remains widespread, mainly among construction workers involved in removal of asbestos-containing material. In all studies estimating the burden of occupational cancer attributable to specific agents, asbestos is found to be the most important carcinogen (see Chap. 20).

Asbestosis

Asbestosis, defined by the Helsinki criteria in 1997 [32] and reclassified by Roggli et al. in 2010 [33], is diffuse pulmonary fibrosis secondary to the inhalation of large quantities of asbestos fibers. Histologically, there is bronchiolar wall fibrosis with extension into the adjacent alveolar septa. Extension of fibrosis to involve alveolar septa away from the small airways occurs as the disease progresses, which may occur even after exposure has ceased.

Asbestos-related diseases (including lung cancer) most commonly occur after a long latency period (measured in decades) with only rare instances occurring in fewer than 10 years following onset of exposure. Signs and symptoms

Table 9.7 Occupational exposure category, pleural plaques, and asbestosis in 419 lung cancer cases with lung fiber burden analysis (authors' series)

Exposure category	No.	Pleural plaques[a]	Asbestosis[a]	AB/g (med)	AB/g (rg.)	AF/g (med.)	AF/g (rg.)
Shipyard worker[b]	67	36/54	16/67	3,100	2–1,400,000	39,500	330–7,530,000
Insulators[c]	47	28/39	25/44	45,400	32–343,000	294,000	3,910–8,540,000
Pipefitter[d]	28	15/20	1/25	1,130	<3.3–11,600	16,200	1,550–171,000
Construction[e]	19	7/14	2/19	240	2–41,900	7,890	<530–310,000
Asbestos manufacturing	15	5/7	3/12	130	<7–79,000	114,000	1,060–1,540,000
Oil/chemical	15	6/10	2/14	32	<3–3,620	5,380	<460–77,600
Boiler worker	14	7/13	3/14	360	7.0–7,650	17,400	840–64,400
US Navy[f]	13	2/9	0/13	110	28–2,660	2,640	840–20,000
Railroad	11	6/10	0/11	22	3.0–6,350	1,890	490–434,000
Electrician	9	5/9	1/9	13	<7–1,630	7,820	<490–27,600
Maintenance/mechanic	7	2/4	1/7	6.6	2–36,600	4,270	<730–149,000
Molten metal[g]	5	2/4	0/5	22	3.3–230	6,980	<640–14,300
Sheet metal	5	0/2	0/4	165	34–1,600	10,500	1,690–39,600
Power plant	5	2/4	2/5	1,160	<3.3–58,800	62,700	<490–217,000
Automotive	4	1/4	0/4	<6	<3–<38	2,450	<440–43,300
Machinist	2	0/1	0/2	100	6.6–245	2,350	880–19,000
Papermill	1	1/1	0/1	73		8,960	
Asbestos worker NOS	4	2/3	2/7	10,900	3.0–75,200	96,500	2,400–712,000
Other[h]	27	9/19	1/26	54	<3.3–6,200	3,480	<490–149,000
HHC	5	1/2	0/5	730	5.0–3,670	20,500	3,480–45,000
ND	116	38/65	18/111	200	2–266,000	7,370	<160–3,350,000

AB/g = asbestos bodies per gram of wet lung as determined by light microscopy
AF/g = asbestos fibers ≥5 μm in length per gram of wet lung as determined by scanning electron microscopy
NOS not otherwise specified, *HHC* household contact, *ND* no data, *med* median, *rg.* range
[a]Informative cases
[b]Other than insulators
[c]Includes pipecoverers, asbestos sawers, asbestos sprayers
[d]Includes welders and plumbers
[e]Includes laborer, carpenter, painter, drywall/plasterer
[f]Includes merchant marine
[g]Includes steel, aluminum, and iron foundry workers
[h]Includes engineer (machine room), grain elevator operator, General Electric, heating/AC, aircraft maintenance, coal miner, building occupant, copper wire manufacture, military laundry, RCF worker, pressman, printing industry, public utility worker, radioman, neighborhood, motor home installer, textile mill, transit manager/oil field worker, superintendent of schools, asbestos exposure (NOS)

Table 9.8 Lung cancer histologic type in 419 cases with lung fiber burden analysis[a] (Authors' series)

Histologic type	No.	%
Adenocarcinoma[b]	197	47
Squamous cell ca.[c]	110	26
Small cell ca.[d]	49	12
Large cell ca.[e]	42	10
Adenosquamous ca.	10	2
Bronchogenic ca. (NOS)[f]	18	4

NOS not otherwise specified, *ca.* carcinoma
[a]Includes seven cases of metachronous primaries: squamous cell + adenocarcinoma (three cases), small cell + giant cell carcinoma, small cell + squamous cell carcinoma, adenocarcinoma + small cell carcinoma, adenosquamous + small cell carcinoma (one case each)
[b]Includes cases formerly referred to as mucinous bronchioloalveolar cell carcinoma (ten cases) and pseudomesotheliomatous adenocarcinoma (five cases)
[c]Includes spindle cell squamous carcinoma (one case)
[d]Includes combined small cell carcinoma (three cases)
[e]Includes pleomorphic carcinoma (ten cases), sarcomatoid carcinoma (four cases), large cell neuroendocrine carcinoma (two cases), non-small cell carcinoma (two cases), basaloid carcinoma, and mixed small cell/large cell carcinoma (one each)
[f]Includes carcinoma of lung NOS (three cases)

Table 9.9 Relative risk of dying from lung cancer

Nonsmokers and smokers	Relative risk
Nonsmokers	
No asbestos exposure	1
Asbestos exposure	5
Smokers	
No asbestos exposure	11
Asbestos exposure	53

Modified from Hammond et al. [28]

Table 9.10 2000 International Labor Office scoring system of radiographs

Frequency category	Frequency subcategory
	0/–
0	0/0
	0/1
	1/0
1	1/1
	1/2
	2/1
2	2/2
	2/3
	3/2
3	3/3
	3/+
Round opacities	*Size*
p	≤1.5 mm
q	>1.5–3 mm
r	>3–10 mm
Irregular opacities	*Size*
s	≤1.5 mm
t	>1.5–3 mm
u	>3–10 mm

Data from International Labour Office [34]

are related to the interstitial fibrosis of asbestosis and include dyspnea, dry cough, and inspiratory basilar crackles/rales. Clubbing of fingers may or may not be present [32, 33].

Radiographic features of lung cancers in asbestos-exposed individuals are essentially the same as for any peripherally or centrally located carcinoma (see the above discussion). With asbestosis, radiographic profusion (frequency) of irregular opacities increases with disease progression. The International Labor Office (ILO) guidelines along with a set of standard chest roentgenograms, for the purpose of comparison of the patient's films, are used in the classification process. Films are graded for the frequency of small opacities using a 4-point scale (from 0 to 3) with subcategories allowing for a considered alternative category (Table 9.10). Opacity size and shape are designated by the letters p (≤1.5 mm), q (>1.5–3 mm), and r (>3–10 mm) for round opacities and s (≤1.5 mm), t (>1.5–3 mm), and u (>3–10 mm) for irregular opacities. Large opacities are categorized as A (one opacity up to 50 mm in greatest dimension), B (one opacity >50 mm in greatest dimension), and C (one large or several large opacities equaling the area of the right upper lung zone) [34].

The diagnosis of asbestosis is often made without histologic examination of lung tissue based on the presence of the following [33]:

1. Exposure history: moderate to heavy asbestos exposure, usually occupational, with latency period of a decade or more
2. Clinical features: signs and symptoms of interstitial fibrosis
3. Radiographic studies: reticular-linear diffuse opacities in lower lung zones
4. Pulmonary function test: restrictive physiology

Conventional computed tomography and high-resolution computed tomography (HRCT) are more sensitive and specific than plain chest films in the diagnosis of asbestos-related pleuropulmonary disease. HRCT findings include isolated dot-like structures in the periphery of the lower lung and branching structures that do not reach the pleural surface. Other findings include ground glass attenuation, pleural-based intra- and interlobular lines, and honeycomb changes (Fig. 9.6). It should be noted that there is overlap between the HRCT findings in asbestosis and idiopathic pulmonary fibrosis (usual interstitial pneumonia or UIP). The finding of asbestos-related pleural changes can be helpful in making this distinction [33].

A histologic assessment for asbestosis is helpful when the aforementioned features are atypical or nondiagnostic. The differential diagnosis in cases of asbestosis includes the fibrosing interstitial pneumonias, such as UIP. Respiratory bronchiolitis-associated interstitial lung disease, which is caused by cigarette smoking, may confound the radiographic interpretation of chest films in asbestos-exposed individuals with lung cancer [35].

Pathologic Features

The histologic type of lung cancer does not assist in proving causation in an asbestos-exposed person. A meta-analysis by Churg found no difference in the histologic type of lung cancer between asbestos-exposed subjects and control cases [36]. A histologic diagnosis of asbestosis requires (1) diffuse interstitial fibrosis in the appropriate distribution in well-fixed/inflated lung tissue away from tumor or mass lesions and (2) two or more asbestos bodies per cm^2 of lung tissue or an asbestos fiber count within the range of asbestosis recorded by the same laboratory [32, 33]. Asbestosis is graded histologically from 1 to 4 depending on the extent of parenchymal fibrosis (Table 9.11).

Assessment of Asbestos Exposure

Industrial hygienists are sometimes asked to reconstruct past exposures based upon simulations of workplace

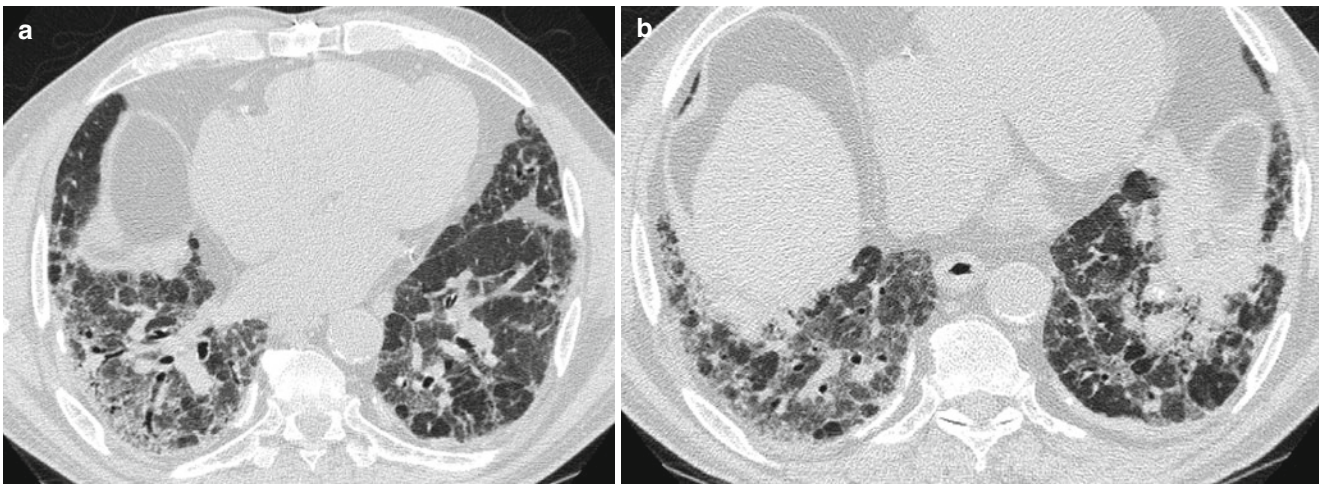


Fig. 9.6 High-resolution computed tomography (*HRCT*) images in a patient with asbestosis, showing lower lung zone reticulonodular opacities consistent with interstitial fibrosis. Calcified pleural plaques are also apparent (Images courtesy of Dr. Page McAdams, Duke University Radiology, Durham, NC)

Table 9.11 Histologic grading of asbestosis

Asbestosis grade	Extent of parenchymal fibrosis
Asbestos airways disease (grade 0)	Fibrosis confined to bronchiolar walls
Grade 1	Fibrosis of respiratory bronchioles with extension into first tier of alveoli
Grade 2	Fibrosis of respiratory bronchioles with extension to and beyond the second tier of alveoli
Grade 3	Fibrosis extends to involve all alveoli between two or more respiratory bronchioles
Grade 4	Honeycomb change

Modified from Roggli et al. [33] with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2010. College of American Pathologists

environments from the past in which exposure measurements were not obtained. This may either be done for an individual patient or as part of an epidemiological analysis. There are several methods of assessing exposure. Exposure reconstructions can be qualitative (low, medium, or high exposure), semiquantitative (defined limits for low, <1 % exposure limit; medium, 1–10 % exposure limit; and high, 100 % of the exposure limit), or quantitative which is based on exposure measurement data with modifying factors taken into consideration. If retrospective, the analysis depends on the assimilation of historical exposures and tasks/jobs performed. An example of questionnaire used for retrospective exposure assessment of asbestos among insulators is shown in Table 9.15. For asbestos, the exposure dose unit is fibers/cc-years, which is the concentration of fibers (f/cc) in 8-h time-weighted average (TWA) day multiplied by the years exposed at that concentration [37]. The cumulative asbestos exposure required for the development of asbestosis is estimated to be at least 25 fibers/cc-years [38]. Others have indicated that 25–100 fiber/cc-years is required [39, 40].

Histologic assessment of asbestos exposure requires identification of asbestos bodies, defined as iron-coated asbestos fibers with a thin translucent core [41]. Asbestos body (AB) quantitation may be performed on a Perl's iron-stained sections of paraffin-embedded tissue. The 2010 committee on asbestosis recommends that a diagnosis only be made when there is interstitial fibrosis with at least 2 AB/cm^2. Alternatively, if asbestos bodies are present, yet fail to reach 2 AB/cm^2, or if there is no appreciable interstitial fibrosis, lung tissue fiber analysis can be performed to determine if the uncoated asbestos fiber content is within the range of asbestosis as previously determined by the same laboratory. For asbestos-related carcinoma of the lung in the absence of asbestosis, we require 50,000 amphibole asbestos fibers 5 μm or greater in length per gram of wet lung tissue to establish causation/attribution [42]. The absence of asbestos bodies on iron-stained sections of lung tissue indicates that asbestos is unlikely to be a contributing factor.

Fiber analysis for lung tissue fiber content can be performed on formalin-fixed or paraffin-embedded lung tissue retrieved via surgical procedure or autopsy. Optimal samples are from peripheral lung parenchyma, weigh 0.3 g, and are (as much as possible) free of tumor and fibrosis, as such will artifactually increase the weight of lung tissue. Lung tissue is first digested using the sodium hypochlorite technique as previously described [43], and residue is collected on 0.4 μm pore-size Nuclepore filters. Other methods of tissue digestion include chemical digestion with sodium hydroxide and low-temperature plasma ashing. For analysis by light microscopy, one filter is mounted on a glass slide for asbestos body quantification with only bodies with thin translucent cores counted as asbestos bodies. Filter counting may be performed at a magnification of 200× (whole filter) or 400× (requires at least two asbestos bodies on two perpendicular

passes at greatest diameter), and results are reported as asbestos bodies (AB) per gram of wet lung tissue. One fiber per gram of wet lung is approximately equivalent to one fiber per cubic centimeter which is approximately equivalent to ten fibers per gram of dry lung. The normal range for our laboratory is 0–20 AB/g. For scanning electron microscopy (SEM), filters are mounted on a carbon disk with colloidal graphite, sputter-coated with platinum or gold, and counted at 1,000× magnification. All fibers >5 μm in length with an aspect ratio of ≥3:1 are counted. For our protocol, 100 fields or 200 fibers are counted, whichever comes first. The first 20 uncoated asbestos fibers and the first 10 asbestos bodies are analyzed by energy-dispersive x-ray analysis (EDXA) to determine fiber type [44]. Since chrysotile does not have the biopersistence in lung tissues that is associated with amphiboles, risk assessment is better determined by cumulative dose reconstruction for this fiber type [32].

Many laboratories prefer to use transmission electron microscopy (TEM) for fiber analysis. The preparation techniques vary slightly from those indicated above for SEM. Particles and fibers may be recovered from the tissue by either wet chemical digestion (e.g., sodium hypochlorite) or low-temperature plasma ashing. After the residue has been collected on the filter surface, a portion of the filter is selected for mounting on a TEM grid, and the filter medium removed by the Jaffe wick technique with the residue collected on a carbon replica [44]. Sequential grid openings are then examined for the numbers and types of fibers in the specimen, with results typically reported in terms of fibers per gram of dry lung tissue. It should be noted that methodology and counting rules vary from one laboratory to another, so numerical results from one laboratory are not equivalent to those from another. Furthermore, each laboratory should establish its own reference range to permit interpretation of analytical results [33, 34].

With respect to coated versus uncoated fibers, it should be noted that the percentage of fibers that are coated is a function of both fiber type and fiber dimensions. For example, anthophyllite readily forms asbestos bodies and typically does so with greater efficiency than amosite which in turn is more efficient than crocidolite. Asbestos bodies are unlikely to form on fibers that are less than 20 μm in length. Because of the poor biopersistence of chrysotile, it tends to form asbestos bodies very inefficiently. In addition, there is individual variation with respect to coating efficiency. These factors should be taken into account when determining causation based upon asbestos body and asbestos fiber counts.

Beryllium

Beryllium has many highly desirable properties including high melting point, resistance to corrosion, and high tensile strength. As such, beryllium contributes its properties in alloys which today are predominantly used in aerospace, defense, automotive, and electronic industries. Human exposure to beryllium can have dermal, ocular, oral cavity, hematologic, cardiac, gastrointestinal, renal, and nervous system effects and in the lung has two main manifestations: (1) acute chemical pneumonitis (acute berylliosis) and (2) chronic beryllium disease [45]. A short but intense exposure tends to cause the former, while chronic beryllium disease may develop decades after occupational exposure has ceased.

Studies by Steenland and Ward [46] in 1991 and Ward et al. [47] in 1992 suggested an increased risk of lung cancer in humans exposed to beryllium/beryllium compounds, and 1 year later the IARC classified beryllium as reasonably anticipated to be carcinogenic in humans. The 1992 study by Ward and colleagues reviewed mortality rates at seven beryllium plants in the United States and demonstrated a statistically significant excess lung cancer mortality rate for all seven beryllium plants with a standard mortality ratio (SMR) of 1.26 with a confidence interval of 1.12–1.42. They also noted that the highest SMRs were at the two oldest beryllium plants in the study [47]. The Beryllium Industry Scientific Advisory Committee (BISAC) noted that the increment in lung cancer mortality related to beryllium is the smallest for which a designation of carcinogenic has been given, the increment is of the same order of magnitude as passive tobacco smoke exposure, and confounding and selection biases were not accounted for [48]. Several reanalyses of the NIOSH study were performed in subsequent years, including a nested case-ontrol study in one of the plants [49] and an update of the follow-up with additional dose-response analyses [50]. A recent review concluded that the excess lung cancer mortality was restricted to workers employed in the 1940s and 1950s in two plants, and no risk can be detected in other workers [51]: it remains unclear whether the excess in the former group is attributable to very high beryllium exposure experienced by these workers or to other occupational or nonoccupational exposures present in those workers. In short, there is considerable controversy with respect to beryllium exposure as a cause of lung cancer in humans, although it is unlikely that beryllium exposure represents a carcinogenic hazard under modern exposure circumstances.

Cadmium

Cadmium, an odorless metal with a low boiling point, occurs in nature complexed with zinc and also with lead. It is used in the production of batteries and paint pigments, in electroplating/coating, and as a stabilizer in polyvinyl chloride and polymers. During World War II, cadmium was used as a substitute for tin. Currently, all of the aforementioned uses have declined with the exception of battery production which accounts for approximately 80 % of its use in Western countries [52]. Occupational exposure occurs mainly through

inhalation of fumes and dust, and occupations associated with high exposure include cadmium production and refining, pigment manufacture, battery and alloy production, and plating. When inhaled acutely in sufficient concentrations, cadmium is toxic to the lungs and can cause pulmonary edema though its effects are slightly delayed (4–10 h after exposure) or pneumonitis with intense exposure. Additional symptoms include dyspnea, cough, chest tightness, and flu-like signs with fever and myalgias. Chronic exposure can affect renal tubular function, and some studies have reported carcinogenicity of cadmium.

In 1980, Cadmium was listed as "reasonably anticipated" to be carcinogenic which was revised in 1987 as limited evidence, and finally, in 1993 there was "sufficient evidence" for a designation of "carcinogenic to humans" [9, 53, 54]. A number of epidemiological studies have evaluated the potential carcinogenicity of cadmium, and some of the cohorts have been followed for many years through various studies. A cohort of cadmium recovery workers in the United States was followed by Lemen [55], Thun [56], Stayner [57], Lamm [58], Sorahan [59–61], and Doll [62] with mixed findings. Thun and Stayner, both with NIOSH, found a statistically significant dose-response relationship between occupational cadmium exposures, yet Stayner could not exclude arsenic as a confounder and further work was needed. Lamm cautioned that the excess lung cancer mortality in the cohort could be explained by the confounding effects of arsenic and tobacco smoke. Sorahan found two flaws in the NIOSH data – (1) there were inconsistencies in job history definitions and (2) the accuracy of the job history data – and thus set to further examine the cohort using available detailed data on job histories for the workers. Sorahan's reanalysis of the data with the addition of detailed job histories [59] as well as the later addition of mortality data through 2001 [60] led to the conclusion that (1) arsenic was a human carcinogen and (2) there was inadequate evidence to associate cadmium exposure with increased risk of lung cancer.

Several other cohorts of cadmium workers have also been studied. In the United Kingdom, a group of workers exposed to cadmium between 1942 and 1970 was followed until 1979 and revisited with data in 1983 [63–65]. Only the last publication in this cohort series shows a substantial excess risk from lung cancer among cadmium-exposed workers. Attention was then drawn to a nonferrous smelter in the United Kingdom where a cohort of 4,393 men was exposed to cadmium as well as lead, arsenic, zinc, and SO_2. In those employed for more than 20 years, there was evidence of excess lung cancer. However, it was not possible to attribute the increase in lung cancer cases to cadmium exposure. Lung cancer mortality was instead associated with arsenic and lead exposure although they could not draw any conclusions as to causation/attribution, and it should be noted that smoking was not accounted for [66].

Two cohorts of nickel–cadmium battery works in Sweden and in the United Kingdom were observed by Elinder [67] and Sorahan [68], respectively, with opposing conclusions. Sorahan found no support for the carcinogenicity of cadmium hydroxide while it seems that Elinder's supportive position was largely based on prior reports of elevated SMRs among studies which Sorahan found were flawed. The body of scientific evidence in support of cadmium as a cause of lung cancer in humans appears to be diminishing and overall lacks accountability for confounders such as smoking and the myriad of other exposures encountered by cadmium workers. The assessment of cadmium levels in whole blood and scalp hair is possible by electrothermal atomic absorption spectrometry [69].

In conclusion, there are concerns on the presence or absence of a risk of cancer among workers occupationally exposed to cadmium.

Bis(chloromethyl) Ether and Chloromethyl Methyl Ether

Bis(chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME) are volatile, flammable, colorless liquids which in water rapidly hydrolyze to form hydrochloric acid (HCl), methanol, and formaldehyde. CMME contains between 1 % and 7 % BCME. BCME and CMME were previously manufactured in the United States; however, with the IARC classification as carcinogenic in humans in 1974, its use has been curtailed [70]. BCME ceased commercial production in 1982, and in 2003 CMME was no longer produced. These two chemicals were primarily used as alkylating agents and as chemical intermediates. BCME had other uses such as in the manufacture of plastics, polymers, and ion-exchange resins. It is also noted that BCME was once used in the manufacture of flame-retardant fabrics. The primary routes of exposure include vapor inhalation and dermal contact, and in the occupational setting, the former is most common. Currently, production of BCME or CMME occurs inadvertently in the production of other chemicals [71]. A number of studies in the 1960s and 1970s reported an increased risk of lung cancer, specifically of small cell type, among workers with high exposure to BCME/CMME [72–83]. These findings, however, are mainly of historical interest, since the population of workers with such exposures appears to be diminishing.

Chromium

Chromium, a transitional metal, does not occur naturally as a free element but instead as chromite or chromium iron ore. Countries producing chromite ore include South Africa (the lead producer), Russia, Turkey, Finland, Albania, India, and

Greece. Mines are no longer found in the United States [84]. Chromium is often added to other metals as the resulting alloys are harder and more resistant to corrosion. Stainless steel is a prime example of such an alloy, accounting for approximately 70 % of chromium usage. Chromium is also used in refractory brick and electroplating. Workers can be exposed via fumes, mists, and dust containing chromium, and health complications related to chromium exposure include asthma, nasal mucosal irritation/ulceration, and skin irritation. Additionally, there is an increased risk of lung, sinonasal, and gastrointestinal cancers with chromium exposure [85].

In the late 1800s, chromium was first linked to cancer of the respiratory tract [86]. Yet it was not until 1990 that the IARC monograph on chromium and chromium compounds concluded that there was "sufficient evidence" to classify Cr(VI) as "carcinogenic to humans" [84]. Cr(VI) includes a number of compounds, of which exposure to water-soluble alkaline chromates during steel smelting and welding; to insoluble chromates of lead and zinc used in pigment production and spray painting; to sodium, potassium, calcium, and ammonium chromates and dichromates used in chromate production; to chromium trioxide during chrome plating; and to various chromates used during cement production is most important [84]. To date, there has been "inadequate evidence in humans" for the carcinogenicity of metallic chromium and chromium [III] compounds.

Since the classification of Cr(VI) as carcinogenic, several of the supporting studies' cohorts have been reexamined. In 1998, Sorahan et al. reexamined a cohort of workers from a UK electroplating and light engineering plant. They observed a higher incidence of lung cancer mortality in men with exposure to chrome bath work versus men with other exposures to chrome and similar findings in women [87]. Although their data supports hexavalent chromium as a lung carcinogen, smoking history was not available. In 2000, the Yorkshire cohort, originally studied by Royle, was revisited by Sorahan and Harrington with the addition of extended mortality data from 1972 to 1997 [88]. This cohort originally consisted of 1,087 chrome platers exposed to Cr(VI) in the form of chromic acid mist between1969 and 1972. During the additional years, data regarding smoking history were collected [88]. Both authors suggested that excess mortality from lung cancer in workers was due to chrome plating, but they could not be definitive in their findings.

The Hayes et al. cohort from a Baltimore, MD, chromate manufacturing facility consisted of 2,357 workers followed from 1950 to 1974 [89]. Smoking data were available in 91 % of workers, and in a majority, data on packs smoked per day were available. However, smoking data were limited to the worker's smoking status at time of hire [90]. Hayes concluded that there were insufficient data to associate increased lung cancer risk with exposure to Cr(VI) due to latency and lack of sufficient follow-up time in the cohort. The cohort was revisited by Gibb et al. who continued to follow the cohort until 1992 or date of death and concluded that there was a clear increased risk of lung cancer following occupational exposure to Cr(VI). The Gibb/Hayes cohort was yet again revisited by Park et al. who concluded that an exposure–response relationship exists between hexavalent chromium exposure and lung cancer which could not be explained by smoking in the cohort. Park's conclusions were consistent with those of Gibb [91].

In 2006, OSHA amended its permissible exposure limit (PEL) for CR(VI) from 0.1 mg/m^3 to 0.05 mg/m^3 for 8-h time-weighted average exposure [92]. Reconstruction by an industrial hygienist and/or measurement of work environment levels is beneficial in determining whether a worker's exposure had exceeded the PELs for a given compound. However, the presence of chromium compounds in lung tissue is the major criterion for determining whether a causal relationship exists between occupational exposure and the development of lung cancer [85]. Though tissue from the tumor itself is not useful, analysis can/should be performed on areas of "normal" lung tissue. With regard to the histologic type in cases of chromium-related lung cancer, squamous cell carcinoma was found in workers involved primarily with the second phase of chromate reduction with heavy exposure to Cr(VI) dust, and small cell carcinoma was found in workers involved in the second, third, and fourth phase of chromate production with increased exposure to refined Cr(VI). Additionally, squamous cell carcinoma was seen in workers with prolonged low-level exposure, while small cell carcinoma was in the setting of short-term high exposure [93]. In summary, epidemiological evidence is convincing that exposure to Cr(VI) is associated with an increased risk of lung cancer.

Coal Dust

Coal, the Earth's most abundant fossil fuel, is actively mined with the largest reserves in the United States and Russia. Coal is derived from organic material largely from plants which through compression, heat, and time yield a variety of coals which are classified by type, grade, and rank. As coal is formed in the Earth's crust and subject to groundwater, it may contain traces of other mineral elements [94, 95]. Coal workers are exposed to both coal dust and silica in proportions dependent on their location and role in the mining of coal as well as the method of mining used [95]. The pulmonary manifestations of coal dust exposure include simple coal workers' pneumoconiosis, seen histologically as coal dust macules within lung parenchyma with or without silicotic nodules (Fig. 9.7), and progressive massive fibrosis, a more advanced stage with extensive pulmonary fibrosis most prominent in the upper and posterior lung zones.

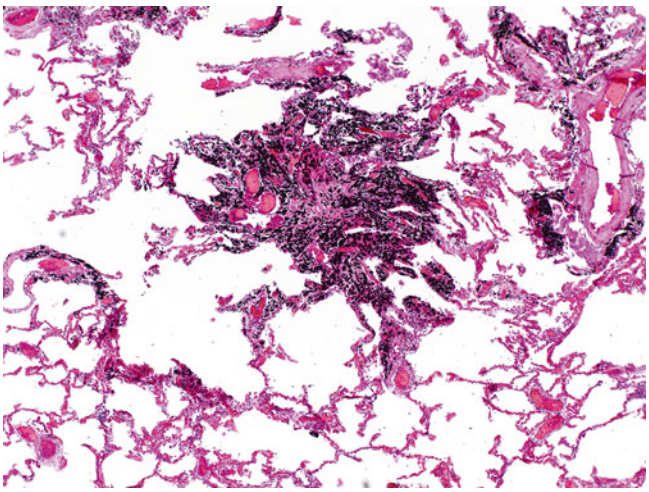


Fig. 9.7 Coal dust macule with perifocal emphysema and incidental adenocarcinoma of the lung [H&E stain, original magnification ×400]

There have been several studies examining the relationship between coal mining and lung cancer with different results. A lower than expected lung cancer mortality was observed by Kennaway [96], Goldman [97], Stocks [98], Liddell [99], and Attfield [100], while Enterline [101] and Rockett [102] reported elevated rates of lung cancer as did Scarano in the setting of anthracosilicosis [103]. There are confounding factors such as cigarette smoking which must be accounted for, and in 1983 Ames et al. reviewed four cohorts of coal miners to assess the lung cancer risk of coal mine dust exposure with respect to tobacco smoking. They conclude that (1) underground mining for greater than 25 years was not a risk factor for lung cancer mortality, (2) there was no dust–cigarette smoke interaction (unlike what is seen with asbestos exposure and cigarette smoking), and (3) cigarette smoking predicted lung cancer mortality in the coal miners [104]. In 2004, Isidro Montes et al. reviewed a cohort of 2,579 coal miners of which follow-up data was available in 2,170. Although the statistical power of this study was low, no increase in lung cancer cases was observed among those with follow-up data [105]. The absence of an increased risk of lung cancer in coal workers casts further doubt on the alleged association between silica and lung cancer.

Diesel Emissions

Diesel engine emissions/exhaust is a complex mixture of particulates and gas which varies depending on the type of engine, operating conditions, fuel composition, lubricating oils, etc. Gaseous components can include carbon dioxide, carbon monoxide, nitrogen and nitrogen compounds, water vapor, and oxygen. The diesel particles are composed of carbon with absorbed organic compounds which include polycyclic aromatic hydrocarbons, aromatic hydrocarbons, aldehydes, and nitrogen oxides [106]. Acute intense exposure may cause respiratory irritation as well as irritation to the eyes and nose, lightheadedness, nausea, emesis, and numbness/tingling of extremities. Information regarding symptomatology of chronic exposure is more limited in humans. Individuals whose occupation is associated with heavy exposure to diesel exhaust include truckers, firefighters, railroad workers, mechanics, miners, and other workers operating diesel-powered equipment [107, 108].

Diesel exhaust is classified as established carcinogen by the IARC based on sufficient evidence of carcinogenicity in animal models and in humans [109]. This classification was mainly based on the results of US studies of non-metal miners, which showed an association with estimated diesel exhaust exposure, which could not be explained by confounding by smoking [110, 111]. Supportive evidence comes from studies of railroad workers and truck drivers and case–control studies in the general population [109]. A number of inconsistencies remain in the results of the main studies of diesel exhaust exposure and lung cancer (e.g., in the US miners study, the mortality for lung cancer is higher in surface workers than in underground workers, despite the much higher exposure of the latter; in the same study, there is an apparent negative interaction – i.e., an antagonistic effect – between tobacco smoking and diesel exhaust exposure, which is not biologically plausible.

Even if the association between diesel exhaust and lung cancer is established, there remains the important issue of the relevance of epidemiological studies, which are based on the experience of workers exposed 10 or more years ago, to current circumstances of exposure.

As Gamble [112] has noted, diesel fuel has undergone a major overhaul since 1988 and the exhaust seen today and since 2007 contains 100 times fewer particulates than traditional diesel exhaust, and emissions were reduced by 40 %. The available epidemiological results need therefore to be interpreted with caution in order to derive estimates of risk currently experienced by workers.

Nickel

Nickel is a heat- and corrosion-resistant metal used in the production of stainless steel and corrosion-resistant alloys. Nickel compounds can be classified into those that are soluble, including nickel sulfate and nickel chloride, and those which are not, including nickel subsulfide and nickel oxide. Pure nickel is found in alkaline batteries, coins, electrical contacts, machinery parts, and prosthetic surgical and dental devices. Interestingly, nickel is also present in tobacco smoke. In the United States, primary nickel production ceased in 1998. Since that time, secondary production of

Table 9.12 Data for nickel exposure, smoking, and lung cancer

	Relative risk	95 % Confidence interval
No nickel exposure		
Never smoker	RR = 1.0[a]	N/A
Ever smoker	RR = 6.1	(3.0–12.4)
Nickel exposure		
Never smoker	RR = 3.6	(1.1–12)
Ever smoker	RR = 23	(11–48)

Data from Andersen et al. [115]
[a]Study reference population

nickel and importation of nickel have been the main source of activity.

The first evidence of nickel's carcinogenic effect was described by Morgan in 1958. Since that time, there has been additional evidence to support its role in the development of lung cancer. In 1990, Sir Richard Doll chaired the International Committee on Nickel Carcinogenesis in Man which reported that soluble nickel at a concentration greater than 1 mg Ni/m^3 and less soluble nickel at concentrations greater than 10 mg Ni/m^3 were related to a risk of lung cancer [113]. Some controversy has remained regarding the carcinogenicity of soluble nickel compounds. Antilla et al. examined the carcinogenicity of different nickel species in a cohort of 1,388 nickel refinery workers in Harjavalta, Finland, and determined that nickel refinery workers, who were exposed to soluble nickel sulfate, had a statistically significant increased risk of lung cancer above those who worked in nickel smelting which could not be explained by occupational exposure to other compounds, cigarette smoking habits, or lifestyle. However, there was no clear increase in risk with increased duration [114].

In 1996, Anderson et al. suggested a multiplicative effect between nickel exposure and "ever" smokers versus never smokers in male nickel refinery workers (Table 9.12) [115]. Their data also show that the risk of lung cancer from smoking alone is greater than the risk of lung cancer from nickel exposure alone.

Nickel refinery workers are at risk for exposure to many other carcinogenic compounds, and Grimsrud and colleagues examined these potentially confounding factors in 2005. They determined that other occupational exposures to asbestos, arsenic, sulfuric acid, and cobalt were not confounding factors; however, as exposure to carcinogenic substances in work performed outside of the refinery increased, so did the odds ratio. Cigarette smoking had a low to moderate confounding effect. They also observed an exposure–response effect for soluble nickel with regard to carcinogenic potential [116]. Data on metallic nickel exposure in humans is less informative although it has been shown to be carcinogenic in animal models [113].

Signs and symptoms of nickel exposure include dermal manifestations and asthma. A fibrosing form of lung disease has not been associated with exposure, and to date, there is no association between nickel exposure and a specific histologic type of lung carcinoma. It is also worth noting that nickel has been associated with an increased risk of sinonasal carcinomas [117]. The determination of nickel concentration in human lung tissue can be through atomic emission spectroscopy, flame atomic absorption spectroscopy, particle-induced x-ray emission, and energy-dispersive x-ray analysis. Edelman and Roggli developed a model to estimate the average amount of nickel accumulation in lung tissue and proposed that it may be useful in determining the nickel burden in lung tissue resulting from occupational exposures [118]. Epidemiological data support a causal association between exposure to nickel and an increased risk of lung cancer.

Painters

Painters may be exposed to the chemicals found in paint products during their application and removal. During the application of paint, workers are exposed primarily to solvents, while during mechanical removal of paint, they are exposed to pigments and fillers. In addition, as bystanders during construction or demolition activities, painters may be exposed to agents such as asbestos and silica.

Approximately 20 cohort studies and 30 case-control studies have investigated the risk of lung cancer among painters (the count of the studies is imprecise because of partial overlap of the populations between studies). They have been reviewed by IARC [119], Bachand et al. [120], and Guha et al. [121]. In particular, Guha et al. [121] conducted a meta-analysis of 18 cohort and 29 case–control studies: these authors found a summary relative risk of lung cancer equal to 1.35 (95 % CI 1.29–1.41). Restricting the meta-analysis to studies which adjusted for tobacco smoking produced similar results. A duration–risk relation was suggested: the summary relative risks were 1.13 (95 % CI 0.77–1.65) for less than 10 years of exposure and 1.95 (95 % CI 1.26–3.02) for 10 or more years of exposure. Bachand et al. [120] performed a meta-analysis of a slightly different set of studies (16 cohorts and 23 case–control studies) and derived a summary relative risk of lung cancer equal to 1.29 (95 % CI 1.10–1.51); separate meta-analyses for cohort and case–control studies resulted in summary relative risk of 1.36 (95 % C: 1.34–1.41) and 1.22 (95 % CI 1.16–1.29), respectively.

Potential lung carcinogens to which painters can be exposed include heavy metals (cadmium, chromium, and nickel) as pigments, arsenic compounds as antifouling agents, and coal tar pitch in waterproofing coating, in addition to asbestos and silica as part of general exposures in construction. For none of these agents can exposure prevalence and level of painters explain their excess risk of lung

cancer, when compared to the risk experienced by workers with much higher exposure. The possibilities remain of interaction between multiple carcinogens, each at low level of exposure, or that one or more unknown agents are responsible for the risk of painters. In any case, the fact that no specific carcinogen has been identified as cause of lung cancer in painters decreases the credibility of the causal nature of the association observed in epidemiological studies.

Mixtures of Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are a class of chemicals, characterized by the presence of two or more benzene rings, which derive mainly from the incomplete combustion of organic material. These include hundreds of compounds, among which the best known is benzo[a]pyrene, often used as a marker of exposure to PAH. Benzo[a]pyrene is the only PAH classified as human carcinogen by IARC, because of data on cancer-related biomarkers in exposed humans [122]. Workers are exposed to mixtures of PAHs, not individual compounds. The composition of the mixture, both in qualitative and quantitative terms, varies depending on the raw material, the conditions under which combustion takes place, and other parameters. Workers employed in occupations and industries entailing PAH exposure might therefore experience different hazard conditions depending on the presence and level of specific compounds.

Circumstances of high exposure to PAH mixtures have been studied, mainly in the past, in several industries and occupations, including aluminum production (Södeberg process), coal gasification, coke production, iron and steel foundries, coal tar distillation, creosote use, shale oil extraction, roofing, road paving, carbon black and carbon electrodes production, and chimney sweeps. Some of these industries and occupations, such as coal gasification, shale oil extraction, and chimney sweeps, are mainly of historical interest. Diesel exhaust comprises nitro-PAHs, in addition to non-nitrosated hydrocarbons, and has been reviewed separately.

The evidence of an increased risk of cancer from occupational exposure to PAHs has been reviewed by Bosetti and colleagues [123] and by the International Agency for Research on Cancer (IARC) [122]: Table 9.13 shows the IARC classifications, together with the results of the meta-analyses by Bosetti et al., for a number of occupations entailing high exposure to mixtures of PAHs. The evidence of an increased risk of lung cancer is strong (summary relative risk >1.5, highly statistically significant) for exposure circumstances entailing high PAH exposure levels, mainly in the past: this is the case of coal gasification, coke production, and chimney sweeps. Relatively strong (summary relative risk = 1.4) and consistent evidence is also available for workers in iron and steel founding. For other occupations and industries entailing exposure to PAHs, on the other hand, the available evidence from epidemiological studies does not suggest a clear increased risk of lung cancer (summary relative risk in the range 1.0–1.2, which did not reach the level of statistical significance): this is the case of aluminum production and coal tar distillation and workers exposed to creosote. Among PAH-related industries and occupations with less than sufficient evidence of carcinogenicity according to IARC, only for roofers there was evidence of an increased risk (summary relative risk, based on two cohorts, 1.51; 95 % CI 1.28–1.78). For workers involved in road paving, carbon black production, and carbon electrode production, the evidence was essentially negative. Based on the results of the occupational studies summarized in Table 9.13, IARC has classified coal tar pitch and soot as lung carcinogens.

The interpretation of results of studies of PAH-exposed workers is complicated by the lack of information on tobacco smoking in most of the studies (and PAHs represent one of

Table 9.13 Selected occupations entailing high exposure to polycyclic aromatic hydrocarbons: IARC evaluations and results of meta-analysis of cohort studies [123]

Occupation	IARC evaluation[a]	N cohort studies	Summary relative risk	95 % confidence interval	Heterogeneity*
Aluminum production	S	8	1.03	0.95–1.11	0.04
Coal gasification	S	4	2.29	1.98–2.64	<0.0001
Coal tar distillation	S	3	1.21	0.95–1.55	0.3
Coke production	S	10	1.58	1.47–1.69	<0.0001
Iron and steel founding	S	9	1.40	1.32–1.49	0.007
Roofing	L	2	1.51	1.28–1.78	0.3
Creosote-exposed occup.	L[b]	2	1.14	0.85–1.51	0.1
Carbon electrode manuft.	L	6	1.00	0.82–1.23	0.04
Road paving	I	2	1.14	1.07–1.22	<0.0001
Carbon black manuft.	I[b]	2	1.30	1.06–1.59	<0.001

*p-value of test for heterogeneity

[a]IARC evaluation of evidence of carcinogenicity in humans: *S* sufficient, *L* limited, *I* inadequate, *NA* not available

[b]The evaluation refers to the mixture, not to the occupation

the main groups of carcinogens in tobacco smoking), heterogeneity in exposure circumstances in different geographic regions and time periods, and poor assessment of past exposures. Despite the limitations, the evidence supports the notion that high-level occupational exposure to mixtures of PAHs represents a causal factor in lung cancer, although the actual level of risk in most circumstances currently encountered by exposed workers is likely to be very low and often not measurable.

Ionizing Radiation/Radon

Radon is a naturally occurring odorless and colorless radioactive gas produced from the decay of radium in the uranium decay series which eventually leads to lead. There are numerous isotopes of radon, of which radon-222 is the most common and has the longest half-life of 3.82 days. When radon decay products are produced, ionizing radiation in the form of alpha particles is emitted. Exposure occurs primarily through inhalation and ingestion. Although radon is nearly ubiquitous, levels of radon are quite variable with the highest concentration of radon found in the earth where there are uranium ore deposits. Radon has no major industrial use, and occupational exposure is most often found in uranium, hard-rock, and phosphate miners. Additionally, exposure to radon can also occur in the home if it is situated over an area where radon is abundant; however, the level of exposure is much less than that of those exposed in mines. The EPA estimated that radon accounted for slightly less than 15 % of lung cancers in the United States for the year 1995, but this is an extrapolation from higher exposures encountered by the uranium miners [124]. The number of uranium mines has decreased over the past three decades as has the number of uranium mine workers [125].

The IARC classified radon-222 and radon-220 as known human carcinogens in 1988 based on studies of underground mine workers with increased mortality from lung cancer [126]. In 1995, Lubin et al. pooled data from 11 cohorts of underground miners from which the IARC designation was largely based. An attempt was made to control for the effects of smoking; however, detailed data were not available for all cohorts. Additionally, the authors mention potential confounding effects of arsenic, diesel exhaust, and silica dust. Arsenic and silica have been addressed elsewhere in the chapter, and there was lack of sufficient evidence that silica was a lung carcinogen. Arsenic, on the other hand, is a potential valid source for confounding effects [127]. Lubin also demonstrated a linear exposure–response relationship and described an inverse exposure–rate effect such that the risk was greater in those exposed at a low level for a long period of time compared to those who were exposed at a higher level for a short period of time [128].

More recent studies have only confirmed prior evidence that radon exposure increased the risk of lung cancer. It is now known that radon decay products are more carcinogenic than radon. In 2010, Kreuzer et al. [129] reviewed a well-studied cohort of 58,987 German uranium miners to determine if radon exposure led to increased risk of mortality from cardiovascular disease and cancer. The authors found within this large cohort an increased risk of mortality from lung cancer among those with exposure to radon. Smoking was not accounted for; however, in studies by Schnelzer and Brüske-Hohlfeld, which were nested in the same cohort of German uranium miners, it was demonstrated that a number of workers were smokers, yet there was little correlation between smoking and cumulative radon exposure [130] and little change in risk after accounting for the confounding effect of smoking and asbestos [131]. Brüske-Hohlfeld et al. also observed a decrease in risk of lung cancer with increased time since last exposure, and unlike Lubin, the authors did not observe an inverse exposure–rate effect. In an analysis of three European uranium miner case–control studies, Leuraud et al. focused on the effects of radon exposure and smoking on risk of mortality from lung cancer. Their results showed a sub-multiplicative interaction between smoking and radon [132]. This is consistent with Lubin et al. who noted that the best-fitting relationship between smoking and radon was between additive and multiplicative [127].

Studies to date consistently support a causal relationship between radon exposure and lung cancer which cannot be accounted for by the confounding effects of smoking. There is little data regarding histologic type of lung cancer in the setting of radon exposure.

Silica

Silica is the most abundant mineral in the Earth's crust, and there is a wide variety of industries and occupations in which exposure to respirable silica occurs (Table 9.14). Occupations where there is significant exposure include mining, drilling, quarrying, and tunneling. Stonecutters, sandblasters, and refractory brick, foundry, pottery, and ground silica workers are also at risk. Sandblasting carries a particularly high risk even when personal protective equipment is used. Some

Table 9.14 Occupations with crystalline silica exposure

Stonecutting
Sandblasting
Quarry work
Refractory brick
Foundry work, molding, and grinding
Mining, drilling, quarrying, and tunneling

Modified from Gibbs [133]

occupations newly recognized to be at risk include construction workers, surface strip miners, silica flour mixers, and tombstone sandblasters [133, 134]. Exposure to coal mining/coal dust imparts variable exposure to silica depending on the specific job of the coal miner and the employed mining technique. Silicosis is a fibrotic lung disease secondary to prolonged heavy exposure to free crystalline silica [94], most often in the form of alpha quartz [135]. Additionally, exposure to crystalline silica in the form of cristobalite or tridymite is cytotoxic and fibrogenic in experimental settings; however, they are of less importance in occupational settings [135]. It is more common for a diagnosis of silicosis to occur after exposure to silica has ceased and for the disease to slowly progress over a period of decades [134].

The 1996 official statement of the American Thoracic Society (ATS) concluded that silicosis produces increased risk for bronchogenic carcinoma [134] yet made a point that it is unclear whether silicosis is a prerequisite for increased risk of lung cancer. Also that year, the International Agency for Research on Cancer (IARC) classified silica, in the form of quartz and cristobalite, as carcinogenic to humans [136]. Despite this statement, controversy remains as to whether silica is truly carcinogenic. Those who believe that silica has no role in the development of lung cancer cite studies which poorly controlled for tobacco smoking and radon exposure [137–139]. In particular, Hessel reviewed 18 studies of silica and lung cancer, some of which were used by the IARC. Of those, only 13 were felt to be acceptably constructed (controlled for smoking with internal controls, complete enumeration of data, and exposure–response analysis). Several of the studies giving evidence to the carcinogenicity of silica used by the IARC were poorly controlled for smoking and failed to show a clear exposure–response relationship, while another had confounding exposures [138].

In 1986, Steenland and Beaumont reviewed mortality data in a cohort of granite cutters. There was a slight but not significant excess in lung cancer (97 observed and 81.1 expected), but trend was seen with duration of exposure. The authors note limited evidence that lung cancer could be associated with silicosis [140]. Merlo et al. in 1991 studied 1,022 refractory brick workers with exposure to crystalline silica. They found elevated mortality from lung cancer with an SMR of 1.77, yet smoking was not appropriately controlled for [141]. Interestingly, a later study by Merlo reviewed 1,291 males employed at a graphite electrode plant in Italy. The investigators found no excess in mortality from lung cancer (SMR = 0.97) although smoking was not addressed [142].

In 1999, Ulm et al. reviewed 247 lung cancer cases with 795 controls looking for an association between silica dust exposure and lung cancer in the German stone, quarrying, and ceramics industry. Workers with silicosis were excluded. They found no association between exposure to crystalline silica and lung cancer [143]. Steenland and Sanderson in 2001 reviewed the personnel records of 5,086 workers from 18 industrial sand plants covering 11 states. The SMR for cancer of the lung, trachea, and bronchus (ICD-9 code 162) was elevated at 1.60, but smoking data was limited and inadequately controlled for, and the authors failed to show a significant relationship between cumulative exposure to respirable silica and mortality from lung cancer [144].

In 2011, Gamble reviewed the epidemiology literature surrounding occupational exposure to crystalline silica and lung cancer. He found the associations between the two to be consistently weak, and only 3 of 27 studies had clear positive exposure–response trends, while 9 had a flat or negative exposure–response curve. Gamble concluded that the epidemiological data to date do not support a causal association between lung cancer and silica exposure [139]. In their review, Churg and Green concluded that silica is a possible carcinogen in agents producing carcinoma of the lung [40]. Therefore, the causal nature of the relationship between silica exposure and carcinoma of the lung in humans remains controversial.

Silicotic Lung Disease

The presenting signs and symptoms of lung cancer remain as described above regardless of silica exposure, and pulmonary manifestations of silica exposure include silicosis, chronic bronchitis with airflow obstruction, and pulmonary tuberculosis. Simple silicosis is often asymptomatic and there may be no radiographic evidence of disease [136]. Patients with complicated silicosis are often hypoxic with restrictive pulmonary physiology. Progressive disease can lead to pulmonary hypertension and cor pulmonale. Historically, pulmonary tuberculosis complicated 0.5–5 % of simple silicosis cases and as many as 40–60 % of those with complicated/conglomerate silicosis. One more recent study of a population with a high tuberculosis prevalence showed that the incidence of tuberculosis increased by threefold in workers with silicosis versus those without silicosis and the incidence of tuberculosis increased as the category of silicosis increased [145]. A 2005 study by NIOSH reviewing mortality secondary to tuberculosis among US industries from 1990 to 1999 indicated mortality from tuberculosis that continued to be elevated in workers with silica exposure [146]. The increased susceptibility to tuberculosis is secondary to macrophage dysfunction caused by silica leading to impaired resistance [147].

Radiographic features of silicosis are classified into (1) simple silicosis and (2) conglomerate silicosis. Simple silicosis consists of small round opacities within the upper lung zones. With time and disease progression, the mid to lower lung zones are involved and the size and profusion of opacities increase. Calcification of nodules is not uncommon and is usually centrally located within nodules. Complicated or

conglomerate silicosis manifests as simple silicosis plus irregular, coalescing lesions greater than 2 cm (by histologic standards). Progressive massive fibrosis is a term used synonymously with complicated or conglomerate silicosis and is also used in the context of coal workers' pneumoconiosis [148]. The ILO classification of radiographic silicosis is the same as for asbestosis, with silicosis associated with rounded opacities and asbestosis associated with irregular opacities (Table 9.10). Eggshell calcification of hilar lymph nodes is classic for silica exposure yet may also be seen in the setting of remote granulomatous lymphadenitis from *Histoplasma* infection or from sarcoidosis.

Pathologic Findings

The histomorphologic hallmark of silica exposure is the silicotic nodule, a hyalinized collagenous lesion with associated pigment from dusts inhaled along with the silica. Additionally, nodules may have central calcifications or even ossification and can be surrounded by perifocal emphysema when located within the pulmonary parenchyma. Hilar lymph nodes are almost always involved and may contain silicotic nodules prior to their presence within the parenchyma. Birefringent particulates are typically found within the hyalinized nodules but can be found in the lungs of virtually all adults from industrialized nations and should be cautiously interpreted as evidence of significant silica exposure. Silicotic nodules may also be seen in the context of individuals with exposure to a mixture of crystalline silica and silicates termed mixed-dust pneumoconiosis. Mixed-dust pneumoconiosis, as defined by Honma et al., consists of dust macules and mixed-dust fibrosis with or without silicotic nodules in a person with known exposure to mixed dusts. Silicotic nodules should not be as prevalent as mixed-dust macules. Otherwise, the term silicosis is more appropriate [149].

Secondhand Tobacco Smoke

It is well documented that tobacco smoking is a potent cause of lung cancer for smokers, yet they are not the only people exposed to carcinogens when smoking tobacco products. Cigarette smoke contains more than 50 carcinogens and exists in two forms: mainstream smoke (MSS), generated when a puff of smoke is drawn through the tobacco product to the smoker's lungs only to be exhaled, and sidestream smoke (SSS), emitted from the smoldering end of the tobacco product. Secondhand tobacco smoke (SHTS) is a mixture of the two, but consists mostly of SSS. The chemical composition of MSS and SSS is similar; however, SSS is more potent in some regards with higher concentrations of ammonia, nitrogen oxides, some carcinogens, and aniline. However, one must remember that SSS is quickly diluted with ambient air.

In 1986, the IARC classified tobacco smoke as carcinogenic in humans based on "sufficient evidence" in human studies and stated that tobacco smoke also affects those who are passively exposed. That same year the National Research Council (NRC) came to the conclusion that lung cancer in persons exposed to SHTS was unlikely to be due to chance or bias [150], and in 1992, the EPA declared a causal relationship between SHTS and lung cancer [151]. Finally, in 2004, the IARC determined there was "sufficient evidence" that SHTS caused lung cancer in humans [152]. There were 30 supportive epidemiological studies, of which a majority focused on nonsmoking women who are exposed to a smoker in the home [153–155].

Critique and criticism that came from the tobacco industry and consultants cited that excess risk of lung cancer in nonsmokers is attributable to misclassification bias as well as confounding effects of lifestyle. These issues were addressed in 2006 by the US Surgeon General as well as other studies which assessed sources of misclassification and concluded that misclassification of ever smokers as never smokers would not account for the association between lung cancer and SHTS [151, 156–160]. It is accepted that there is no risk-free level of exposure to SHTS.

SHTS used to be the most prevalent occupational carcinogen. Its importance has decreased in many countries following a ban of smoking in all workplaces, including bars, restaurants, and other public settings.

Welding

Welding involves joining materials through fusion or coalescence via a mediator (filler material) and energy, resulting in the formation of an alloy. Materials consist of metals or thermoplastics, and the source of energy may be mechanical (forge, friction, vibration, and explosive), electrical (arc and electron beam), chemical (oxy-gas and thermite), or optical (laser). Occupational exposures of welders consist of fumes (with particulates) and gases and largely depend on the materials used and form of energy employed. Fumes often contain iron and magnesium with silicates and carbonates. Cadmium, nickel, chromium, titanium, and aluminum have also been identified. Gases can include carbon monoxide, ozone, and nitrogen oxides. Acute toxic effects of welding include pulmonary edema and chemical pneumonitis. Additionally, chronic rhinitis and bronchitis, wheezing, and dyspnea have also been described, though more common in nonsmokers [63, 134]. Welder's pneumoconiosis will be described below.

In 1990, the IARC determined that there was "limited evidence" for carcinogenicity of welding fumes and gases in humans and classified welding fumes as "possibly carcinogenic" [84]. Tola et al. reviewed the incidence of lung cancer

among welders in shipyards and machine shops between 1945 and 1960. They found a 20 % increase in lung cancer incidence among welders, and although they felt it unlikely that smoking, asbestos, and metal fumes were confounders, they acknowledge that these would be the most likely explanation for elevated lung cancer incidence [161]. Stern at the Danish Welding Institute also found an increase in lung cancer among welders which could be accounted for by asbestos exposure, smoking, and chromium exposure (from welding stainless steel) [162].

Steenland et al. revisited a cohort of 3,247 welders and 5,432 controls from the state of Washington between 1950 and 1976. They note that the prior analysis of this cohort by Beaumont and Weiss showed a slight increase in SMR for lung cancer (SMR = 1.32) which was not statistically significant. Their reanalysis using Cox regression showed similar results [163]. A later study by Steenland reviewed 4,459 mild steel welders who lacked asbestos exposure and lacked exposure to stainless steel fumes, which contained chromium and nickel. They found no exposure–response trend for welders and lung cancer, and the rate of lung cancer in welders compared to non-welders was 0.90 [164].

Sjögren et al. in a meta-analysis of five welder cohorts attempted to account for smoking and asbestos exposure among welders and demonstrated an increased pooled relative risk of 1.94 which left chromium exposure to be accounted for; however, Langard proposed that there is no evidence to attribute the increased risk of lung cancer in welders to nickel or Cr(VI) [165].

Studies thus far have been contradictory and have yet to provide convincing evidence for causality between welding fumes and lung cancer which could not be accounted for by confounding factors [166–168].

Welder's Pneumoconiosis

The effect on lung tissue following prolonged exposure to welding fumes varies based on the fume content. Exposure to fumes containing aluminum can cause severe interstitial fibrosis, while titanium and iron have little effect. Microscopically, the predominant finding among welders is interstitial accumulation of large amounts of dust without a significant fibrotic response. The dust is largely composed of golden-brown particles with dark centers, consisting of iron oxide surrounded by an outer layer of iron hydroxide. In addition, iron can encrust silicates within the lung forming pseudoasbestos bodies with broad yellow cores. Welding may involve exposure to asbestos which can be demonstrated by the presence of asbestos bodies and, in some cases, peribronchiolar and alveolar septal fibrosis (e.g., asbestosis). Radiographic findings include increased interstitial markings which may be secondary to dust accumulation and macrophages within the interstitium although rarely true fibrosis can occur in the setting of aluminum or concomitant asbestos exposure. Emphysema is also a common radiographic finding among welders, yet it may be mostly related to smoking [94].

Detection of Occupational Exposure via Tissue Analysis

If lung tissue is available via bronchoscopic biopsy, surgery, or autopsy, several methods can be employed to detect inhaled particles such as those described above (Table 9.15). Bronchoalveolar lavage fluid has also proved useful for some techniques. In addition to detection, it is important to have a reference value/range from persons without lung cancer if

Table 9.15 Methods of tissue analysis via analytical electron microscopy

Technique	Uses
Scanning electron microscopy (SEM)	3D analysis of ultrastructure
Transmission electron microscopy (TEM)	2D analysis of ultrastructure
Energy-dispersive x-ray analysis (EDXA)	Qualitative analysis for elements with $Z \geq 4$
Backscattered electron imaging (BEI)	In situ analysis of particles when coupled with EDXA
Selected area electron diffraction (SAED)	Coupled with TEM for crystalline structure analysis of inorganic particles
Electron energy loss spectrometry (EELS)	Detection of elements with $Z \geq 3$
Proton-induced x-ray emission analysis (PIXEA)	Highly sensitive and nondestructive method of multielement analysis. Requires a sample in solution
Secondary ion mass spectrometry (SIMS)	Organic molecules, specific isotopes, elements not detected by EDXA, trace elements
Laser microprobe mass analyzer (LAMMA)	See above SIMS
Atomic absorption spectrometry (AAS)	Highly sensitive. Measures trace elements to ppm or ppb range. Limited use for multielement analysis
Inductively coupled plasma-atomic emission spectroscopy (ICP-AES)	Bulk chemical analysis requiring sample in solution. Highly precise and can analyze multiple elements simultaneously

Modified from Sporn and Roggli [94]

attribution is to be confirmed or refuted through tissue analysis. There is little in the literature regarding the content of exogenous mineral particles in the general population; however, Stettler et al. analyzed particle concentrations of 33 urban lungs [169]. Electron microscopy can be used to detect a number of metals, dusts, and mineral particles within lung tissue. Either transmission electron microscopy (TEM) or scanning electron microscopy (SEM) can be coupled with energy-dispersive x-ray analysis (EDXA) for this purpose, which can be either qualitative or quantitative, detecting most elements with an atomic number (Z) $\geq$ 4. These forms of electron microscopy are collectively termed analytical electron microscopy (AEM) or microprobe analysis. It is also an excellent method for the detection and quantitation of asbestos fibers in lung tissue with the benefit of being able to determine fiber type [94, 170].

In preparing samples of lung tissue for AEM, formalin-fixed wet lung tissue or paraffin-embedded tissue may be used. Digestion techniques for quantitative assessment may be for bulk tissue analysis, using either wet chemical or ashing. In situ quantitation may also be performed via counting particles in a section of tissue. The methodology for wet tissue digestion has been described above under *Asbestos Exposure Assessment*. It is important to note that the particle content in small samples of various lung tissue regions vary from five- to tenfold and thus adequate sampling of several sites is encouraged [171]. If an ashing method is to be used, one should be aware that this procedure may cause fiber breakage and thus falsely elevate fiber content [170].

Often there are areas of interest in lung tissue seen on hematoxylin and eosin-stained sections which suggest exposure to exogenous particles. Another method involving AEM allows for the selection of the corresponding area of interest from the lung tissue paraffin block. A section is cut and placed onto a carbon disk, heated, deparaffinized, and air-dried. The tissue is then available for analysis with preserved tissue architecture. In this setting, we find backscattered electron imaging (BEI) coupled with SEM and EDXA to be quite useful in identifying minerals with medium to heavy atomic number within lung tissue. Selected area electron diffraction (SAED) is useful for examining a crystalline substance via TEM. The diffraction pattern of a crystalline substance can then be compared to an index of known substances for identification. SAED can thus function as a complementary technique to EDXA as some minerals cannot be fully classified based on elemental composition alone [173].

Several other methods are worth mentioning briefly; an in-depth review is beyond the scope of this chapter. More detailed information can be found in the referenced material. Auger electron spectroscopy (AES) involves the interaction of an electron beam with sample atoms creating excess energy which is dissipated through ejection of an outer shell electron (termed the Auger electron) whose kinetic energy is characteristic of its elemental origin. AES is more sensitive than EDXA and can detect elements with Z <9 [172]. Electron energy loss spectrometry (EELS) again involves the interaction of an electron beam with specimen atoms. This results in electron transitions characteristic of the sample's elemental composition. EELS offers detection of elements with Z$\geq$3. For elements with low atomic number such as beryllium, EELS may be used as well as secondary ion mass spectrometry (SIMS) or laser microprobe mass analysis (LAMMA). SIMS involves the interaction of an ion beam with a solid specimen and has broad elemental detection coverage, and LAMMA uses a laser beam directed at the sample causing it to vaporize/ionize [170, 172]. AEM with state-of-the-art EDXA detectors is also a promising methodology for detection of beryllium [173].

Atomic absorption spectrometry (AAS) allows for absorption of radiant energy by an atom which occurs at wavelengths specific to its elemental composition. This technique has the ability to measure trace metals in solution. For lung tissue, the analysis of trace elements via AAS requires a solution, and thus, tissue digestion is required. Similarly, inductively coupled plasma-atomic emission spectroscopy (ICP-AES) uses argon plasma as the energy source for absorption by an atom and requires a sample in solution. One advantage over AAS is that ICP-AES allows for broader elemental detection [172].

Conclusion

Lung remains by far the most important target organ of occupational carcinogens. The fact that more occupational carcinogens have been identified for the lung than for all other organs combined has to do with the importance of inhalation as route of exposure and deposition, absorption, and retention into the lung as result of the interaction between the agents and the epithelium of the lower respiratory tract. Synergy with tobacco smoking, which has been shown for several carcinogens, is another reason for the large number of occupationally related lung cancers. The strong potency of tobacco smoking as lung carcinogen, on the other hand, complicates the attribution of individual cases of the disease to specific agents. Control measures, including in particular removal of the carcinogen from the workplace, have been shown in several instances to decrease the risk of lung cancer among exposed workers (see Chap. 31). This phenomenon suggests that many, if not all, occupational lung carcinogens act on late stages of the carcinogenic process, which stresses the importance of prevention even in workers with substantial past exposure.

Appendix

Table 9.16 Example of questionnaire used for retrospective assessment of asbestos exposure of insulation workers

Working with insulation materials or fiber panels	Identification number Job number	From year To year		
Q1: Where were the insulation materials or fiber panels installed? ……			*Y/N/DK*	*Hours/Week*
	Around pipes			
	Ovens, boilers			
	Buildings			
	Electrical equipment			
	If other, please specify:			
Q2: Which of the following materials were you in contact with? ……..			*Y/N/DK*	*Hours/Week*
	Fiberglass			
	Mineral wool			
	Polystyrene			
	Polyurethane foam			
	Asbestos			
	Ceramic fibers			
	Urea/formaldehyde foam			
	Polyurethane foam			
	If other, please specify:			
	Note for translation: give examples of trade names or usual names when possible			
Q3: If you install yourself insulating materials, how did you do it? ……			*Y/N/DK*	*Hours/Week*
	By injection of foam			
	Splattering			
	Blown up of powder			
	Rigid panels			
	Pipe sheathing			
	If other, please specify:			
Q4: Were you installing or removing these materials in an enclosed space (under a roof) without any natural or mechanic ventilation? ……..	*Y/N/DK*			
	If yes, hours a week:			
Q5: Did you have to cut or make holes in these materials? ……..	*Y/N/DK*			
	If yes, hours a week:			
	If yes, was it:		*Y/N/DK*	*Hours/Week*
	By hand			
	With electric-powered machines			
Q6: Did you have to work with cement, concrete? ……..	*Y/N/DK*			
	If yes, for which tasks?		*Y/N/DK*	*Hours/Week*
	Making holes in concrete			
	Covering insulation with cement			
	Using a concrete mixer			
	If other, please specify:			
	END SQ14			

References

1. Boffetta P, Autier P, Boniol M, et al. An estimate of cancers attributable to occupational exposures in France. J Occup Environ Med. 2010;52:399–406.
2. Travis WD, World Health Organization, International Agency for Research on Cancer, International Association for the Study of Lung Cancer, International Academy of Pathology. Pathology and genetics of tumours of the lung, pleura, thymus, and heart. Lyon: IARC Press; 2004.
3. Edge SB, American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
4. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. J Thorac Oncol. 2011;6:244–85.
5. Moran C. PATH IQ ImmunoQuery 2.8. https://immunoquery.pathiq.com. Accessed 18 May 2011.
6. Neoplasia. In: Kumar V, Abbas AK, Fausto N, editors. Robbins and Cotran pathologic basis of disease. 7th ed. Philadelphia: Elsevier Saunders; 2005. p. 369–71.
7. Flieder D, Hammar S. Common non-small-cell carcinomas and their variants. In: Tomashefski JF, Dail DH, editors. Dail and Hammar's pulmonary pathology, vol. 2. 3rd ed. New York: Springer; 2008. p. 216–307.
8. Neoplasms of the lungs, airways, and pleura. In: Hansell DM, Lynch DA, McAdams HP, Bankier AA, editors. Imaging of diseases of the chest. 5th ed. Philadelphia: Elsevier Mosby; 2010. p. 787–880.
9. International Agency for Research on Cancer. A review of human carcinogens, IARC monographs on the evaluation of carcinogenic risks to humans, vol 100 A–F. Lyon: IARC; 2012.
10. Rushton L, Bagga S, Bevan R, et al. Occupation and cancer in Britain. Br J Cancer. 2010;102:1428–37.
11. Rosman T. Arsenic. In: Rom WN, Markowitz S, editors. Environmental and occupational medicine. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2007. p. 1006–82.
12. Lee-Feldstein A. Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. J Occup Med. 1986;28:296–302.
13. Enterline PE, Marsh GM, Esmen NA, Henderson VL, Callahan CM, Paik M. Some effects of cigarette smoking, arsenic, and SO2 on mortality among US copper smelter workers. J Occup Med. 1987;29:831–8.
14. Jarup L, Pershagen G, Wall S. Cumulative arsenic exposure and lung cancer in smelter workers: a dose-response study. Am J Ind Med. 1989;15:31–41.
15. Lubin JH, Moore LE, Fraumeni Jr JF, Cantor KP. Respiratory cancer and inhaled inorganic arsenic in copper smelters workers: a linear relationship with cumulative exposure that increases with concentration. Environ Health Perspect. 2008;116:1661–5.
16. Enterline PE, Day R, Marsh GM. Cancers related to exposure to arsenic at a copper smelter. Occup Environ Med. 1995;52:28–32.
17. Lundstrom NG, Englyst V, Gerhardsson L, Jin T, Nordberg G. Lung cancer development in primary smelter workers: a nested case-referent study. J Occup Environ Med. 2006;48:376–80.
18. Lynch KM, Smith WA. Pulmonary asbestosis: carcinoma of the lung in asbestos-silicosis. Am J Cancer. 1935;24:56.
19. Doll R. Mortality from lung cancer in asbestos workers. Br J Ind Med. 1955;12:81–6.
20. Selikoff IJ, Hammond EC, Churg J. Asbestos exposure, smoking, and neoplasia. JAMA. 1968;204:106–12.
21. Gibbs A, Attanoos RL, Churg A, Weill H. The "Helsinki criteria" for attribution of lung cancer to asbestos exposure: how robust are the criteria? Arch Pathol Lab Med. 2007;131:181–3.
22. Roggli VL, Hammar SP, Maddox JC, Henderson DW. Re: The "Helsinki Criteria" for attribution of lung cancer to asbestos exposure: how robust are the criteria? Arch Pathol Lab Med. 2008;132:1386–7; author reply 1387.
23. Henderson DW, Klerk NH, Hammar SP. Asbestos and lung cancer: is it attributable to asbestosis or to asbestos fiber burden? In: Corrin B, editor. Pathology of lung tumors. New York: Churchill Livingstone; 1997. p. 83–118.
24. Henderson DW, Rodelsperger K, Woitowitz HJ, Leigh J. After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004. Pathology. 2004;36:517–50.
25. Churg A. Asbestos, asbestosis, and lung cancer. Mod Pathol. 1993;6:509–11.
26. Roggli VL, Hammar SP, Pratt PC, et al. Does asbestos or asbestosis cause carcinoma of the lung? Am J Ind Med. 1994;26:835–8.
27. Hillerdal G. Pleural plaques and risk for bronchial carcinoma and mesothelioma. A prospective study. Chest. 1994;105:144–50.
28. Hammond EC, Selikoff IJ, Seidman H. Asbestos exposure, cigarette smoking and death rates. Ann N Y Acad Sci. 1979;330:473–90.
29. Lee PN. Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. Occup Environ Med. 2001;58:145–53.
30. Liddell FD. The interaction of asbestos and smoking in lung cancer. Ann Occup Hyg. 2001;45:341–56.
31. Liddell FD. Joint action of smoking and asbestos exposure on lung cancer. Occup Environ Med. 2002;59:494–5; author reply 495–6.
32. Henderson DW, Rantanen J, Bernhart S, et al. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health. 1997;23:311–6.
33. Roggli VL, Gibbs AR, Attanoos R, et al. Pathology of asbestosis-an update of the diagnostic criteria: report of the asbestosis committee of the College of American Pathologists and Pulmonary Pathology Society. Arch Pathol Lab Med. 2010;134:462–80.
34. International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconioses. Geneva: International Labour Office; 2002.
35. Ghio AJ, Roggli VL. Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med. 2005;171:527; author reply 528–30.
36. Churg A. Neoplastic asbestos-induced disease. In: Churg A, Green FHY, editors. Pathology of occupational lung disease. 2nd ed. Baltimore: Williams & Wilkins; 1998. p. 339–91.
37. Keil CB, Simmons CE, Anthony TR. Mathematical models for estimating occupational exposure to chemicals. 2nd ed. Fairfax: AIHA Press; 2009.
38. Hendrick DJ. Occupational disorders of the lung: recognition, management and prevention. London: W. B. Saunders; 2002.
39. Browne K. A threshold for asbestos related lung cancer. Br J Ind Med. 1986;43:556–8.
40. Churg A. Nonneoplastic disease caused by asbestos. In: Churg A, Green FHY, editors. Pathology of occupational lung disease. 2nd ed. Baltimore: Williams & Wilkins; 1998. p. 277–338.
41. Churg A, Warnock ML, Green N. Analysis of the cores of ferruginous (asbestos) bodies from the general population. II. True asbestos bodies and pseudoasbestos bodies. Lab Invest. 1979;40:31–8.
42. Roggli VL, Sanders LL. Asbestos content of lung tissue and carcinoma of the lung: a clinicopathologic correlation and mineral fiber analysis of 234 cases. Ann Occup Hyg. 2000;44:109–17.
43. Roggli VL. Quantitative and analytical studies in the diagnosis of mesothelioma. Semin Diagn Pathol. 1992;9:162–8.
44. Roggli VL, Sharma A. Analysis of tissue mineral fiber content. In: Roggli VL, Oury TD, Sporn TA, editors. Pathology of asbestos-

associated diseases. 2nd ed. New York: Springer; 2004. p. 309–54.
45. Maier LA, Gunn C, Newman LS. Beryllium disease. In: Rom WN, Markowitz S, editors. Environmental and occupational medicine. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2007. p. 1021–38.
46. Steenland K, Ward E. Lung cancer incidence among patients with beryllium disease: a cohort mortality study. J Natl Cancer Inst. 1991;83:1380–5.
47. Ward E, Okun A, Ruder A, Fingerhut M, Steenland K. A mortality study of workers at seven beryllium processing plants. Am J Ind Med. 1992;22:885–904.
48. Beryllium Industry Scientific Advisory Committee. Is beryllium carcinogenic in humans? J Occup Environ Med. 1997;39:205–8.
49. Sanderson WT, Ward EM, Steenland K, Petersen MR. Lung cancer case-control study of beryllium workers. Am J Ind Med. 2001;39:133–44.
50. Schubauer-Berigan MK, Couch JR, Petersen MR, Carreon T, Jin Y, Deddens JA. Cohort mortality study of workers at seven beryllium processing plants: update and associations with cumulative and maximum exposure. Occup Environ Med. 2011;68:345–53.
51. Boffetta P, Fryzek JP, Mandel JS. Occupational exposure to beryllium and cancer risk: a review of the epidemiologic evidence. Crit Rev Toxicol. 2012;42:107–18.
52. Lison D, Verougstraete V. Cadmium. In: Rom WN, Markowitz S, editors. Environmental and occupational medicine. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2007. p. 999–1004.
53. International Agency for Research on Cancer. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: IARC, WHO; 1993.
54. International Agency for Research on Cancer. Overall evaluations of carcinogenicity: an updating of IARC monographs. IARC monographs on the evaluation of carcinogenic risks to humans. Supplement 7. Lyon: IARC; 1987.
55. Lemen RA, Lee JS, Wagoner JK, Blejer HP. Cancer mortality among cadmium production workers. Ann N Y Acad Sci. 1976;271:273–9.
56. Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. Mortality among a cohort of U.S. cadmium production workers–an update. J Natl Cancer Inst. 1985;74:325–33.
57. Stayner L, Smith R, Thun M, Schnorr T, Lemen R. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. Ann Epidemiol. 1992;2:177–94.
58. Lamm SH, Parkinson M, Anderson M, Taylor W. Determinants of lung cancer risk among cadmium-exposed workers. Ann Epidemiol. 1992;2:195–211.
59. Sorahan T, Lancashire RJ. Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: an analysis with detailed job histories. Occup Environ Med. 1997;54:194–201.
60. Sorahan T. Lung cancer mortality in arsenic-exposed workers from a cadmium recovery plant. Occup Med (Lond). 2009;59:264–6.
61. Sorahan T, Lancashire R. Lung cancer findings from the NIOSH study of United States cadmium recovery workers: a cautionary note. Occup Environ Med. 1994;51:139–40.
62. Doll R. Is cadmium a human carcinogen? Ann Epidemiol. 1992;2:335–7.
63. Kazantzis G, Armstrong BG. A mortality study of cadmium workers in the United Kingdom. Scand J Work Environ Health. 1982;8 Suppl 1:157–60.
64. Armstrong BG, Kazantzis G. The mortality of cadmium workers. Lancet. 1983;1:1425–7.
65. Kazantzis G, Lam TH, Sullivan KR. Mortality of cadmium-exposed workers. A five-year update. Scand J Work Environ Health. 1988;14(4):220–3.
66. Ades AE, Kazantzis G. Lung cancer in a non-ferrous smelter: the role of cadmium. Br J Ind Med. 1988;45:435–42.
67. Elinder CG, Kjellstrom T, Hogstedt C, Anderson K, Spang G. Cancer mortality of cadmium workers. Br J Ind Med. 1985;42:651–5.
68. Sorahan T, Esmen NA. Lung cancer mortality in UK nickel-cadmium battery workers, 1947–2000. Occup Environ Med. 2004;61:108–16.
69. Kazi TG, Memon AR, Afridi HI, et al. Determination of cadmium in whole blood and scalp hair samples of Pakistani male lung cancer patients by electrothermal atomic absorption spectrometer. Sci Total Environ. 2008;389:270–6.
70. IARC monographs on the evaluation of carcinogenic risks to humans. Some aromatic amines, hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents. Lyon: IARC, WHO; 1974.
71. National Toxicology Program. Bis(Chloromethyl) ether and technical-grade chloromethyl methyl ether. Rep Carcinog. 2004; 11:III56–7.
72. Figueroa WG, Raszkowski R, Weiss W. Lung cancer in chloromethyl methyl ether workers. N Engl J Med. 1973;288:1096–7.
73. Weiss W, Boucot KR. The respiratory effects of chloromethyl methyl ether. JAMA. 1975;234:1139–42.
74. Weiss W. Chloromethyl ethers, cigarettes, cough and cancer. J Occup Med. 1976;18:194–9.
75. Weiss W, Figueroa WG. The characteristics of lung cancer due to chloromethyl ethers. J Occup Med. 1976;18:623–7.
76. Weiss W, Moser RL, Auerbach O. Lung cancer in chloromethyl ether workers. Am Rev Respir Dis. 1979;120:1031–7.
77. Weiss W. The cigarette factor in lung cancer due to chloromethyl ethers. J Occup Med. 1980;22:527–9.
78. Weiss W. Epidemic curve of respiratory cancer due to chloromethyl ethers. J Natl Cancer Inst. 1982;69:1265–70.
79. Weiss W. Respiratory cancer and chloromethyl ethers. Environ Res. 1991;54:93–7.
80. Weiss W, Nash D. An epidemic of lung cancer due to chloromethyl ethers. 30 years of observation. J Occup Environ Med. 1997;39:1003–9.
81. DeFonso LR, Kelton Jr SC. Lung cancer following exposure to chloromethyl methyl ether. An epidemiological study. Arch Environ Health. 1976;31:125–30.
82. Maher KV, DeFonso LR. Respiratory cancer among chloromethyl ether workers. J Natl Cancer Inst. 1987;78:839–43.
83. McCallum RI, Woolley V, Petrie A. Lung cancer associated with chloromethyl methyl ether manufacture: an investigation at two factories in the United Kingdom. Br J Ind Med. 1983;40:384–9.
84. IARC monographs on the evaluation of carcinogenic risks to humans. Chromium, nickel and welding, vol. 49. Lyon: IARC, WHO; 1990.
85. Cohen M, Costa M. Chromium compounds. In: Rom WN, Markowitz S, editors. Environmental and occupational medicine. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2007. p. 1047–61.
86. Langard S. One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. Am J Ind Med. 1990;17:189–215.
87. Sorahan T, Burges DC, Hamilton L, Harrington JM. Lung cancer mortality in nickel/chromium platers, 1946–95. Occup Environ Med. 1998;55:236–42.
88. Sorahan T, Harrington JM. Lung cancer in Yorkshire chrome platers, 1972–97. Occup Environ Med. 2000;57:385–9.
89. Hayes RB, Lilienfeld AM, Snell LM. Mortality in chromium chemical production workers: a prospective study. Int J Epidemiol. 1979;8:365–74.

90. Gibb HJ, Lees PS, Pinsky PF, Rooney BC. Lung cancer among workers in chromium chemical production. Am J Ind Med. 2000;38:115–26.
91. Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, Lees PS. Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment. Risk Anal. 2004;24:1099–108.
92. Occupational Safety and Health Administration. Occupational exposure to hexavalent chromium. Final rule. Fed Regist. 2006; 71:10099–385.
93. Abe S, Ohsaki Y, Kimura K, Tsuneta Y, Mikami H, Murao M. Chromate lung cancer with special reference to its cell type and relation to the manufacturing process. Cancer. 1982;49:783–7.
94. Sporn TA, Roggli VL. Pneumoconioses, mineral and vegetable. In: Tomashefski JF, Cagle PT, Farver CF, Fraire AE, editors. Dail and Hammar's pulmonary pathology, vol. 2. 3rd ed. New York: Springer; 2008. p. 911–49.
95. Green FH, Vallyathan V. Coal workers' pneumoconiosis and pneumoconiosis due to other carbonaceous dusts. In: Churg A, Green FHY, editors. Pathology of occupational lung disease. 1st ed. New York: Igaku-Shoin Medical Publishers; 1988. p. 129–207.
96. Kennaway EL, Kennaway NM. The incidence of cancer of the lung in coal miners in England and Wales. Br J Cancer. 1953;7:10–8.
97. Goldman KP. Mortality of coal-miners from carcinoma of the lung. Br J Ind Med. 1965;22:72–7.
98. Stocks P. On the death rates from cancer of the stomach and respiratory diseases in 1949–53 among coal miners and other male residents in counties of England and Wales. Br J Cancer. 1962;16:592–8.
99. Liddell FD. Mortality of British coal miners in 1961. Br J Ind Med. 1973;30:15–24.
100. Attfield MD, Kuempel ED. Mortality among U.S. underground coal miners: a 23-year follow-up. Am J Ind Med. 2008;51:231–45.
101. Enterline PE. A review of mortality data for American coal miners. Ann N Y Acad Sci. 1972;200:260–72.
102. Rockette HE. Cause specific mortality of coal miners. J Occup Med. 1977;19:795–801.
103. Scarano D, Fadali AM, Lemole GM. Carcinoma of the lung and anthracosilicosis. Chest. 1972;62:251–4.
104. Ames RG, Amandus H, Attfield M, Green FY, Vallyathan V. Does coal mine dust present a risk for lung cancer? A case-control study of U.S. coal miners. Arch Environ Health. 1983;38:331–3.
105. Isidro Montes I, Rego Fernandez G, Reguero J, et al. Respiratory disease in a cohort of 2,579 coal miners followed up over a 20-year period. Chest. 2004;126:622–9.
106. Lewne M, Plato N, Gustavsson P. Exposure to particles, elemental carbon and nitrogen dioxide in workers exposed to motor exhaust. Ann Occup Hyg. 2007;51:693–701.
107. NTP. Diesel exhaust particulates. In: Department of Health and Human Services PHS, National Toxicology Program, editor. Report on carcinogens. Research Triangle Park: Department of Health and Human Services PHS; 2011.
108. Ris C. U.S. EPA health assessment for diesel engine exhaust: a review. Inhal Toxicol. 2007;19 Suppl 1:229–39.
109. International Agency for Research on Cancer. Diesel and gasoline engine exhausts and some nitroarenes, IARC monographs on the evaluation of carcinogenic risks to humans, vol. 105. Lyon: IARC; 2013.
110. Attfield MD, Schleiff PL, Lubin JH, et al. The Diesel Exhaust in Miners study: a cohort mortality study with emphasis on lung cancer. J Natl Cancer Inst. 2012;104:869–83.
111. Silverman DT, Samanic CM, Lubin JH, et al. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst. 2012;104:855–68.
112. Gamble J. Lung cancer and diesel exhaust: a critical review of the occupational epidemiology literature. Crit Rev Toxicol. 2010;40:189–244.
113. Report of the International Committee on Nickel carcinogenesis in man. Doll R, Chair. Scand J Work Environ Health. 1990; 16(1 Spec No):1–82.
114. Anttila A, Pukkala E, Aitio A, Rantanen T, Karjalainen S. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. Int Arch Occup Environ Health. 1998;71:245–50.
115. Andersen A, Berge SR, Engeland A, Norseth T. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occup Environ Med. 1996;53:708–13.
116. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? Epidemiology. 2005;16:146–54.
117. Cohen M, Klein C, Costa M. Nickel compounds. In: Rom WN, Markowitz S, editors. Environmental and occupational medicine. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2007. p. 1063–82.
118. Edelman DA, Roggli VL. The accumulation of nickel in human lungs. Environ Health Perspect. 1989;81:221–4.
119. International Agency for Research on Cancer. Occupational exposure as a painter. In: Chemical agents and related occupations. IARC monographs on the evaluation of carcinogenic risks to humans, vol. 100 F. Lyon: IARC; 2012. p. 509–40.
120. Bachand A, Mundt KA, Mundt DJ, Carlton LE. Meta-analyses of occupational exposure as a painter and lung and bladder cancer morbidity and mortality 1950–2008. Crit Rev Toxicol. 2010;40:101–25.
121. Guha N, Steenland NK, Merletti F, Altieri A, Cogliano V, Straif K. Bladder cancer risk in painters: a meta-analysis. Occup Environ Med. 2010;67:568–73.
122. International Agency for Research on Cancer. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures, IARC monographs on the evaluation of carcinogenic risks to humans, vol. 92. Lyon: IARC; 2010.
123. Bosetti C, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. Ann Oncol. 2007;18:431–46.
124. Office of Radiation and Indoor Air. EPA assessment of risks from radon in homes. Washington, DC: United States Environmental Protection Agency; 2003.
125. NTP. Radon. In: Department of Health and Human Services PHS, National Toxicology Program, editors. Report on carcinogens, 12th edn. Research Triangle Park: Department of Health and Human Services PHS; 2011.
126. IARC monographs on the evaluation of carcinogenic risks to humans. Ionizing radiation, part 2: some internally deposited radionuclides, vol. 78. Lyon: IARC, WHO; 2001.
127. Lubin JH, Boice Jr JD, Edling C, et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. J Natl Cancer Inst. 1995;87:817–27.
128. Lubin JH, Boice Jr JD, Edling C, et al. Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. Health Phys. 1995;69:494–500.
129. Kreuzer M, Grosche B, Schnelzer M, et al. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: Follow-up 1946–2003. Radiat Environ Biophys. 2010;49:177–85.
130. Schnelzer M, Hammer GP, Kreuzer M, Tschense A, Grosche B. Accounting for smoking in the radon-related lung cancer risk among German uranium miners: results of a nested case-control study. Health Phys. 2010;98:20–8.
131. Bruske-Hohlfeld I, Rosario AS, Wolke G, et al. Lung cancer risk among former uranium miners of the WISMUT Company in Germany. Health Phys. 2006;90:208–16.
132. Leuraud K, Schnelzer M, Tomasek L, et al. Radon, smoking and lung cancer risk: results of a joint analysis of three European case-control studies among uranium miners. Radiat Res. 2011; 176(3):375.

133. Gibbs AR. Occupational lung disease. In: Haselton PS, editor. Spencer's pathology of the lung. 5th ed. New York: McGraw-Hill; 1996. p. 461–506.
134. American Thoracic Society Committee of the Scientific Assembly on Environmental and Occupational Health. Adverse effects of crystalline silica exposure. Am J Respir Crit Care Med. 1997;155:761–8.
135. Silicosis and Silicate Disease Committee. Diseases associated with exposure to silica and nonfibrous silicate minerals. Arch Pathol Lab Med. 1988;112:673–720.
136. Wilbourn J, Partensky C, Morgan WG. IARC evaluates printing processes and printing inks, carbon black and some nitro compounds. Scand J Work Environ Health. 1996;22:154–6.
137. Craighead JE. Do silica and asbestos cause lung cancer? Arch Pathol Lab Med. 1992;116:16–20.
138. Hessel PA, Gamble JF, Gee JB, et al. Silica, silicosis, and lung cancer: a response to a recent working group report. J Occup Environ Med. 2000;42:704–20.
139. Gamble JF. Crystalline silica and lung cancer: a critical review of the occupational epidemiology literature of exposure-response studies testing this hypothesis. Crit Rev Toxicol. 2011;41:404–65.
140. Steenland K, Beaumont J. A proportionate mortality study of granite cutters. Am J Ind Med. 1986;9:189–201.
141. Merlo F, Costantini M, Reggiardo G, Ceppi M, Puntoni R. Lung cancer risk among refractory brick workers exposed to crystalline silica: a retrospective cohort study. Epidemiology. 1991;2:299–305.
142. Merlo DF, Garattini S, Gelatti U, et al. A mortality cohort study among workers in a graphite electrode production plant in Italy. Occup Environ Med. 2004;61:e9.
143. Ulm K, Waschulzik B, Ehnes H, et al. Silica dust and lung cancer in the German stone, quarrying, and ceramics industries: results of a case-control study. Thorax. 1999;54:347–51.
144. Steenland K, Sanderson W. Lung cancer among industrial sand workers exposed to crystalline silica. Am J Epidemiol. 2001;153:695–703.
145. Cowie RL. The epidemiology of tuberculosis in gold miners with silicosis. Am J Respir Crit Care Med. 1994;150:1460–2.
146. Bang KM, Weissman DN, Wood JM, Attfield MD. Tuberculosis mortality by industry in the United States, 1990–1999. Int J Tuberc Lung Dis. 2005;9:437–42.
147. Kleinerman J. The pathology of some familiar pneumoconioses. Semin Roentgenol. 1967;2:244–64.
148. Kleinerman J, Green F, Laquer WM. Pathology standards for coal workers' pneumoconiosis. Report of the Pneumoconiosis Committee of the College of American Pathologists to the National Institute for Occupational Safety and Health. Arch Pathol Lab Med. 1979;103:375–432.
149. Honma K, Abraham JL, Chiyotani K, et al. Proposed criteria for mixed-dust pneumoconiosis: definition, descriptions, and guidelines for pathologic diagnosis and clinical correlation. Human Pathol. 2004;35:1515–23.
150. National Research Council (U.S.), Committee on Passive Smoking. Exposure to environmental tobacco smoke and lung cancer. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, D.C.: National Academy Press; 1986. p. 223–49.
151. Jinot J, Bayard SP, United States Environmental Protection Agency, Office of Health and Environmental Assessment, United States Environmental Protection Agency Indoor Air Division. Respiratory health effects of passive smoking: lung cancer and other disorders. Washington, DC: Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency; 1992.
152. IARC monographs on the evaluation of carcinogenic risks to humans. Tobacco smoke and involuntary smoking. Lyon: IARC, WHO; 2004.
153. Brownson RC, Alavanja MC, Hock ET, Loy TS. Passive smoking and lung cancer in nonsmoking women. Am J Public Health. 1992;82:1525–30.
154. Stockwell HG, Goldman AL, Lyman GH, et al. Environmental tobacco smoke and lung cancer risk in nonsmoking women. J Natl Cancer Inst. 1992;84:1417–22.
155. Fontham ET, Correa P, Reynolds P, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. JAMA. 1994;271:1752–9.
156. Lee P. Misclassification of smoking habits and passive smoking. Berlin: Springer Verlag; 1988.
157. U.S. Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services; Centers for Disease Control and Prevention; Coordinating Center for Health Promotion; National Center for Chronic Disease Prevention and Health; Promotion Office on Smoking and Health; 2006.
158. Wu AH. Exposure misclassification bias in studies of environmental tobacco smoke and lung cancer. Environ Health Perspect. 1999;107:873–7.
159. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does breathing other people's tobacco smoke cause lung cancer? Br Med J. 1986;293:1217–22.
160. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. Br Med J. 1997;315:980–8.
161. Tola S, Kalliomaki PL, Pukkala E, Asp S, Korkala ML. Incidence of cancer among welders, platers, machinists, and pipe fitters in shipyards and machine shops. Br J Ind Med. 1988;45:209–18.
162. Stern RM. Assessment of risk of lung cancer for welders. Arch Environ Health. 1983;38:148–55.
163. Steenland K, Beaumont J, Hornung R. The use of regression analyses in a cohort mortality study of welders. J Chronic Dis. 1986;39:287–94.
164. Steenland K, Beaumont J, Elliot L. Lung cancer in mild steel welders. Am J Epidemiol. 1991;133:220–9.
165. Langard S. Nickel-related cancer in welders. Sci Total Environ. 1994;148:303–9.
166. Antonini JM. Health effects of welding. Crit Rev Toxicol. 2003;33:61–103.
167. Antonini JM, Lewis AB, Roberts JR, Whaley DA. Pulmonary effects of welding fumes: review of worker and experimental animal studies. Am J Ind Med. 2003;43:350–60.
168. Ambroise D, Wild P, Moulin JJ. Update of a meta-analysis on lung cancer and welding. Scand J Work Environ Health. 2006;32:22–31.
169. Stettler LE, Groth DH, Platek SF, Burg JR. Particulate concentrations in urban lungs. In: Ingram P, Shelburne JD, Roggli VL, editors. Microprobe analysis in medicine. New York: Hemisphere; 1989. p. 133–46.
170. McDonald JW, Roggli VL, Churg A, Shelburne JD. Microprobe analysis in pulmonary pathology. In: Ingram P, editor. Biomedical applications of microprobe analysis. San Diego: Academic; 1999. p. 201–56.
171. Morgan A, Holmes A. Distribution and characteristics of amphibole asbestos fibres, measured with the light microscope, in the left lung of an insulation worker. Br J Ind Med. 1983;40: 45–50.
172. Roggli VL, Ingram P, Linton RW, Gutknecht WF, Mastin P, Shelburne JD. New techniques for imaging and analyzing lung tissue. Environ Health Perspect. 1984;56:163–83.
173. Butnor KJ, Sporn TA, Ingram P, Gunasegaram S, Pinto JF, Roggli VL. Beryllium detection in human lung tissue using electron probe x-ray microanalysis. Mod Pathol. 2003;16:1171–7.
174. Travis WD. Pathology of lung cancer. Clin Chest Med. 2011;33:669–92.

Lung Cancer: Mechanisms of Carcinogenesis

10

Sisko Anttila and Penny E.H. Nymark

Keywords
Occupational lung cancer • Pulmonary carcinogenesis • Asbestos carcinogenesis • Oxygen radical damage • Chromosomal aberrations • Epigenetic changes • Carcinogenic metals

Introduction

Inhaled carcinogenic chemicals, mineral fibers and particulates, and carcinogenic metals are the most significant occupational causes of lung cancer. The gases, fumes, and particulates in industrial environments form complex mixtures, the carcinogenic potential of which may differ from that of each component separately. Particulate matter can absorb chemicals on its surface, which is thought to enhance the deposition of chemicals in the lung, their penetration into lung cells, and carcinogenic action. Personal or involuntary tobacco smoking complicates the exposures even further, since tobacco smoke is also a complex mixture containing carcinogenic agents in chemical and particulate forms.

The carcinogenicity of inhaled substances is influenced not only by their chemical composition but also by their retention and biopersistence in the lung. The pulmonary deposition and clearance of inhaled particles and fibers are dependent on particle size and dimension. Particles of 10 μm or more in diameter are deposited in the upper airways, whereas those around 1 μm or less in diameter are most effectively retained in the alveolar lung. Fibrous particles such as asbestos fibers are exceptional in their deposition and clearance, and asbestos fibers up to over 100 μm in length can be found in lung tissue. Inhaled particles and fibers are cleared from the lungs via lymphatics and mucociliary transport. Poorly soluble particles and fibers, which are retained in the lung, form a constant source of toxic damage.

This chapter reviews the carcinogenic mechanisms of the most significant pulmonary carcinogens. For more detailed information, we refer the reader to several recent comprehensive reviews cited in this chapter.

Asbestos

Occupational asbestos exposure and its clinical presentations have been described in Chapters 9, 14, and 15. Asbestos toxicity and carcinogenesis have been studied in a range of experimental settings, and several studies have shown that asbestos can induce malignant transformation in both murine and human cells [1]. Nevertheless, the exact molecular mechanism behind asbestos-related carcinogenesis is still unresolved. It is thought to be very complex, probably involving several parallel pathways (reviewed in [2]. Here, we discuss the specific mechanisms associated with asbestos-induced lung carcinogenesis. Chapter 17 includes a detailed discussion on the carcinogenic mechanisms in mesothelial cells following asbestos exposure. Different mechanisms may dominate in different cell types, and the sensitivity of cells to fibers may differ. Indeed the mesothelial Met5A cell line has been shown to be more sensitive to asbestos exposures than lung cells [3]. It has been

S. Anttila, MD, PhD (✉)
Jorvi Hospital Laboratory of Pathology,
Helsinki University Central Hospital,
Hospital District of Helsinki and Uusimaa,
Laboratory Services, HUSLAB, Helsinki, Finland

Health and Work Ability,
Finnish Institute of Occupational Health, Helsinki, Finland
e-mail: sisko.l.anttila@hus.fi

P.E.H. Nymark, PhD
New Technologies and Risks, Finnish Institute
of Occupational Health, Helsinki, Finland

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_10, © Springer-Verlag London 2014

proposed that this difference in sensitivity lies in the balance between oxidant and antioxidant levels (e.g., glutathione), which seem to be different in epithelial and mesothelial cells [3]. Nevertheless, some mechanisms may be similar or even the same, and it is important to compare the effects of asbestos fibers in different cell types. The molecular mechanisms involved in the carcinogenesis of specific cells may lead to the discovery of clinically useful molecular markers specifically associated with asbestos exposure in lung cancer. These markers are discussed in detail in Chapter 12.

Toxicity and Carcinogenicity of Asbestos Fibers

The genotoxic and carcinogenic effects of asbestos depend largely on the fiber's chemical composition and structure as well as the cell environment [4]. Several experimental studies have shown that the longer the fiber, the more carcinogenic it is per se [5]. However, many researchers argue that fibers of all lengths induce pathological responses and no type of asbestos fiber should be considered noncarcinogenic, based simply on its length [6]. On an epidemiological basis, it has been difficult if not impossible to establish such a hypothesis, since asbestos workers are often exposed to a mixture of different fiber types and sizes [7]. Amphiboles are thought to be more pathogenic in the human body compared to chrysotile, due to the metals they contain, the fiber structure, and their biopersistence. In contrast to chrysotile asbestos, which becomes fragmented and cleared from the lungs, amphiboles are considered to be totally insoluble in the human lung [8, 9]. It has been estimated that chrysotile fibers are needed at several hundred times the levels of amphibole fibers to induce a similar risk of malignancy (reviewed in [10]. On the other hand, there is considerable pathological as well as experimental evidence that also chrysotile is highly carcinogenic [11–13]; in fact, it has been established that chrysotile is as potent as the amphibole crocidolite, per fiber, in its ability to cause lung cancer, even though it is two to four times less potent in evoking mesothelioma [14] (see Chapter 17). However, for mesothelioma to develop, the fibers need to migrate to the pleural or peritoneal linings, while lung cancer development can be considered more direct, since they are "available" directly after inhalation. Thus, it is possible that the more efficient clearance of chrysotile is associated with its lower potency for causing mesothelioma compared to lung cancer.

Mechanisms of Asbestos Carcinogenesis

Oxidative Stress and Inflammation

Asbestos fibers enter the lungs through inhalation. In the bronchi and alveolar spaces, the fibers are surrounded by bronchoalveolar macrophages (BAM), which deposit an iron-protein coating around the fibers. These are then referred to as asbestos bodies. However, due to the larger size of the fibers compared to that of the BAM, the so-called frustrated phagocytosis may take place, leading to the elevated release of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as well as digestive enzymes, proteases, and chemokines/cytokines [4, 15]. Amphibole fibers contain high levels of associated mono-, di-, and trivalent metals such as iron, and it has also been proposed that asbestos is toxic by the particular way iron is bound to the fiber's surface, enabling the generation of ROS and RNS [16, 17].

Asbestos-related carcinogenic pathways are shown in Fig. 10.1. In addition to the generation of ROS and RNS, the main mechanisms behind the toxic effects of asbestos are thought to be alterations in mitochondrial function, mechanical disturbance of cell cycle progression, and the activation of several signal transduction pathways (reviewed in [4, 18, 19]) (see Chapter 17 for a more detailed discussion). Many of these effects are due to the triggering of universal cellular responses, induced by several types of cytotoxic substances. Interestingly, however, mitochondrial metabolism and ROS production appear to be necessary for *KRAS*-induced tumorigenesis in mice, and asbestos is indeed closely associated with mitochondrial dysfunction, which in turn is related to the inflammatory effects of asbestos (reviewed in [2]. Some, [20, 21] but not all, studies [22] have shown *KRAS* mutations to be associated with asbestos exposure in lung cancer (see Chapter 12 for a more detailed description).

Emerging evidence has also indicated that both *TP53* mutations and Myc-induced oncogenic transformation are dependent on mitochondrial dysfunction and ROS production (reviewed in [23], and these have both been implied in asbestos-related lung carcinogenesis [24]; reviewed in [2]). Thus, these mutations may be a consequence of the inflammatory effects associated with asbestos exposure. Lung cancer in general is considered an inflammation-associated cancer (reviewed in [23]. Cancer-related inflammation has been shown to vary between tumor types, and the prolonged inflammation induced by biopersistent fibers may have specific features. Thus, it is important to clarify the specific changes related to certain types of exposures, since this variation could possibly be used in cancer management (e.g., diagnosis and treatment) (reviewed in [23]).

Several genes involved in inflammation-associated expression pathways, such as those in the *TNFα/NF-κB* pathway, have proved to be deregulated in asbestos-related lung cancer. For example, TNFα, an inflammatory cytokine, has been shown to be activated in macrophages after asbestos exposure in vitro [25]. TNFα induces interleukin 8 (*IL8*) expression in macrophages, which attracts neutrophils that in turn release ROS and RNS. This leads to a feedback loop between ROS generation and increased *TNFα* expression, resulting in increased DNA damage [26] and consequently possibly increased mutations in critical genes, such as *KRAS* and *TP53*, as described above.

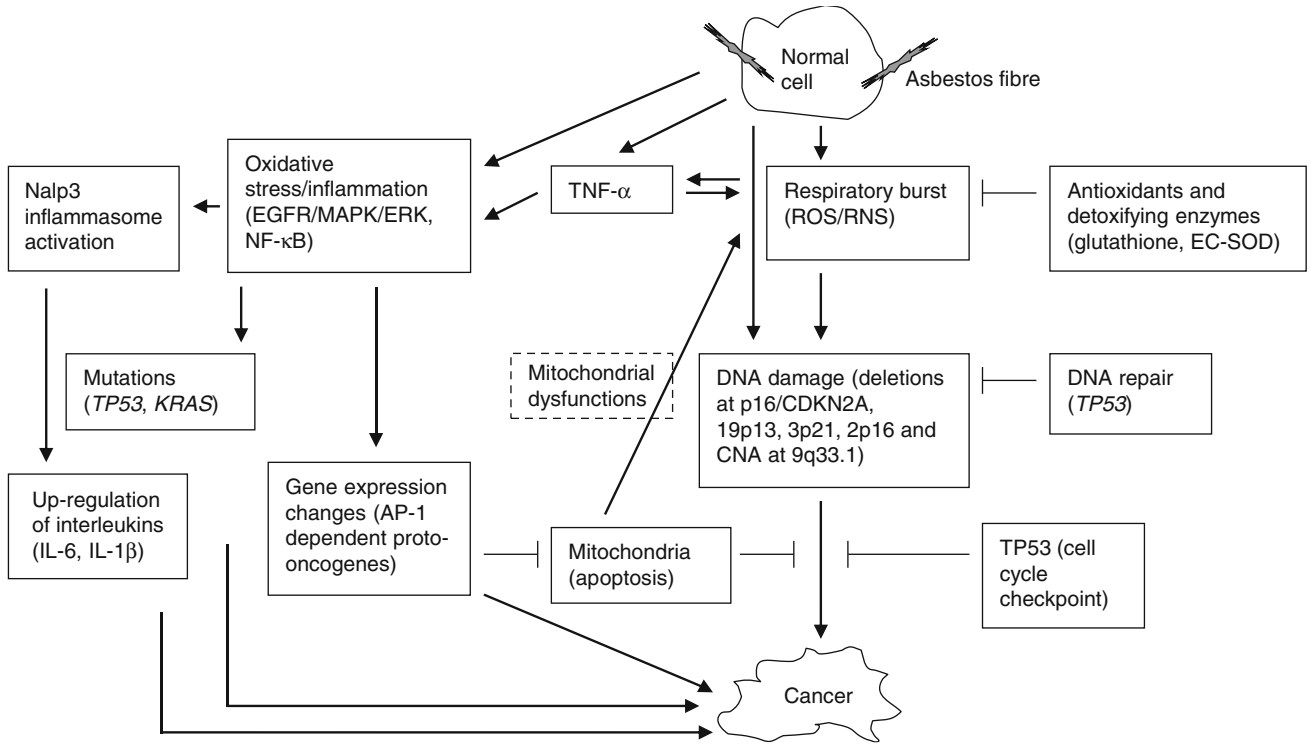


Fig. 10.1 Asbestos-related carcinogenic pathways in the lung (Adapted from Nymark et al. [2]. Copyright 2008. with permission from Elsevier)

Furthermore, several other interleukins are also released by inflammatory cells [27] upon the phagocytosis of fibers. For example, *IL6* has been shown to be upregulated in airway epithelial cells by NF-κB in response to asbestos exposure [28]. Increased IL6 correlates with increased serum levels of C-reactive protein (CRP), which a follow-up study [29] revealed to be significantly elevated in the serum of asbestos-exposed workers who had developed cancer (lung cancer and mesothelioma) as compared to those who had not developed cancer. In addition, *IL1* and *IL10* have been found to be upregulated by asbestos-induced oxidative stress in vitro [30, 31]. Furthermore, the macrophage Nod-like receptor protein (Nalp3) inflammasome is reportedly activated by asbestos in vitro and has been associated with the pathological increase of IL-1β, in, for example, asbestos-induced mesothelioma. It is well known that IL-1β-driven inflammation promotes the development and invasiveness of several tumor types. Therefore, it has been proposed that Nalp3 inflammasome is an innovative therapeutic target with possible translational significance in asbestos-induced cancer (reviewed in [10, 15, 23].

Apoptosis

Apoptosis plays an important role in the inflammatory process and in the resolution of an inflammatory state. Furthermore, apoptosis protects against the abnormal proliferation of cells with nonrepairable DNA damage (discussed below). Many of the asbestos-induced alterations in the cell should eventually lead to apoptosis. However, the apoptotic pathways seem to be inhibited in asbestos-associated lung carcinogenesis as in many other carcinogenic mechanisms. Low doses of asbestos have been shown to promote S-phase entry and thereby cell proliferation through an EGFR-dependent pathway instead of apoptosis [32]. When apoptosis is bypassed, the asbestos-associated dysfunctions in the mitochondrial respiratory chain maintain the increased release of ROS. Furthermore, the expression and phosphorylation of cAMP-responsive element-binding protein (*CREB*) is thought to be an important regulator of apoptosis in asbestos-induced responses, and silencing of the gene dramatically increases asbestos-induced apoptosis in lung epithelial cells [33]. Similarly, overexpression of the oxidative DNA adduct, 8-OHdG (see section "Biomarkers of Oxidative DNA Damage"), repair enzyme, OGG1, and its translocation to the mitochondria has reduced asbestos-induced apoptosis in HeLa cells [34]. Moreover, gene expression profiling of asbestos-transformed tumorigenic lung cell lines has revealed downregulation of an apoptosis-related putative tumor suppressor *DCC* (deleted in colorectal cancer) [35]. Miura et al. have also produced an apoptosis-resistant T-cell cell line through repeatedly exposing the cells to asbestos. By studying this cell line, they proposed a model mechanism for acquiring resistance to asbestos-induced apoptosis, involving the activation of the genes Src family kinase, *IL-10*, *STAT3*, and *BCL2*. Interestingly, *BCL2* was also found to be significantly upreg-

ulated in the T cells of mesothelioma patients as compared to those of healthy volunteers and asbestosis patients, indicating a role in carcinogenesis [31] (see Chapter 17 for a detailed description). Many other *BCL2*-related genes have been implicated in asbestos-induced apoptotic resistance or carcinogenesis, such as *BNIP3L*, *Bax*, and *Bcl-xl* [36, 37].

MAPK/ERK Pathway

EGFR has proven to be activated by asbestos-induced oxidative stress through phosphorylation [27, 38, 39]. Interestingly, EGFR has also been shown to be overexpressed in malignant mesothelioma, even though no mutations have been detected (see Chapter 17). EGFR, in turn, activates the MAPK/ERK pathway through phosphorylation of ERK1/2 and ERK5 [40], and increased levels of phospho-ERK1/2 and phospho-ERK5 induce proliferation and activation of the AP-1 family members (i.e., the proto-oncogenes c-fos, fra-1, and c-Jun) [41–44]. Low levels of asbestos have been shown to cause cytoplasmic localization of phospho-ERK1/2, and this is followed by AP-1-dependent nuclear localization of cyclin D1 [32]. Cyclin D induces cell cycle reentry through progression from G1 to S phase [45]. Reactivation of the cell cycle in a critical DNA repair stage may lead to a DNA damage bypass allowing cells with oncogenic changes to continue proliferating. Other growth factors such as the insulin-like growth factor (IGF) and platelet-derived growth factor (PDGF) are also known to promote S phase after asbestos exposure [46].

Activation of EGFR also appears to be caused by protein kinase C (PKC)-activated matrix metalloproteinases (MMP) [47], and, for example, MMP2 has been found to be upregulated after combined exposure to chrysotile and cigarette smoke in vivo, which will be discussed in detail below [48]. In accordance, PKCδ and its substrate, adducin, have shown to cause cell proliferation through activation of ERK1/2 in response to asbestos exposure [49, 50]. Noticeably, adducin (ADD1) has also been found to be upregulated in the lung tumors of asbestos-exposed patients when compared to those of non-exposed patients [51]. ERK1/2 appears to be activated by the Src family kinase [52]. Src is a growth-promoting tyrosine kinase, which is activated by the urokinase plasminogen activator (PLAU) pathway involved in tissue reorganization events, such as wound healing. The PLAU pathway appears to be activated by asbestos [53].

Clastogenicity of Asbestos Fibers

In vitro studies have shown that asbestos fibers are clastogenic (able to induce disruptions and breaks in chromosomes), even though they are not mutagenic in the Ames assay [54, 55]. These genetic alterations are thought to contribute to the carcinogenic effects of asbestos. Experimental studies, as well as studies on lymphocytes from asbestos workers, have demonstrated asbestos-induced clastogenicity, involving DNA single- and double-strand breaks, deletions, increased sister chromatid exchanges (SCE), and the formation of micronuclei [55–67]. DNA double-strand breaks are the most severe types of DNA damage and can lead to translocations and chromosomal instability (CIN), since they are more difficult to repair than, for example, DNA single-strand breaks. Crocidolite asbestos appears to be able to induce greater amounts of DNA double-strand breaks than silica and titanium dioxide [64]. In addition, asbestos has been reported to cause abnormal chromosome segregation, which can lead not only to chromosomal deletions and other DNA alterations but also to aneuploidy [58]. The fibers have also been shown to sterically block cytokinesis, leading to binucleated cells and consequently polyploidy [68]. Polyploidy may in turn lead to the chaotic segregation of chromosomes during cell division, thus increasing chromosomal instability (CIN), one of the cornerstones of tumorigenesis (reviewed in [23]).

The chromosomal alterations in lung cancer are very chaotic, and it is difficult to draw any conclusion on whether a specific alteration is associated with asbestos or some other exposure type, for example, tobacco smoke. However, experimental studies show that asbestos exposure is primarily associated with losses and deletions [55, 63, 65–67, 69]. Indeed, most of the asbestos-related chromosomal alterations identified in lung tumor samples to this date are losses (see Chapter 12; [70–75]. In contrast, as mentioned above, polyploidy has also been associated with asbestos exposure and has been identified at high frequency in lung tumor samples from asbestos-exposed patients [74]; see Chapter 12). This is also the case in mesothelioma, which often shows polyploidy of hypodiploid clones (i.e., less than 46 chromosomes; see Chapter 19). Thus, the clastogenic effects of asbestos seem to cause deletions in the genome, while the physical blocking of cytokinesis may induce polyploidy. A good example of these effects is described in one of our studies on the asbestos-associated losses at 2p16. Chromosome 2 is often affected by numerical as well as structural alterations in lung tumors, and we showed that the mean signal count of centromere 2 in lung tumor cells was 2.7 irrespective of the asbestos exposure status of a patient, indicating that the chromosome is often affected by trisomy. In the same study, frequent gains were detected at 2p21 [71]. Another study showed that half of the non-small cell lung cancer (NSCLC) cases examined were affected by gains at 2p21.1-2p14 [76]. Despite this complexity of chromosome 2 alterations in lung tumors in general, we were able to show that a higher frequency of loss of DNA and allelic imbalance (AI) at 2p16 was associated with asbestos exposure [71].

Several experimental settings have shown that asbestos induces micronuclei in lung cells. Micronuclei contain fragments of damaged DNA or even whole chromosomes and are often lost during the subsequent cell divisions, providing an explanation as to why losses and deletions of genomic material are so common following asbestos exposure. Recently, we showed that the mechanism behind the loss of 19p13,

which proven to be more frequent among asbestos-related lung tumors (see Chapter 12) [51], may be the formation of asbestos-induced micronuclei containing specifically 19p13 fragments [75]. In addition, monosomy of chromosome 19 has been detected in vitro in asbestos-transformed human bronchial epithelial cells [77]. Loss of 19p13 has also been identified in mesothelioma [78].

Epigenetic Effects

Epigenetic alterations, such as methylation, are thought to contribute significantly to the development of asbestos-related lung cancer, although the mechanisms behind these alterations are still poorly understood [79–81] (see Chapter 3 for epigenetic mechanisms of carcinogenesis). Nevertheless, *P16/CDKN2A*, which is frequently methylated in lung cancer, has been shown to be significantly more frequently affected by homozygous deletion in asbestos-related lung cancer [70]. The frequencies are comparable to those found in malignant mesothelioma (see Chapters 17 and 19 for detailed discussion on these alterations). Interestingly, one of the gene products of *P16/CDKN2A* ($p14^{ARF}$) positively regulates p53. Thus, alterations in these two genes may be mutually exclusive, explaining why *TP53* mutations are less frequent in mesothelioma, therefore also pointing toward a stronger association between these mutations in lung cancer and tobacco smoking (see Chapter 12 for a more detailed discussion).

The mechanism behind asbestos-induced microRNA regulation is still poorly understood, as in malignant mesothelioma (see Chapter 19), but since differences have been detected in miRNA expression between asbestos-related and non-asbestos-related lung cancer, it is obvious that the exposure is able to also affect these small noncoding genes ([82]; see Chapter 12 for a detailed description). It is, of course, possible that some of them are lost or methylated similarly as described above, for coding genes. However, this needs to be investigated on a deeper level in order to be able to draw any conclusions on these mechanisms.

Finally, the widely versatile process of ubiquitination has been associated with asbestos exposure in lung cancer [83]. The process is involved in various key cellular events, such as DNA repair, cell cycle, and apoptosis, which all seem to be altered in different ways in asbestos-induced lung carcinogenesis. Thus, this pathway is an interesting target for further investigation.

Synergistic Mechanisms Between Asbestos and Tobacco Smoke

Asbestos elevates the risk of nonsmokers contracting lung cancer, but the risk seems to increase in an almost multiplicative manner in smokers, indicating that tobacco smoke and asbestos act as synergistic cocarcinogens [84]. Various joint effects ranging from less than additive to more than multiplicative have been reported, but the generally accepted model that seems to fit the best is a more than additive or less than multiplicative one [85].

Several mechanisms are likely to contribute to the synergistic effects of these two carcinogens. For example, some studies demonstrate that cigarette smoke augments the penetration of asbestos fibers in rat tracheal explants by an oxygen radical-mediated mechanism [86]. Tobacco smoke may also interfere with the clearance of asbestos fibers from the lungs [85]. Furthermore, tobacco carcinogens are known to be adsorbed onto the surface of asbestos fibers, increasing their uptake into the cells [84, 87]. In addition, it has been observed that ROS alter the metabolism of the tobacco carcinogen, benzo[a]pyrene, by inhibiting its detoxification pathways [88]. Yet another hypothesis is that asbestos fibers induce cell proliferation and thereby clonal expansion of cells with heritable tobacco carcinogen-induced alterations in critical genes [89]. As mentioned previously, asbestos is not considered to be able to induce point mutations, although some studies on human lung tumors have linked specific *TP53* mutations, i.e., predominantly exon 9–11 mutations to asbestos exposure [90, 91]. However, we could speculate that at least a part of these mutations would primarily be caused by tobacco-specific carcinogens such as benzo[*a*]pyrene [92]. Indeed, as mentioned above, the frequency of *TP53* mutations is also significantly lower in malignant mesothelioma compared to other cancers, indicating that asbestos fibers are not, or at least not directly, involved in the alterations of this gene (see Chapter 12). It has also been shown that p53 may be phosphorylated at Ser15 following exposure to DNA-damaging agents, including asbestos. Phosphorylation causes stabilization and subsequent transactivation, which consequently leads to sustained expression levels (reviewed in [90]).

Finally, it has been proposed that the synergistic properties of asbestos and tobacco smoke may be caused by separate activation of the ERK genes and JNK1/2, respectively, which both transactivate AP-1, as mentioned above [40]. The cocarcinogenic mechanisms mediated by the transcription factors, nuclear factor-erythroid 2-related factor (NRF2) and aryl hydrocarbon receptor (AHR), which regulate oxidative stress- and tobacco carcinogen-induced gene expression, respectively, are discussed below (see section "Cocarcinogenesis Mechanism of Tobacco Smoking and Inhaled Particulates").

Polycyclic Aromatic Hydrocarbons and Complex Mixtures

Occupational Exposure to Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons arise in the incomplete combustion of fossil and carbonaceous materials and also occur in crude oil deposits. The highest occupational exposures are

Table 10.1 Examples of biomarkers of internal dose, biologically effective dose, and early effects in relation to occupational exposures to PAH and complex mixtures

Examples of exposures	Markers of internal dose	Markers of effective dose	Markers of early biological effects
Involuntary tobacco smoking Coke-oven workers Foundry workers Bitumen workers Petrochemical industry Rubber vulcanizing Diesel exhaust/working in traffic Firefighting Soil remediation Waste handling	Urinary metabolites of tobacco constituents Cotinine (nicotine metabolite) NNAL and NNAL/cotinine ratio 1,3-Butadiene Urinary PAH metabolites 1-Hydroxypyrene and other PAH metabolites	DNA adducts in blood lymphocytes or lung Bulky DNA adducts Anti-B[a]PDE-DNA adducts 8-OxodGuo adducts Protein adducts Hemoglobin adducts Urinary/plasma markers of oxidative DNA damage Excretion of 8-oxo-7,8-dihydroguanine	Cytogenetic aberrations detected in blood lymphocyte culture Micronucleus formation Sister chromatid exchanges Chromosomal aberrations DNA strand brakes in blood lymphocytes (measured by comet assay) Changes in global and gene-specific promoter methylation Shorter telomere length

Abbreviations: *PAH* polycyclic aromatic hydrocarbon, *NNAL* tobacco-specific nitrosamine metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, *anti-B[a]PDE* anti-benzo[a]pyrene diol epoxide, comet assay, alkaline single-cell gel electrophoresis assay

found in petrochemical industry workers, especially in coke-oven workers, and in workers of metal plants and foundries [93]. Sources of indoor PAH exposure include tobacco smoke, meat and fish roasting and frying, and charcoal grilling in poorly ventilated environments [94]. Examples of occupations with PAH exposure are given in Table 10.1. Workers in the petrochemical industry and in foundries are typically exposed to complex mixtures, in which chemical compounds are bound to metal and mineral particulates of respirable size. Some of these metals and minerals are known or suspected lung carcinogens as such; examples include arsenic, some chromium and nickel compounds, cadmium, vanadium, silica, and fibrous minerals including asbestos. PAH levels and the distribution of different PAH compounds between gaseous and particulate phases have been studied in air samples from foundries. While the gas phase contains on average three times more carcinogenic four- and five-ring PAHs, the total PAH load increases with increasing particle size in individual fractions [95–98]. The distribution of PAHs between gaseous and particulate phases is important because the mechanisms and biomarkers of chemical and particle/fiber carcinogenesis are different. While pure PAH procarcinogens are metabolized via the AH receptor-mediated pathway to DNA-reactive intermediates or detoxified and excreted from the body, particulates, some metals, and fibers induce the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and oxidative DNA damage.

Involuntary Tobacco Smoking

Environmental tobacco smoke (ETS) is a significant source of PAH and other tobacco carcinogens for nonsmokers in workplaces, especially in poorly ventilated environments. ETS is a complex mixture of gaseous and particulate-bound compounds, including known carcinogens such as acrolein, aromatic amines, acetaldehydes, benzene, cadmium, 1,3-butadiene, tobacco-specific nitrosamines, and polycyclic aromatic hydrocarbons [98–100]. ETS consists mainly of sidestream smoke emitted from smoldering cigarettes between puffs and to a lesser extent of mainstream smoke exhaled by tobacco smokers [101]. The delivery of different compounds by mainstream and sidestream tobacco smoke is influenced by the efficiency of combustion and differs between tobacco brands due to tobacco blends, ingredients, design, and differences in manufacture. The harmful chemicals in sidestream tobacco smoke are principally responsible for the deleterious health effects of involuntary tobacco smoking. Lodovici et al. studied the PAH content in mainstream and sidestream tobacco smoke from 14 tobacco brands and found that sidestream smoke contained about ten times higher PAH levels than mainstream smoke from most cigarette brands [102]. While the tar content of cigarettes is a good predictor of the release of PAHs in mainstream smoke, PAHs in sidestream smoke do not correlate with tar content [102, 103]. Furthermore, levels of carcinogenic PAH compound benzo[a]pyrene are especially high in sidestream tobacco smoke [102]. Most carcinogenic PAH compounds are present in the particulate phase of tobacco smoke.

Metabolic Activation of PAH Procarcinogens

PAH compounds enter cells as procarcinogens which require metabolic activation to exert their carcinogenic potential. In lung cells, PAH compounds bind to a cytoplasmic aryl hydrocarbon (dioxin) receptor (AHR) which, after ligand binding, is translocated to the nucleus and dissociates from

the cytoplasmic chaperone complex. It then associates with its dimerization partner, ARNT protein, and binds to xenobiotic (dioxin)-responsive elements (XRE) in the promoter (enhancer) regions of AHR-responsive genes, turning on their transcription (e.g., [104, 105]). AH receptor regulates the transcription of several cytochrome P450 (CYP) enzymes, which are involved in the Phase I metabolism of xenobiotics, and also the transcription of a few Phase II enzymes, including UDP-glucuronosyltransferases 1A1 and 1A6, glutathione S-transferase A2, and NAD(P)H:quinone oxidoreductase 1 (NQO1). Generally speaking, Phase I metabolism is responsible for the initial activation step of metabolism, often leading to the formation of reactive intermediates, whereas Phase II metabolism involves the conversion to more polar and water-soluble compounds and detoxification [104, 106].

In the lung, cytochrome P450 enzymes CYP1A1 and CYP1B1 and epoxide hydrolase catalyze the conversion of PAH procarcinogens to proximate carcinogenic metabolites, PAH diols, and CYPs further to ultimate carcinogenic metabolites PAH diol epoxides. CYP1A1, CYP1B1, and a third PAH-metabolizing lung enzyme, CYP2S1, are under the regulative control of the AH receptor. In general, CYP2S1 is a PAH-detoxifying rather than a PAH-activating enzyme. In the presence of an oxidizing agent, such as hydrogen peroxide, CYP2S1 has been shown to oxidize benzo[a]pyrene-7,8-dihydrodiols into epoxides with a high turnover [107]. This finding may have relevance in human exposures to various particulate and complex mixtures that induce oxidative stress.

Reactive metabolites may bind to proteins and DNA, thereby forming adducts, or become detoxified by Phase II enzymes, such as glutathione S-transferases, UDP-glucuronosyltransferases, and sulfotransferases [106, 108]. PAH diols are also metabolized by aldo-keto reductase into reactive PAH *o*-quinones, which are able to form stable and depurinated DNA adducts. Furthermore, PAHs are catalyzed by peroxidase activities into radical cations that form depurinated adducts [106, 109–111].

Bulky DNA adducts, which mainly originate from PAH, are considered a measure of internal dose of PAH and, if not repaired, may lead to DNA damage. Denissenko and colleagues mapped the distribution of benzo[a]pyrene diol epoxide (BPDE)-DNA adducts along exons of the *TP53* gene and observed strong and selective adduct formation at guanine positions in codons 157, 248, and 273. These same codons are the mutational hotspots in human lung cancer [112]. Subsequent studies have shown that methylated CpG dinucleotides are the preferential target for BPDE adduct formation and G:C to T:A transversions at *TP53* codons 157, 248, 249, and 273 [113, 114]. The molecular alterations caused by tobacco-derived PAH and occupational PAH exposures are not separable.

Cocarcinogenesis Mechanism of Tobacco Smoking and Inhaled Particulates

It has long been known in epidemiology that tobacco smoking and asbestos exposure have a synergistic, almost multiplicative effect on lung cancer risk as compared to the risk caused by either exposure alone. The exact mechanisms for the synergism are not known, but the emerging knowledge of the cooperation between the transcription factors and signaling pathways that are induced by tobacco carcinogens and oxidative stress offers a plausible view on cocarcinogenesis. Oxidative stress, together with its effects on cellular structure and function, plays a central role in the carcinogenic process induced by inhaled particulates, including asbestos fibers, silica, and carcinogenic metals, as well as ionizing radiation.

PAH compounds exert their effects via the AH receptor, which regulates the transcription of a number of xenobiotic-metabolizing enzymes by binding to xenobiotic-responsive elements (XRE) in the promoters of responsive genes. Recent research has shown that the AH receptor plays an additional role in the control of cell proliferation and apoptosis, differentiation, and inflammation, for example, via interactions with pRB, EGFR, and NF-κB signaling [104].

Several other transcription factors are linked to AHR, for example, the nuclear factor-erythroid 2-related factor 2 (NFR2), which controls the antioxidant gene battery [115, 116]. NRF2 regulates gene expression via binding to antioxidant responsive elements (ARE) in the regulatory sequences of NRF2-driven genes. Many of the NRF2-regulated genes encode enzymes which are responsible for the detoxification of reactive electrophiles formed by Phase I metabolism by CYPs or for the elimination of reactive oxygen species, including enzymes such as NAD(P)H:quinone oxidoreductase 1 (NQO1), glutathione transferases, UDP-glucuronosyltransferases, aldehyde dehydrogenase, and several antioxidant enzymes [117, 118]. Interestingly, AHR- and NRF2-regulated signaling is coordinated by several mechanisms, for example, *AHR* and *NRF2* genes contain each others' binding elements in their regulatory enhancer regions [115]. Furthermore, induction of the expression of a group of genes, such as detoxification enzyme NQO1, requires both AHR and NRF2 [116].

It has been shown recently that loss of the regulative control of NRF2 in human lung cancer cells may result from several aberrations, such as mutations in the *NRF2* gene or its repressor *KEAP1* [119, 120]. *KEAP1*, which is considered a tumor suppressor, may also be silenced by hypermethylation or the deletion of the chromosomal region 19p [75, 121]. These aberrations, which lead to constant NRF2 activation, may arise as a protective response against reactive eletrophiles and oxygen species or become selected by means of giving a growth advantage and permitting cancer

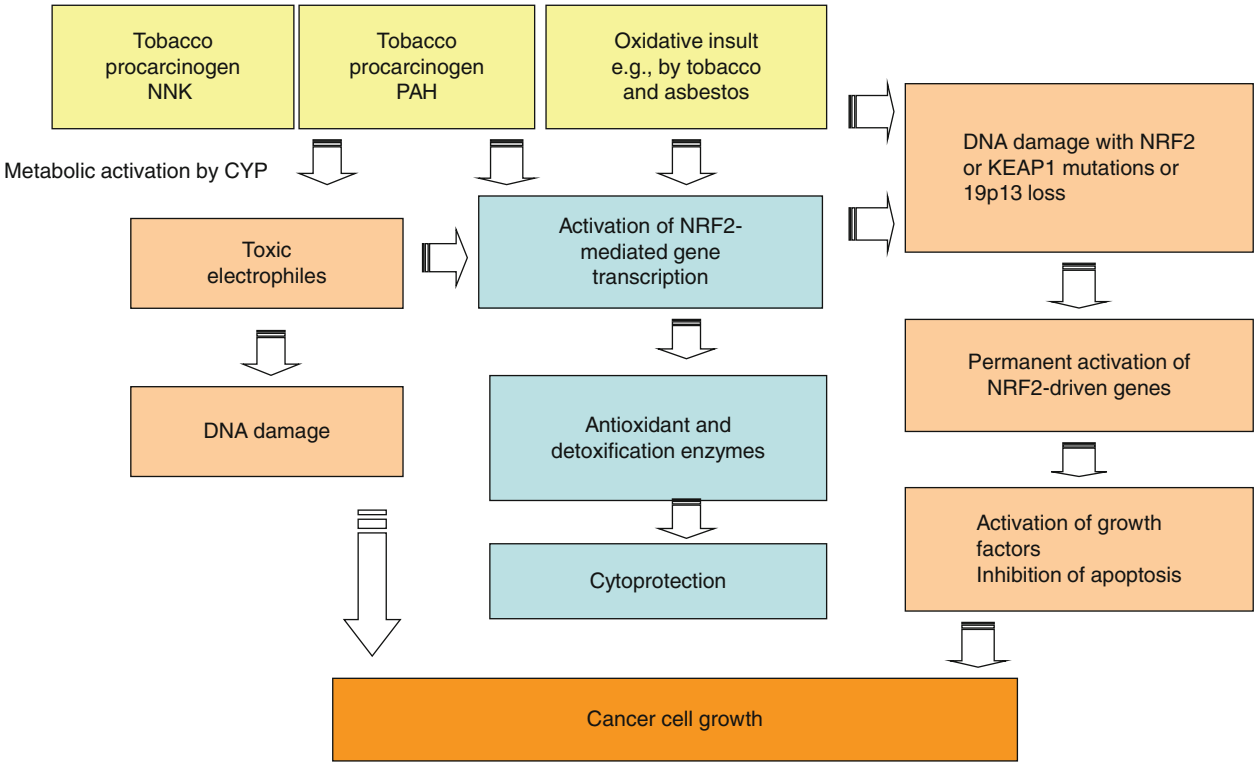


Fig. 10.2 Cocarcinogenesis mechanism of tobacco carcinogens and oxidative stress damage (Reprinted with permission of the American Thoracic Society. Copyright 2013 American Thoracic society. Anttila et al. [108])

cells to avoid apoptosis [108, 122]. Constant NRF2 activation results in overexpression of a number of NRF2-dependent genes, most of them cytoprotective and antioxidant enzymes. Upregulation of NRF2-mediated gene expression seems to involve genes that may promote cancer cell growth, including growth factors such as fibroblast growth factor 13; TGF-α, TGF-β1, and TGF-β2; and growth factor receptors [122]. It has been shown that NRF2 activity regulates the sensitivity of death signals and NRF2 overexpression antagonizes Fas-induced apoptosis [122–124]. Furthermore, one such NRF2-regulated antioxidant enzyme, peroxiredoxin 1 (PRX1), which is commonly upregulated in human cancer, has a dual role as it may provide resistance to oxidative stress in cancer cells by the inhibition of apoptosis-signal regulating kinase 1 (ASK1) activation and subsequent ASK1-induced apoptosis [125]. The enhancement of the oxidative stress and consequent apoptotic pressure by combined exposures to tobacco and asbestos may lead to DNA damage in critical genes, resulting in uncontrolled expression of NRF2-regulated genes, inhibition of apoptosis, and growth advantage to cancer cells. One of these critical aberrations, the deletion of the 19p chromosomal region, is especially common in asbestos-related lung cancer [51, 75]. The postulated mechanism of cocarcinogenesis of tobacco carcinogens and oxidative stress is shown in Fig. 10.2.

Biomarkers

Biomarkers of PAH Exposure

The biomarkers of PAH exposure most commonly used are urinary PAH metabolites, in particular 1-hydroxypyrene. 1-Hydroxypyrene and another urinary biomarker, hydroxybenzanthracene, are noncarcinogenic metabolites and are thought to reflect total PAH exposure. The level of urinary PAH metabolites is influenced not only by occupational exposure but also by diet, tobacco smoking, and environmental air pollution. Typically, in air samples from foundries and petrochemical plants, PAH concentrations are about three orders of magnitude higher than those in environmental exposures. Similarly, urinary 1-hydroxypyrene concentrations reflect the exposure levels well at the group level. PAH-DNA or protein adducts are considered the measure of an effective dose of PAH exposure.

Biomarkers of Oxidative DNA Damage

DNA strand brakes and 8-hydroxyguanine (8-hydroxydeoxyguanosine, 8-OHG) formation are the most commonly used tests for oxidative DNA damage caused by

exposure to PAH and inhaled particulates in the scientific literature. The oxidized DNA product 8-OHG is formed in the reaction of guanine with hydroxyl radical [126]. This mutagenic and carcinogenic DNA product is a good biomarker of oxidative stress and can be determined in urine or circulating white blood cells [126]. 8-OHG levels in urine are also influenced by gender, age, body mass index, and lifestyle factors, such as tobacco smoking, hard physical labor, and diet [127, 128]. DNA strand brakes can be studied by comet assay (alkaline single-cell gel electrophoresis assay) in cultured cells or in the circulating blood lymphocytes of exposed individuals [129]. Tarantini et al. studied the relative contribution of DNA strand brakes and DNA adducts to the diol epoxide metabolite of B[a]P in the cellular effects of pure B[a]P and complex mixtures collected from an urban peri-industrial site and a metallurgical plant [130]. Treatment of HepG2-cultured human hepatocytes with pure B[a]P or with a fraction of atmospheric particles containing soluble PAH did not induce DNA strand brakes in comet assay or the formation of 8-OHG, whereas B[a]PDE adducts were observed with even low concentrations. In contrast, samples filtered from industrial and especially those from urban sites induced DNA strand brakes and the formation of 8-OHG and less BPDE adducts, suggesting that a component other than PAH, possibly particulate matter in the mixture, modulates the genotoxic properties of complex mixtures [130].

The most commonly used biomarkers of internal dose, biologically effective dose, and early effects in relation to occupational exposures to PAH and complex mixtures are listed in Table 10.1.

Metal-Induced Lung Carcinogenesis

Metal-induced carcinogenesis has been covered in detail in several recent reviews [126, 131–142]. For more information regarding metal carcinogenesis, readers are referred to these and other reviews, and for the basic biological mechanisms of carcinogenesis, Chap. 3. The principal mechanisms of metal carcinogenesis are listed in Table 10.2.

Arsenic

Arsenic and its compounds have been identified by IARC as group I human carcinogen, causing cancers of the skin, liver, kidney, bladder, and lung [143]. Globally, arsenite [As(III)] or arsenate [As(V)] is a significant contaminant of drinking water, causing an excess of cancers especially of the skin and

Table 10.2 Mechanisms related to metal-induced lung carcinogenesis

Metal	Target molecule/effect	Result in cellular structure/function
Arsenic	Oxidative stress	Activation of signaling pathways responsive to oxidative stress
	Defective DNA ligation during excision repair	Oxidative damage causing DNA strand breaks and chromosomal aberrations
	Global DNA hypomethylation	Altered gene transcription
	Hypermethylation of promoters of tumor suppressor genes	Loss of function of tumor suppressor genes
Cadmium	Oxidative stress and disruption of cellular antioxidant (glutathione) system	Oxidative damage causing DNA strand breaks and chromosomal aberrations
		Activation of signaling pathways responsive to oxidative stress
	Induction of acquired apoptotic resistance Inhibition of DNA damage repair	Accumulation of inherent DNA damage in proliferating cell population resulting in malignant transformation
	Global DNA hypomethylation	Altered gene expression
	Hypermethylation of promoters of tumor suppressor genes	Loss of function of tumor suppressor genes
Chromium	Oxidative stress via reduction of Cr(VI) to Cr(V), Cr(IV), and Cr(III)	Oxidative DNA damage Activation of signaling pathways responsive to oxidative stress
	Reaction of Cr with DNA	Cr-DNA adducts and DNA-protein and DNA-DNA cross-links
	Dysregulation of mismatch repair	Genomic instability
	Cross-linking complexes in promoters of several genes	Inhibition of gene transcription
	Hypermethylation of promoters of tumor suppressor genes	Loss of function of tumor suppressor genes
Nickel	Weak inducer of oxidative stress	Oxidative DNA damage
	Inhibition of histone acetylation	Inhibition of gene transcription
	Induction of de novo DNA methylation	
	Disruption of iron and zinc homeostasis (zinc finger proteins)	Inhibition of enzymes involved, e.g., in DNA repair, histone methylation, and hypoxic signaling
	Activation of hypoxic signaling	Induction of cell proliferation, migration, invasion, and angiogenesis

bladder. Occupational exposure, via inhalation of arsenic compounds such as arsenic trioxide, arsenic trisulfide, and calcium arsenate, increases lung cancer risk in ore smelters, insecticide manufacture, and sheep dip workers [131].

The inorganic arsenics can be methylated in vivo to form monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) in a process of repeated reductions and oxidative methylations, which enhance excretion from the body. However, methylated arsenicals also have a more adverse effect in human cells than the parent compound. MMA and DMA are also ingredients in weed killer chemicals. Trivalent methylated arsenicals are biologically highly reactive and can interact with cellular targets such as proteins and DNA [131, 144–146]. Arsenic metabolism in cells leads to the generation of a variety of reactive oxygen and nitrogen species, including superoxide, singlet oxygen, hydrogen peroxide, the peroxyl radical, nitric oxide, dimethylarsinic peroxyl radicals, and the dimethylarsinic radical [126, 132]. The exact mechanism for the generation of these reactive species is not clear, but the formation of intermediary arsine species or the oxidation of As(III) to As(V) has been suggested [126, 147]. The formation of 8-hydroxyl-2′deoxyguanosine (8-OHdG) DNA adducts is a biomarker of oxidative stress to DNA. Increased levels of 8-OHdG adducts have been detected after exposure to arsenic in cells, in animal models, and in arsenic-induced lesions of human skin [132, 147–149].

Arsenic is not mutagenic in standard assays, but it is genotoxic and induces chromosomal aberrations, sister chromatid exchange, aneuploidy, micronuclei formation, and DNA-protein cross-links [150–153]. Arsenite has been demonstrated by alkaline single-cell gel electrophoresis (comet) assay to induce DNA strand breaks in various human and rodent cells [132, 154–156]. Arsenite-induced DNA strand breaks are caused by ROS production, and breaks may lead to chromosomal rearrangements. Wang et al. [157] have shown that arsenite-induced DNA strand breaks largely result from excision of oxidative DNA adducts and DNA-protein cross-links during excision repair [157]. Arsenic inhibits completion of DNA excision repair via effects on DNA ligase activity perhaps due to being a phosphate analog and interfering with phosphorylation reactions and phosphate transport [132, 158–160].

Arsenic exposure has been related especially with squamous cell histological lung cancer type [161, 162]. Martinez et al. studied gene copy number alterations in squamous cell lung carcinomas from nonsmokers exposed to arsenic in drinking water and observed the most recurrent losses at chromosomal regions 1q21.1, 7p22.3, 9q12, and 19q13.31 and gain at 19q13.33 [163]. These findings are in agreement with the ability of arsenic to induce DNA strand breaks.

Arsenic exposure activates several signal transduction pathways which enhance cell proliferation or reduce antiproliferative signaling, inhibit differentiation, and override the cell cycle checkpoints that control cell division and apoptosis [133].

Epigenetic mechanisms are involved in arsenic-induced carcinogenesis. Arsenic treatment of rat liver cells and human keratinocytes has resulted in reduced expression and activity of DNA methyltransferases, inducing global DNA hypomethylation [134, 164, 165]. Arsenic treatment or exposure has also been associated with the silencing of tumor suppressor genes by hypermethylation of their promoter regions, such as *RASSF1A* and *RPSS3* in human bladder cancer [166], *p16*(*INK4a*) and *RASSF1A* in murine lung cancer [167], *DEPK* in SV-40-immortalized human urothelial cells and in human urothelial (bladder) carcinomas from the arsenic-contaminated area [168, 169], *TP53* in human lung adenocarcinoma A549 cells [170], and *TP53* and *P16*(*INK4A*) in whole blood DNA of people exposed to arsenic in drinking water [171]. Both the global hypomethylation and hypermethylation of promoter regions of tumor suppressor genes are common alterations in malignant tumors. It has also been shown that arsenite changes global histone methylation levels in human lung adenocarcinoma A549 cells [165, 172].

Arsenic is a powerful cocarcinogen and is able to enhance the carcinogenicity of other agents, such as ultraviolet and ionizing radiation, benzo[a]pyrene, N-methyl-N-nitrosourea, diepoxybutane, and methylmethane sulfonate [173–179] in cell and animal models. The interference of arsenic with DNA repair has been suggested as a possible mechanism of cocarcinogenesis. In the study of Chiang and Tsou, which used human lung cell lines, arsenic potentiated the effect of the model PAH procarcinogen, benzo[a]pyrene, to induce BPDE-DNA adducts, without influencing the rate of adduct repair [180].

There is epidemiological evidence of the synergistic effect of ingested arsenic and tobacco smoking on lung cancer risk [181, 182]. A Taiwanese study demonstrated the synergy for the squamous and small cell but not for the adenocarcinoma of the lung [183]. The same group demonstrated that arsenic increased the metabolism of a tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), via activation of CYP2a in mouse liver, and the metabolism of another tobacco carcinogen, benzo[a]pyrene, by enhancement of CYP1A1 expression and activity via the AH receptor with a mechanism involving oxidative stress, in a human adenocarcinoma cell line [184, 185]. CYP enzymes catalyze the initial step (Phase I) in the metabolism of nitrosamine and PAH procarcinogens, which is necessary for the subsequent reactions leading to the formation of DNA-reactive metabolites, as well as detoxification (Fig. 10.2).

Beryllium

Beryllium and beryllium-containing compounds are classified as human carcinogens or likely human carcinogens, causing lung cancer [135, 186]. Much of the human

epidemiological data demonstrating increased lung cancer risk are associated with very high exposures which took place before the 1950s in plants involved in the extraction of beryllium hydroxide from beryl ore, ore refining, and beryllium processing including the production of beryllium oxide, pure beryllium metal, and beryllium copper alloy and the machining of beryllium-containing materials [135].

There is no extensive research data concerning the mechanisms of beryllium-related carcinogenesis. Gordon and Bowser have reviewed the studies on the genotoxicity and carcinogenicity of beryllium [136]. The different chemical forms have had differing effects on mutagenicity and carcinogenicity, and there are no data concerning the beryllium forms relevant to human exposures, i.e., respirable size particles of beryllium metal, alloys, or ceramics [135, 136]. Mammalian test systems have shown evidence of beryllium-induced mutations, chromosomal aberrations, and cell transformation, whereas bacterial tests have been negative [136].

Epigenetic alterations have been detected in beryllium metal-induced rat lung tumors. Belinsky et al. observed hypermethylation of the promoter and loss of transcription in the *p16*(*INK4a*) tumor suppressor gene in 80 % of beryllium-induced rat lung tumors [187].

Cadmium

Cadmium (Cd) is classified as a human lung carcinogen by the International Agency for Research on Cancer [186]. Exposure to Cd is common because the metal is widely used in industry, for example, in electroplating, paints and pigments, welding, and Ni-Cd batteries. Significant amounts of Cd are also released into the environment by human activities [137]. Moreover, Cd is present in the Earth's crust and is selectively taken up by certain edible plants and by, for example, the tobacco plant, making tobacco smoke a significant source of Cd for smokers. The amount of Cd stored in organs depends on their content of a Cd-binding protein, metallothionein. The half-life of Cd in humans is 15–20 years; in lung tissue, Cd is cleared with a half-life of 9 years after quitting smoking [137, 188].

Several mechanisms contribute to the carcinogenicity of Cd (see Table 10.2) [137, 138]. Cd is a weak genotoxic agent and its genotoxicity, i.e., chromosomal aberrations, sister chromatid exchange, DNA strand brakes, and DNA-protein cross-links, is partially mediated by oxygen radical damage [137, 189–191]. Cd is able to induce the generation of ROS in vitro and in vivo, including superoxide anion, hydrogen peroxide, hydroxyl radical, and lipid radicals, in spite of not functioning as a catalyst in the Fenton reaction [138]. It has been proposed that Cd can replace iron and copper in cytoplasmic and membrane proteins, thus increasing the amount of free or chelated copper and iron, which in turn may induce oxidative stress via Fenton reactions [126, 192]. Following exposure to Cd, several transcription factors and pathways are activated that are responsive to oxidative stress, including transcription factors AP-1, NF-κB, and a nuclear factor-erythroid 2-related factor 2 (NRF2) and mitogen-activated protein kinases (MAPKs) signal transduction pathways [138]. MAPKs play an important role in programmed cell death (apoptosis) for the elimination of cells with oxidative DNA damage.

There is evidence that Cd may promote a selective enrichment of cells with genetic damage and resistance to apoptosis, leading to cell proliferation and malignant transformation. The mechanisms of apoptosis resistance induced by Cd are not fully known, but downregulation of several members of the caspase family mediators of apoptosis and reduced expression of the anti-apoptotic gene, *bax*, have been observed in gene expression profiling of Cd-transformed human prostate epithelial cells [193].

The potential of Cd to inhibit the repair of oxidative DNA damage has been demonstrated in several in vitro and in vivo studies, and it is considered a major mechanism of Cd-induced carcinogenesis [137, 194, 195]. Inhibition of DNA damage repair by Cd is thought to be attributable to its effects on enzymes involved in oxidative damage repair, as Cd can be substituted for zinc in zinc finger proteins, resulting in the enzyme's defective repair capacity [137, 196].

The role of epigenetic mechanisms in Cd carcinogenesis is uncertain [134]. In human prostate cells and in another study using rat liver cells, Cd initially induced global DNA hypomethylation followed by hypermethylation after prolonged exposure [197, 198]. In human prostate cells, promoter hypermethylation and reduced expression of *RASSF1A* and *p16* tumor suppressor genes were observed [198]. It is hypothesized that global DNA hypomethylation is associated with Cd-induced cell proliferation [134, 199]. The possible effect of Cd on histone tail posttranslational modifications is not known [134].

Chromium

Chromium VI (hexavalent chromium, CrVI) compounds have been identified as human lung carcinogens [200]. CrVI is widely used in a variety of industries, for example, in paints, metal finishes, stainless steel manufacturing, alloys, welding, and wood treatment. In contrast to other oxidation states of Cr, CrVI is easily transported into cells by an anionic transport system and subsequently reduced to lower oxidation states by a number of reducing agents, such as glutathione, NADPH-dependent glutathione reductase, ascorbate, cystein, lipoic acid, hydrogen peroxide, fructose, and ribose [139, 201]. It is thought that CrIII is unable to cross cell membranes, but recently it has been suggested that certain CrV and CrIII forms generated by reduction in the extracellular space have high permeability through cell membranes [126,

202, 203]. Insoluble Cr compounds can enter cells via phagocytosis. Particulate or water-insoluble CrVI compounds are more potent than soluble species in causing DNA damage, possibly because of the fast clearance of soluble CrVI, whereas poorly soluble particulates may form a persistent source of carcinogenic Cr species in the lung [204, 205].

Intracellular reduction of CrVI is the main source of reactive intermediates and the extensive formation of Cr-DNA adducts and subsequent DNA damage [126, 133, 139]. CrV, when formed, can have a Fenton-like reaction with hydrogen peroxide, generating hydroxyl radical. Other associated reactions can produce thiyl and superoxide radicals [126, 139]. In addition to free radical-induced DNA damage, the formation of Cr-DNA adducts, above other CrIII-mediated DNA cross-links of glutathione, cysteine, histidine, and ascorbate, is responsible for the mutagenicity and genotoxicity of CrVI [126, 140]. Other Cr-induced structural genetic lesions include DNA strand breaks, DNA-protein cross-links, oxidized bases, abasic sites, and DNA inter- and intra-strand cross-links [139, 206].

The DNA damage caused by Cr can lead to dysfunctional DNA replication and transcription and promote genomic instability by dysregulated repair mechanisms, especially by loss of mismatch repair. Microsatellite instability (MSI) reflects the loss of functional mismatch repair mechanism. A Japanese group has compared the presence of replication error phenotype between lung cancers in chromate-exposed and non-exposed individuals. They observed significantly more frequent MSI and repression of DNA mismatch repair proteins hMLH1 and hMLH2 in the lung cancers of chromate-exposed workers [207, 208]. These findings are contradicted by the lung cell experiments by Rodrigues et al., who observed aneuploid phenotype but did not find MSI or reduced expression of mismatch repair proteins in human bronchial epithelial cells malignantly transformed by hexavalent Cr [209]. These differences suggest that replication error phenotype may not be the initial event leading to cancer development in chromate-exposed workers.

In earlier studies on chromate-exposed lung cancer patients, mutations of *RAS* oncogenes and *TP53* tumor suppressor gene were infrequent [210, 211]. However, *TP53* mutations were unusual changes of AT base pairs and double missense mutations [211].

Chromates have induced gene expression changes by epigenetic mechanisms in tumor suppressors and other critical genes both in experimental settings and in vivo. Interesting data have recently been published concerning mechanisms contributing to the cocarcinogenesis of hexavalent Cr and a model polycyclic aromatic hydrocarbon procarcinogen, benzo[a]pyrene. In mouse hepatoma cells, treatment with potassium chromate represses the expression of the benzo[a]pyrene-metabolizing Cyp1a1 enzyme, blocking the detoxification pathway, and consequently enhances the formation of benzo[a]pyrene diol epoxide-DNA adducts [212]. It was shown that Cr cross-links histone deacetylase 1-methyltransferase complexes to the Cyp1a1 promoter and inhibits gene transactivation. The same research group previously demonstrated approximately 50 other benzo[a]pyrene-inducible genes that were repressed by Cr in a similar manner, including receptor-associated kinases, transcription factors, and genes associated with cell cycle regulation, differentiation, and apoptosis [213]. In human lung adenocarcinoma cell line, potassium chromate induced global changes in various histone tail modifications, including an increase in H3K9 dimethylation in the promoter of the DNA mismatch repair gene, *hMLH1*, and a decrease of its expression [214]. Furthermore, hypermethylation of the promoter regions of several tumor suppressor genes, particularly *hMLH1*, *APC*, and *P16* genes, was recently reported in lung carcinomas of patients with over 15 years' occupational exposure to chromates [215, 216].

Nickel

All nickel [Ni(II)] compounds are classified into group I human carcinogens, which can cause nasal and lung cancer, and metallic nickel as possibly carcinogenic to humans (group 2B) [200]. Nickel is an abundant element in the Earth's crust. It is used in the metallurgical industry in the production of stainless steel and alloys, in electroplating, in stainless steel welding, in Ni-Cd batteries, and in the production of nanoparticles [217]. Nickel pollution in the environment originates from the combustion of fossil fuels in vehicles and power plants, industrial sources, waste incinerators, disposal of nickel compounds, and volcanic eruptions. Nickel also deposits in the soil and plants, which increases exposure via food, drinking water, and tobacco smoking.

Inhalation is the main route of exposure for workers exposed to carcinogenic nickel compounds in industry. While both soluble and poorly soluble nickel compounds are considered carcinogenic, water-insoluble compounds, which enter cells via phagocytosis, are readily dissolved in cellular lysosomes and generate high intracellular levels of Ni^{2+} cations and consequently exhibit higher cytotoxicity and genotoxicity [141]. Potential carcinogens are insoluble dusts of nickel subsulfides and nickel oxides, the vapor of nickel carbonyl, and the soluble aerosols of nickel sulfate, nitrate, or chloride [218].

The different mechanisms involved in nickel-induced carcinogenesis have been described in detail in several recent reviews [133, 134, 141, 142]. Although nickel compounds are not mutagenic in traditional mutation tests, they can induce malignant transformation in human and rodent cells [141, 219–223]. Soluble and insoluble nickel compounds induce genetic abnormalities, preferentially in heterochromatin. Genetic aberrations, such as DNA strand breaks, DNA-protein cross-links, deletion/insertion and single gene

mutations, sister chromatid exchanges, micronuclei, and microsatellite mutations, have been observed in mammalian or human cells in vitro [224].

Compared with Cd and Cr, Ni(II) is a weak inducer of oxidative stress [225, 226]. However, the reactivity of Ni(II) with oxygen derivatives can be modulated by chelation with certain histidine- and cysteine-containing ligands, and free radicals may arise from the reaction of Ni(II)-thiol complexes and molecular oxygen or lipid hydroperoxides [226]. G → T transversion mutations, typical of oxidative DNA damage, have been detected in codon 12 of K-ras oncogene in rat renal sarcomas induced with nickel subsulfide and iron [227]. Several nickel compounds have been shown to increase oxidative DNA damage and the formation of 8-hydroxydeoxyguanosine (8-OHdG) adducts in cultured cells and in rat lungs after intratracheal instillation of nickel compounds [228].

Epigenetic mechanisms are considered more important than genetic changes in nickel-induced carcinogenesis (see also Chap. 3 and Fig. 3.2). Nickel binds to heterochromatin rather than euchromatin, where it alters the heterochromatin structure, causing chromatin condensation, inhibition of histone H4 acetylation, and de novo DNA methylation [134, 141, 229, 230]. Histone acetylation is necessary for transcriptional activation. Nickel restricts the acetylation of histone H4 by binding with its N-terminal histidine-18 and by influencing histone acetyltransferase (HAT) activity [142, 231, 232]. Nickel also increases histone H3 lysine 9 dimethylation [233]. Chen et al. demonstrated that nickel inhibits the activation of dioxygenase enzymes, such as histone demethylase MJD1A and DNA repair enzyme ABH2, by replacing the nonheme iron at their catalytic center [234, 235]. The loss of histone acetylation and de novo DNA methylation silences genes, and the silencing of critical genes, such as tumor suppressor genes, contributes to carcinogenesis. The promoter of tumor suppressor gene *p16* has been constantly hypermethylated in the nickel sulfide-induced malignant fibrous histiocytomas of wild-type mice and mice heterozygous for the tumor suppressor *p53* gene [236]. Also, methylation has been observed in the enhancer regions of *RAR-β2*, *RASSF1A*, and *CDKN2A* genes of rat muscle tumors induced by nickel subsulfide [237].

Activation of hypoxic signaling is another main alteration with significance in nickel-induced carcinogenesis. Gene expression profiling with Affymetrix chips on wild-type or the hypoxia-inducible factor-1 (HIF-1) knockout mouse embryo cells found that after $NiCl_2$ treatment, 114 genes were upregulated and 66 genes downregulated in a manner characteristic of the activation of the hypoxic signaling pathway [238]. The HIF-1 transcription factor is a dimer consisting of two subunits, HIF-1α and HIF-1β (ARNT), which is formed in response to low oxygen tension in cells and, together with transcriptional co-activators, regulates the transactivation of HIF-dependent genes. HIF-1α acts as an oxygen sensor, which, in the presence of hypoxia or nickel, avoids ubiquitylation and proteasomal degradation and accumulates in cells [133]. Hypoxic signaling is thought to be one of the pathways that nickel exposure can induce by disrupting cellular iron homeostasis [239, 240]. In hypoxic cancer and stromal cells, HIF-1 transactivates growth and survival factors, such as VEGF, FGF, PAI-I, adrenomedullin, and NOS, which induce endothelial cell proliferation, migration, invasion, and angiogenesis [141].

Nickel influences carcinogenesis through a number of mechanisms not described in detail here, such as by inhibiting DNA repair, inducing *TP53* mutations, and influencing c-Myc, NF-κB, and MAPK signaling pathways, among others. Nucleotide and base excision repair pathways are impaired by nickel compounds, at least partially by the damage of zinc fingers in DNA repair proteins [241]. Nickel compounds induce carcinogenesis by a number of different mechanisms, including genetic and epigenetic changes, affecting signal transduction pathways, especially hypoxic signaling, and inhibiting DNA repair. There is evidence that nickel interferes with cellular metabolism by disrupting iron homeostasis and inhibiting the function of iron-dependent enzymes.

Mechanisms of Ionizing Radiation-Induced Carcinogenesis

Exposure via inhalation to uranium-containing particles and radon decay products, including high linear energy transfer (LET) alpha-particles, through the mining and processing of ore for nuclear power and weapons is associated with increased lung cancer risk [242]. Uranium is a radioactive heavy metal, the radioactivity of which is attributable to the ^{222}Rn and ^{220}Rn isotopes and their decay products. Studies among miners have been complicated by complex exposures to particulate and non-particulate matter in mines, including arsenic, silica, and diesel exhaust [243, 244].

Ionizing radiation (IR) produces reactive oxygen and nitrogen species that are responsible for oxidative stress and inflammatory response. The inflammatory reaction and oxidative damage are dependent on the dose of IR. Large deletions resulting in partial or complete deletion of entire genes and loss of heterozygosity in the neighboring chromosomal regions are the predominant event induced by alpha-irradiation in vitro [244, 245]. High-LET alpha-emitters including radon, plutonium, and Thorotrast induce double-strand breaks and clustered lesions, which are more difficult to repair than single-strand breaks and depurinated, oxidized, or deaminated bases, produced by low-LET X-rays and gamma-rays [246–250]. High-LET alpha-emitters also induce genomic instability through the inactivation of DNA mismatch repair [251, 252]. Most DNA damage produced by IR is repaired by base excision repair, and nucleotide excision repair, double-strand break repair, and mismatch repair

have lesser roles [253]. Erroneous rejoining of double-strand breaks can result in genomic instability.

In normal cells, IR induces apoptosis or cellular senescence through increased expression of tumor suppressor genes *P16*(*INK4A*) and *TP53* via the DNA damage response. An early study has reported a predominance of the *TP53* codon 249 AGGarg → ATGmet mutation in lung cancer of uranium miners, whereas subsequent studies have failed to show any mutational hotspots related to radon exposure [254, 255]. There is evidence that epigenetic changes are related to exposure to IR and its early biological effects. The cumulative exposure to radon gas in Chinese uranium miners correlated positively with promoter hypermethylation of the *P16*(*INK4A*) tumor suppressor and *O*^{6}*-methylguanine-DNA methyltransferase* (MGMT) DNA repair genes in sputum [256]. In another cohort of New Mexico uranium miners, exposure to radon gas did not increase the aberrant methylation of these genes in sputum, as compared to exposure to tobacco smoke alone [257]. Belinsky et al. have shown a higher prevalence of *P16*(*INK4A*) promoter methylation in the lung adenocarcinomas of workers exposed to ^{239}plutonium than that among non-exposed controls [258].

Conclusion

Many carcinogenic chemicals, including polycyclic aromatic hydrocarbons, present in combustion products and tobacco smoke, enter cells as procarcinogens and require metabolic activation by cytochrome P450 (CYP) enzymes to exert their deleterious effects, including binding to DNA and formation of DNA adducts which, if not repaired, may lead to mutations in critical genes and cancer initiation. The induction of oxygen radical damage is considered the main mechanism of particle and fiber carcinogenesis. In addition, asbestos fibers are clastogenic, giving rise to chromosomal aberrations. Carcinogenic metals are thought to induce oxidative stress-mediated DNA damage. Recent studies have shown that carcinogenic metals may replace metal ions, such as iron and zinc, in critical enzymes involved in DNA repair, histone methylation, and hypoxic signaling, for example. Epigenetic carcinogenic mechanisms have recently been found to play a larger role than previously thought, in environmental carcinogenesis.

Acknowledgments The writing of this chapter was financially supported by the Jalmari and Rauha Ahokas Foundation, Helsinki (PN), and Helsinki and Uusimaa Health Care District Research Funds (SA).

References

1. Barrett JC, Lamb PW, Wiseman RW. Multiple mechanisms for the carcinogenic effects of asbestos and other mineral fibers. Environ Health Perspect. 1989;81:81–9.
2. Nymark P, Wikman H, Hienonen-Kempas T, Anttila S. Molecular and genetic changes in asbestos-related lung cancer. Cancer Lett. 2008;265(1):1–15.
3. Puhakka A, Ollikainen T, Soini Y, et al. Modulation of DNA single-strand breaks by intracellular glutathione in human lung cells exposed to asbestos fibers. Mutat Res. 2002;514(1–2):7–17.
4. Mossman BT, Churg A. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1666–80.
5. Donaldson K, Brown G, Brown D, Bolton R, Davis J. Inflammation generating potential of long and short fibre amosite asbestos samples. Br J Ind Med. 1989;46(4):271–6.
6. Dodson RF, Atkinson MAL, Levin JL. Asbestos fiber length as related to potential pathogenicity: a critical review. Am J Ind Med. 2003;44(3):291–7.
7. Anttila S, Karjalainen A, Taikina-aho O, Kyyrönen P, Vainio H. Lung cancer in the lower lobe is associated with pulmonary asbestos fiber count and fiber size. Environ Health Perspect. 1993;101(2):166–70.
8. Stanton M, Wrench C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. J Natl Cancer Inst. 1972;48(3):797–821.
9. Bernstein DM, Hoskins JA. The health effects of chrysotile: current perspective based upon recent data. Regul Toxicol Pharmacol. 2006;45(3):252–64.
10. Kamp DW. Asbestos-induced lung diseases: an update. Transl Res. 2009;153(4):143–52.
11. Nicholson W. The carcinogenicity of chrysotile asbestos–a review. Ind Health. 2001;39(2):57–64.
12. Pezerat H. Chrysotile biopersistence: the misuse of biased studies. Int J Occup Environ Health. 2009;15(1):102–6.
13. Suzuki Y, Yuen S, Ashley R. Short, thin asbestos fibers contribute to the development of human malignant mesothelioma: pathological evidence. Int J Hyg Environ Health. 2005;208(3):201–10.
14. Landrigan P, Nicholson W, Suzuki Y, Ladou J. The hazards of chrysotile asbestos: a critical review. Ind Health. 1999;37(3):271–80.
15. Mossman BT, Lippmann M, Hesterberg TW, Kelsey KT, Barchowsky A, Bonner JC. Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. J Toxicol Environ Health. 2011;14(1–4):76–121.
16. Lund LG, Aust AE. Iron mobilization from crocidolite asbestos greatly enhances crocidolite-dependent formation of DNA single-strand breaks in oX174 RFI DNA. Carcinogenesis. 1992;13(4):637–42.
17. Gazzano E, Turci F, Foresti E, et al. Iron-loaded synthetic chrysotile: a new model solid for studying the role of iron in asbestos toxicity. Chem Res Toxicol. 2007;20(3):380–7.
18. Jaurand MC. Mechanisms of fiber-induced genotoxicity. Environ Health Perspect. 1997;105 Suppl 5:1073–84.
19. Upadhyay D, Kamp DW. Asbestos-induced pulmonary toxicity: role of DNA damage and apoptosis. Exp Biol Med (Maywood, NJ). 2003;228(6):650–9.
20. Husgafvel-Pursiainen K, Hackman P, Ridanpaa M, et al. K-ras mutations in human adenocarcinoma of the lung: association with smoking and occupational exposure to asbestos. Int J Cancer. 1993;53(2):250–6.
21. Nelson HH, Christiani DC, Wiencke JK, Mark EJ, Wain JC, Kelsey KT. k-ras mutation and occupational asbestos exposure in lung adenocarcinoma: asbestos-related cancer without asbestosis. Cancer Res. 1999;59(18):4570–3.
22. Husgafvel-Pursiainen K, Karjalainen A, Kannio A, et al. Lung cancer and past occupational exposure to asbestos. Role of p53 and K-ras mutations. Am J Respir Cell Mol Biol. 1999;20(4):667–74.
23. Kamp DW, Shacter E, Weitzman SA. Chronic inflammation and cancer: the role of the mitochondria. Oncology (Williston Park, NY). 2011;25(5):400–410, 413.
24. Fan J, Wang Q, Liu S. Chrysotile-induced cell transformation and transcriptional changes of c-myc oncogene in human embryo lung cells. Biomed Environ Sci. 2000;13(3):163–9.
25. Cheng N, Shi X, Ye J, et al. Role of transcription factor NF-[kappa] B in asbestos-induced TNF[alpha] response from macrophages. Exp Mol Pathol. 1999;66(3):201–10.
26. Xie C, Reusse A, Dai J, Zay K, Harnett J, Churg A. TNF-alpha increases tracheal epithelial asbestos and fiberglass binding via a

NF-kappa B-dependent mechanism. Am J Physiol Lung Cell Mol Physiol. 2000;279(3):L608–14.
27. Bhattacharya K, Dopp E, Kakkar P, et al. Biomarkers in risk assessment of asbestos exposure. Mutation research/fundamental and molecular mechanisms of mutagenesis/inflammation, cellular and redox signalling mechanisms in cancer and degenerative diseases. Mutation Research. 2005;579(1–2):6–21.
28. Simeonova P, Toriumi W, Kommineni C, et al. Molecular regulation of IL-6 activation by asbestos in lung epithelial cells: role of reactive oxygen species. J Immunol. 1997;159(8):3921–8.
29. Lange A, Karabon L, Tomeczko J. Interleukin-6- and interleukin-4-related proteins (C-reactive protein and IgE) are prognostic factors of asbestos-related cancer. Ann NY Acad Sci. 1995;762:435–8.
30. Luster M, Simeonova P. Asbestos induces inflammatory cytokines in the lung through redox sensitive transcription factors. Toxicol Lett. 1998;102–103:271–5.
31. Miura Y, Nishimura Y, Katsuyama H, et al. Involvement of IL-10 and Bcl-2 in resistance against an asbestos-induced apoptosis of T cells. Apoptosis. 2006;11(10):1825–35.
32. Yuan Z, Taatjes DJ, Mossman BT, Heintz NH. The duration of nuclear extracellular signal-regulated kinase 1 and 2 signaling during cell cycle reentry distinguishes proliferation from apoptosis in response to asbestos. Cancer Res. 2004;64(18):6530–6.
33. Barlow CA, Barrett TF, Shukla A, Mossman BT, Lounsbury KM. Asbestos-mediated CREB phosphorylation is regulated by protein kinase A and extracellular signal-regulated kinases 1/2. Am J Physiol Lung Cell Mol Physiol. 2007;292(6):L1361–9.
34. Shukla A, Jung M, Stern M, et al. Asbestos induces mitochondrial DNA damage and dysfunction linked to the development of apoptosis. Am J Physiol Lung Cell Mol Physiol. 2003;285(5):L1018–25.
35. Zhao Y, Piao C, Hei T. Downregulation of Betaig-h3 gene is causally linked to tumorigenic phenotype in asbestos treated immortalized human bronchial epithelial cells. Oncogene. 2002;21(49):7471–7.
36. Nymark P, Lindholm P, Korpela M, et al. Specific gene expression profiles in asbestos-exposed epithelial and mesothelial lung cell lines. BMC Genomics. 2007;8:62.
37. Kamp D, Panduri V, Weitzman S, Chandel N. Asbestos-induced alveolar epithelial cell apoptosis: role of mitochondrial dysfunction caused by iron-derived free radicals. Mol Cell Biochem. 2002;234–235(1–2):153–60.
38. Wang X, Samet JM, Ghio AJ. Asbestos-induced activation of cell signaling pathways in human bronchial epithelial cells. Exp Lung Res. 2006;32(6):229–43.
39. Zanella CL, Posada J, Tritton TR, Mossman BT. Asbestos causes stimulation of the extracellular signal-regulated kinase 1 mitogen-activated protein kinase cascade after phosphorylation of the epidermal growth factor receptor. Cancer Res. 1996;56(23):5334–8.
40. Mossman BT, Lounsbury KM, Reddy SP. Oxidants and signaling by mitogen-activated protein kinases in lung epithelium. Am J Respir Cell Mol Biol. 2006;34(6):666–9.
41. Shukla A, Flanders T, Lounsbury KM, Mossman BT. The {gamma}-glutamylcysteine synthetase and glutathione regulate asbestos-induced expression of activator protein-1 family members and activity. Cancer Res. 2004;64(21):7780–6.
42. Manning CB, Cummins AB, Jung MW, et al. A mutant epidermal growth factor receptor targeted to lung epithelium inhibits asbestos-induced proliferation and proto-oncogene expression. Cancer Res. 2002;62(15):4169–75.
43. Timblin CR, Janssen YWM, Mossman BT. Transcriptional activation of the proto-oncogene c-jun by asbestos and H2O2 is directly related to increased proliferation and transformation of tracheal epithelial cells. Cancer Res. 1995;55(13):2723–6.
44. Zhao YL, Piao CQ, Wu LJ, Suzuki M, Hei TK. Differentially expressed genes in asbestos-induced tumorigenic human bronchial epithelial cells: implication for mechanism. Carcinogenesis. 2000;21(11):2005–10.
45. Haegens A, van der Vliet A, Butnor KJ, et al. Asbestos-induced lung inflammation and epithelial cell proliferation are altered in myeloperoxidase-null mice. Cancer Res. 2005;65(21):9670–7.
46. Brody A. Asbestos-induced lung disease. Environ Health Perspect. 1993;100:21–30.
47. Shukla A, Barrett TF, Nakayama KI, Nakayama K, Mossman BT, Lounsbury KM. Transcriptional up-regulation of MMP12 and MMP13 by asbestos occurs via a PKC{delta}-dependent pathway in murine lung. FASEB J. 2006;20(7):997–9.
48. Morimoto Y, Tsuda T, Nakamura H, et al. Expression of matrix metalloproteinases, tissue inhibitors of metalloproteinases, and extracellular matrix mRNA following exposure to mineral fibers and cigarette smoke in vivo. Environ Health Perspect. 1997;105 Suppl 5:1247–51.
49. Lounsbury KM, Stern M, Taatjes D, Jaken S, Mossman BT. Increased localization and substrate activation of protein kinase C{delta} in lung epithelial cells following exposure to asbestos. Am J Pathol. 2002;160(6):1991–2000.
50. Shukla A, Lounsbury KM, Barrett TF, et al. Asbestos-induced peribronchiolar cell proliferation and cytokine production are attenuated in lungs of protein kinase C-{delta} knockout mice. Am J Pathol. 2007;170(1):140–51.
51. Wikman H, Ruosaari S, Nymark P, et al. Gene expression and copy number profiling suggests the importance of allelic imbalance in 19p in asbestos-associated lung cancer. Oncogene. 2007;26(32):4730–7.
52. Scapoli L, Ramos-Nino M, Martinelli M, Mossman B. Src-dependent ERK5 and Src/EGFR-dependent ERK1/2 activation is required for cell proliferation by asbestos. Oncogene. 2004;23(3):805–13.
53. Barchowsky A, Lannon B, Elmore L, Treadwell M. Increased focal adhesion kinase- and urokinase-type plasminogen activator receptor-associated cell signaling in endothelial cells exposed to asbestos. Environ Health Perspect. 1997;105 Suppl 5:1131–7.
54. Daniel F. In vitro assessment of asbestos genotoxicity. Environ Health Perspect. 1983;53:163–7.
55. Hei TK, Piao CQ, He ZY, Vannais D, Waldren CA. Chrysotile fiber is a strong mutagen in mammalian cells. Cancer Res. 1992;52(22):6305–9.
56. Dopp E, Schuler M, Schiffmann D, Eastmond DA. Induction of micronuclei, hyperdiploidy and chromosomal breakage affecting the centric/pericentric regions of chromosomes 1 and 9 in human amniotic fluid cells after treatment with asbestos and ceramic fibers. Mutation Res/Fundam Mol Mech Mutagen. 1997;377(1):77–87.
57. Dopp E, Yadav S, Ansari F, et al. ROS-mediated genotoxicity of asbestos-cement in mammalian lung cells in vitro. Part Fibre Toxicol 2005;2:9.
58. Fatma N, Jain A, Rahman Q. Frequency of sister chromatid exchange and chromosomal aberrations in asbestos cement workers. Br J Ind Med. 1991;48(2):103–5.
59. Fatma N, Khan S, Aslam M, Rahman Q. Induction of chromosomal aberrations in bone marrow cells of asbestotic rats. Environ Res. 1992;57(2):175–80.
60. Hardy JA, Aust AE. The effect of iron binding on the ability of crocidolite asbestos to catalyze DNA single-strand breaks. Carcinogenesis. 1995;16(2):319–25.
61. Lu J, Keane M, Ong T, Wallace W. In vitro genotoxicity studies of chrysotile asbestos fibers dispersed in simulated pulmonary surfactant. Mutat Res. 1994;320(4):253–9.
62. Marczynski B, Czuppon A, Marek W, Reichel G, Baur X. Increased incidence of DNA double-strand breaks and anti-ds DNA antibodies in blood of workers occupationally exposed to asbestos. Hum Exp Toxicol. 1994;13(1):3–9.
63. Hei TK, He ZY, Suzuki K. Effects of antioxidants on fiber mutagenesis. Carcinogenesis. 1995;16(7):1573–8.
64. Msiska Z, Pacurari M, Mishra A, Leonard SS, Castranova V, Vallyathan V. DNA double strand breaks by asbestos, silica and titanium dioxide: possible biomarker of carcinogenic potential. Am J Respir Cell Mol Biol 2009:2009-0062OC.

65. Huang S, Saggioro D, Michelmann H, Malling H. Genetic effects of crocidolite asbestos in Chinese hamster lung cells. Mutat Res. 1978;57(2):225–32.
66. Lohani M, Dopp E, Becker H-H, Seth K, Schiffmann D, Rahman Q. Smoking enhances asbestos-induced genotoxicity, relative involvement of chromosome 1: a study using multicolor FISH with tandem labeling. Toxicol Lett. 2002;136(1):55–63.
67. Xu A, Smilenov L, He P, et al. New insight into intrachromosomal deletions induced by chrysotile in the gpt delta transgenic mutation assay. Environ Health Perspect. 2007;115(1):87–92.
68. Jensen C, Jensen L, Rieder C, Cole R, Ault J. Long crocidolite asbestos fibers cause polyploidy by sterically blocking cytokinesis. Carcinogenesis. 1996;17(9):2013–21.
69. Valerio F, De Ferrari M, Ottaggio L, Repetto E, Santi L. Cytogenetic effects of Rhodesian chrysotile on human lymphocytes in vitro. IARC Sci Publ. 1980;30:485–9.
70. Andujar P, Wang J, Descatha A, et al. p16INK4A inactivation mechanisms in non-small-cell lung cancer patients occupationally exposed to asbestos. Lung Cancer (Amsterdam, Netherlands). 2010;67(1):23–30.
71. Kettunen E, Aavikko M, Nymark P, et al. DNA copy number loss and allelic imbalance at 2p16 in lung cancer associated with asbestos exposure. Br J Cancer. 2009;100(8):1336–42.
72. Marsit CJ, Hasegawa M, Hirao T, et al. Loss of heterozygosity of chromosome 3p21 is associated with mutant TP53 and better patient survival in non-small-cell lung cancer. Cancer Res. 2004;64(23):8702–7.
73. Nymark P, Wikman H, Ruosaari S, et al. Identification of specific gene copy number changes in asbestos-related lung cancer. Cancer Res. 2006;66(11):5737–43.
74. Nymark P, Kettunen E, Aavikko M, et al. Molecular alterations at 9q33.1 and polyploidy in asbestos-related lung cancer. Clin Cancer Res. 2009;15(2):468–75.
75. Ruosaari ST, Nymark PE, Aavikko MM, et al. Aberrations of chromosome 19 in asbestos-associated lung cancer and in asbestos-induced micronuclei of bronchial epithelial cells in vitro. Carcinogenesis. 2008;29(5):913–7.
76. Dehan E, Ben-Dor A, Liao W, et al. Chromosomal aberrations and gene expression profiles in non-small cell lung cancer. Lung Cancer. 2007;56(2):175–84.
77. Suzuki M, Piao C, Zhao Y, Hei T. Karyotype analysis of tumorigenic human bronchial epithelial cells transformed by chrysolite asbestos using chemically induced premature chromosome condensation technique. Int J Mol Med. 2001;8(1):43–7.
78. Ivanov SV, Miller J, Lucito R, et al. Genomic events associated with progression of pleural malignant mesothelioma. Int J Cancer. 2009;124(3):589–99.
79. Mossman BT, Lippmann M, Hesterberg TW, Kelsey KT, Barchowsky A, Bonner JC. Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. J Toxicol Environ Health Part B. 2011;14(1–4):76–121.
80. Dammann R, Strunnikova M, Schagdarsurengin U, et al. CpG island methylation and expression of tumour-associated genes in lung carcinoma. Eur J Cancer. 2005;41(8):1223–36.
81. Kraunz KS, Nelson HH, Lemos M, Godleski JJ, Wiencke JK, Kelsey KT. Homozygous deletion of p16/INK4a and tobacco carcinogen exposure in nonsmall cell lung cancer. Int J Cancer. 2006;118(6):1364–9.
82. Nymark P, Guled M, Borze I, et al. Integrative analysis of microRNA, mRNA and aCGH data reveals asbestos- and histology-related changes in lung cancer. Genes Chromosomes Cancer. 2011;50(8):585–97.
83. Ruosaari S, Hienonen-Kempas T, Puustinen A, et al. Pathways affected by asbestos exposure in normal and tumour tissue of lung cancer patients. BMC Med Genomics. 2008;1:55.
84. Nelson H, Kelsey K. The molecular epidemiology of asbestos and tobacco in lung cancer. Oncogene. 2002;21(48):7284–8.
85. Henderson D, Rödelsperger K, Woitowitz H, Leigh J. After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004. Pathology. 2004;36(6):517–50.
86. Churg A, Hobson J, Berean K, Wright J. Scavengers of active oxygen species prevent cigarette smoke-induced asbestos fiber penetration in rat tracheal explants. Am J Pathol. 1989;135(4):599–603.
87. Fournier J, Pezerat H. Studies on surface properties of asbestos: III. Interactions between asbestos and polynuclear aromatic hydrocarbons. Environ Res. 1986;41(1):276–95.
88. Flowers N, Miles P. Alterations of pulmonary benzo[a]pyrene metabolism by reactive oxygen metabolites. Toxicology. 1991;68(3):259–74.
89. Haugen A, Harris C. Asbestos carcinogenesis: asbestos interactions and epithelial lesions in cultured human tracheobronchial tissues and cells. Recent Results Cancer Res. 1982;82:32–42.
90. Liu G, Beri R, Mueller A, Kamp DW. Molecular mechanisms of asbestos-induced lung epithelial cell apoptosis. Chem Biol Interact. 2010;188(2):309–18.
91. Moyer V, Cistulli C, Vaslet C, Kane A. Oxygen radicals and asbestos carcinogenesis. Environ Health Perspect. 1994;102 Suppl 10:131–6.
92. Loli P, Topinka J, Georgiadis P, et al. Benzo[a]pyrene-enhanced mutagenesis by asbestos in the lung of lambda-lacI transgenic rats. Mutat Res. 2004;553(1–2):79–90.
93. Hansen AM, Mathiesen L, Pedersen M, Knudsen LE. Urinary 1-hydroxypyrene (1-HP) in environmental and occupational studies–a review. Int J Hyg Environ Health. 2008;211(5–6):471–503.
94. Georgiadis P, Stoikidou M, Topinka J, et al. Personal exposures to PM(2.5) and polycyclic aromatic hydrocarbons and their relationship to environmental tobacco smoke at two locations in Greece. J Expo Anal Environ Epidemiol. 2001;11(3):169–83.
95. Liu HH, Yang HH, Chou CD, Lin MH, Chen HL. Risk assessment of gaseous/particulate phase PAH exposure in foundry industry. J Hazard Mater. 2010;181(1–3):105–111.
96. Knecht U, Elliehausen HJ, Woitowitz HJ. Gaseous and adsorbed PAH in an iron foundry. Br J Ind Med. 1986;43(12):834–8.
97. Pleil JD, Vette AF, Rappaport SM. Assaying particle-bound polycyclic aromatic hydrocarbons from archived PM2.5 filters. J Chromatogr. 2004;1033(1):9–17.
98. Luceri F, Pieraccini G, Moneti G, Dolara P. Primary aromatic amines from side-stream cigarette smoke are common contaminants of indoor air. Toxicol Ind Health. 1993;9(3):405–13.
99. Grimmer G, Naujack KW, Dettbarn G. Gas chromatographic determination of polycyclic aromatic hydrocarbons, aza-arenes, aromatic amines in the particle and vapor phase of mainstream and sidestream smoke of cigarettes. Toxicol Lett. 1987;35(1):117–24.
100. Guerin M, Jenkins RA, Tomkins BA. Mainstream and sidestream cigarette smoke. In: Eisenberg M, editor. The chemistry of environmental tobacco smoke: composition and measurement. Chelsea: Lewis Publishers; 1992.
101. IARC. Tobacco smoke and involuntary smoking. IARC monographs on the evaluation of carcinogenic risks to human. Lyon: IARC; 2004.
102. Lodovici M, Akpan V, Evangelisti C, Dolara P. Sidestream tobacco smoke as the main predictor of exposure to polycyclic aromatic hydrocarbons. J Appl Toxicol. 2004;24(4):277–81.
103. Lee HL, Hsieh DP, Li LA. Polycyclic aromatic hydrocarbons in cigarette sidestream smoke particulates from a Taiwanese brand and their carcinogenic relevance. Chemosphere. 2011;82(3):477–482.
104. Bock KW, Köhle C. The mammalian aryl hydrocarbon (Ah) receptor: from mediator of dioxin toxicity toward physiological functions in skin and liver. Biol Chem. 2009;390(12):1225–35.

105. Fujii-Kuriyama Y, Kawajiri K. Molecular mechanisms of the physiological functions of the aryl hydrocarbon (dioxin) receptor, a multifunctional regulator that senses and responds to environmental stimuli. Proc Jpn Acad. 2010;86(1):40–53.
106. Shimada T. Xenobiotic-metabolizing enzymes involved in activation and detoxification of carcinogenic polycyclic aromatic hydrocarbons. Drug Metab Pharmacokinet. 2006;21(4): 257–76.
107. Bui PH, Hankinson O. Functional characterization of human cytochrome P450 2S1 using a synthetic gene-expressed protein in Escherichia coli. Mol Pharmacol. 2009;76(5):1031–43.
108. Anttila S, Raunio H, Hakkola J. Cytochrome p450-mediated pulmonary metabolism of carcinogens: regulation and cross-talk in lung carcinogenesis. Am J Respir Cell Mol Biol. 2011;44(5): 583–90.
109. Melendez-Colon VJ, Luch A, Seidel A, Baird WM. Comparison of cytochrome P450- and peroxidase-dependent metabolic activation of the potent carcinogen dibenzo[a, l]pyrene in human cell lines: formation of stable DNA adducts and absence of a detectable increase in apurinic sites. Cancer Res. 1999;59(7): 1412–6.
110. Jiang H, Shen YM, Quinn AM, Penning TM. Competing roles of cytochrome P450 1A1/1B1 and aldo-keto reductase 1A1 in the metabolic activation of (+/−)-7,8-dihydroxy-7,8-dihydro-benzo[a] pyrene in human bronchoalveolar cell extracts. Chem Res Toxicol. 2005;18(2):365–74.
111. Palackal NT, Burczynski ME, Harvey RG, Penning TM. The ubiquitous aldehyde reductase (AKR1A1) oxidizes proximate carcinogen trans-dihydrodiols to o-quinones: potential role in polycyclic aromatic hydrocarbon activation. Biochemistry. 2001;40(36):10901–10.
112. Denissenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. Sci (New York, NY). 1996;274(5286):430–2.
113. Hussain SP, Amstad P, Raja K, et al. Mutability of p53 hotspot codons to benzo(a)pyrene diol epoxide (BPDE) and the frequency of p53 mutations in nontumorous human lung. Cancer Res. 2001;61(17):6350–5.
114. Yoon JH, Smith LE, Feng Z, Tang M, Lee CS, Pfeifer GP. Methylated CpG dinucleotides are the preferential targets for G-to-T transversion mutations induced by benzo[a]pyrene diol epoxide in mammalian cells: similarities with the p53 mutation spectrum in smoking-associated lung cancers. Cancer Res. 2001;61(19):7110–7.
115. Köhle C, Bock KW. Coordinate regulation of Phase I and II xenobiotic metabolisms by the Ah receptor and Nrf2. Biochem Pharmacol. 2007;73(12):1853–62.
116. Yeager RL, Reisman SA, Aleksunes LM, Klaassen CD. Introducing the "TCDD-inducible AhR-Nrf2 gene battery". Toxicol Sci. 2009;111(2):238–46.
117. Itoh K, Chiba T, Takahashi S, et al. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem Biophys Res Commun. 1997;236(2):313–22.
118. Jaiswal AK. Regulation of genes encoding NAD(P)H:quinone oxidoreductases. Free Radic Biol Med. 2000;29(3–4): 254–62.
119. Shibata T, Ohta T, Tong KI, et al. Cancer related mutations in NRF2 impair its recognition by Keap1-Cul3 E3 ligase and promote malignancy. Proc Natl Acad Sci U S A. 2008;105(36): 13568–73.
120. Singh A, Misra V, Thimmulappa RK, et al. Dysfunctional KEAP1-NRF2 interaction in non-small-cell lung cancer. PLoS Med. 2006;3(10):e420.
121. Wang R, An J, Ji F, Jiao H, Sun H, Zhou D. Hypermethylation of the Keap1 gene in human lung cancer cell lines and lung cancer tissues. Biochem Biophys Res Commun. 2008;373(1):151–4.
122. Hayes JD, McMahon M. NRF2 and KEAP1 mutations: permanent activation of an adaptive response in cancer. Trends Biochem Sci. 2009;34(4):176–88.
123. Kotlo KU, Yehiely F, Efimova E, et al. Nrf2 is an inhibitor of the Fas pathway as identified by Achilles' Heel method, a new function-based approach to gene identification in human cells. Oncogene. 2003;22(6):797–806.
124. Morito N, Yoh K, Itoh K, et al. Nrf2 regulates the sensitivity of death receptor signals by affecting intracellular glutathione levels. Oncogene. 2003;22(58):9275–81.
125. Kim SY, Kim TJ, Lee KY. A novel function of peroxiredoxin 1 (Prx-1) in apoptosis signal-regulating kinase 1 (ASK1)-mediated signaling pathway. FEBS Lett. 2008;582(13):1913–8.
126. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 2006;160(1):1–40.
127. Kasai H, Iwamoto-Tanaka N, Miyamoto T, et al. Life style and urinary 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage: effects of exercise, working conditions, meat intake, body mass index, and smoking. Jpn J Cancer Res. 2001;92(1): 9–15.
128. Tamae K, Kawai K, Yamasaki S, et al. Effect of age, smoking and other lifestyle factors on urinary 7-methylguanine and 8-hydroxydeoxyguanosine. Cancer Sci. 2009;100(4): 715–21.
129. Collins AR. The comet assay for DNA damage and repair: principles, applications, and limitations. Mol Biotechnol. 2004;26(3): 249–61.
130. Tarantini A, Maitre A, Lefebvre E, et al. Relative contribution of DNA strand breaks and DNA adducts to the genotoxicity of benzo[a]pyrene as a pure compound and in complex mixtures. Mutat Res. 2009;671(1–2):67–75.
131. Huang C, Ke Q, Costa M, Shi X. Molecular mechanisms of arsenic carcinogenesis. Mol Cell Biochem. 2004;255(1–2):57–66.
132. Shi H, Shi X, Liu KJ. Oxidative mechanism of arsenic toxicity and carcinogenesis. Mol Cell Biochem. 2004;255(1–2):67–78.
133. Salnikow K, Zhitkovich A. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. Chem Res Toxicol. 2008;21(1):28–44.
134. Arita A, Costa M. Epigenetics in metal carcinogenesis: nickel, arsenic, chromium and cadmium. Metallomics. 2009;1(3): 222–8.
135. Hollins DM, McKinley MA, Williams C, et al. Beryllium and lung cancer: a weight of evidence evaluation of the toxicological and epidemiological literature. Crit Rev Toxicol. 2009;39 Suppl 1: 1–32.
136. Gordon T, Bowser D. Beryllium: genotoxicity and carcinogenicity. Mutat Res. 2003;533(1–2):99–105.
137. Joseph P. Mechanisms of cadmium carcinogenesis. Toxicol Appl Pharmacol. 2009;238(3):272–9.
138. Liu J, Qu W, Kadiiska MB. Role of oxidative stress in cadmium toxicity and carcinogenesis. Toxicol Appl Pharmacol. 2009;238(3): 209–14.
139. Nickens KP, Patierno SR, Ceryak S. Chromium genotoxicity: a double-edged sword. Chem Biol Interact. 2010;188(2):276–288.
140. Zhitkovich A. Importance of chromium-DNA adducts in mutagenicity and toxicity of chromium(VI). Chem Res Toxicol. 2005;18(1):3–11.
141. Lu H, Shi X, Costa M, Huang C. Carcinogenic effect of nickel compounds. Mol Cell Biochem. 2005;279(1–2):45–67.
142. Cameron KS, Buchner V, Tchounwou PB. Exploring the molecular mechanisms of nickel-induced genotoxicity and carcinogenicity: a literature review. Rev Environ Health. 2011;26(2):81–92.
143. IARC. Some metals and metallic compounds. IARC monographs on the evaluation of carcinogenic risk to human. Lyon: IARC; 1980.
144. Cohen SM, Arnold LL, Eldan M, Lewis AS, Beck BD. Methylated arsenicals: the implications of metabolism and carcinogenicity

studies in rodents to human risk assessment. Crit Rev Toxicol. 2006;36(2):99–133.
145. Kitchin KT. Recent advances in arsenic carcinogenesis: modes of action, animal model systems, and methylated arsenic metabolites. Toxicol Appl Pharmacol. 2001;172(3):249–61.
146. Styblo M, Del Razo LM, Vega L, et al. Comparative toxicity of trivalent and pentavalent inorganic and methylated arsenicals in rat and human cells. Arch Toxicol. 2000;74(6): 289–99.
147. Yamanaka K, Takabayashi F, Mizoi M, An Y, Hasegawa A, Okada S. Oral exposure of dimethylarsinic acid, a main metabolite of inorganic arsenics, in mice leads to an increase in 8-Oxo-2′-deoxyguanosine level, specifically in the target organs for arsenic carcinogenesis. Biochem Biophys Res Commun. 2001;287(1): 66–70.
148. Matsui M, Nishigori C, Toyokuni S, et al. The role of oxidative DNA damage in human arsenic carcinogenesis: detection of 8-hydroxy-2′-deoxyguanosine in arsenic-related Bowen's disease. J Invest Dermatol. 1999;113(1):26–31.
149. Wanibuchi H, Hori T, Meenakshi V, et al. Promotion of rat hepatocarcinogenesis by dimethylarsinic acid: association with elevated ornithine decarboxylase activity and formation of 8-hydroxydeoxyguanosine in the liver. Jpn J Cancer Res. 1997;88(12):1149–54.
150. Hei TK, Liu SX, Waldren C. Mutagenicity of arsenic in mammalian cells: role of reactive oxygen species. Proc Natl Acad Sci USA. 1998;95(14):8103–7.
151. Barrett JC, Lamb PW, Wang TC, Lee TC. Mechanisms of arsenic-induced cell transformation. Biol Trace Elem Res. 1989;21: 421–9.
152. Nakamuro K, Sayato Y. Comparative studies of chromosomal aberration induced by trivalent and pentavalent arsenic. Mutat Res. 1981;88(1):73–80.
153. Dong JT, Luo XM. Arsenic-induced DNA-strand breaks associated with DNA-protein crosslinks in human fetal lung fibroblasts. Mutat Res. 1993;302(2):97–102.
154. Mouron SA, Golijow CD, Dulout FN. DNA damage by cadmium and arsenic salts assessed by the single cell gel electrophoresis assay. Mutat Res. 2001;498(1–2):47–55.
155. Lee-Chen SF, Gurr JR, Lin IB, Jan KY. Arsenite enhances DNA double-strand breaks and cell killing of methyl methanesulfonate-treated cells by inhibiting the excision of alkali-labile sites. Mutat Res. 1993;294(1):21–8.
156. Hartmann A, Speit G. Comparative investigations of the genotoxic effects of metals in the single cells gel (SCG) assay and the sister chromatid exchange (SCE) test. Environ Mol Mutagen. 1994; 23(4):299–305.
157. Wang TS, Hsu TY, Chung CH, Wang AS, Bau DT, Jan KY. Arsenite induces oxidative DNA adducts and DNA-protein cross-links in mammalian cells. Free Radic Biol Med. 2001;31(3):321–30.
158. Li JH, Rossman TG. Inhibition of DNA ligase activity by arsenite: a possible mechanism of its comutagenesis. Mol Toxicol. 1989;2(1):1–9.
159. Lynn S, Lai HT, Gurr JR, Jan KY. Arsenite retards DNA break rejoining by inhibiting DNA ligation. Mutagenesis. 1997;12(5): 353–8.
160. Hu Y, Su L, Snow ET. Arsenic toxicity is enzyme specific and its affects on ligation are not caused by the direct inhibition of DNA repair enzymes. Mutat Res. 1998;408(3):203–18.
161. Taeger D, Johnen G, Wiethege T, et al. Major histopathological patterns of lung cancer related to arsenic exposure in German uranium miners. Int Arch Occup Environ Health. 2009;82(7): 867–75.
162. Guo HR, Wang NS, Hu H, Monson RR. Cell type specificity of lung cancer associated with arsenic ingestion. Cancer Epidemiol Biomarkers Prev. 2004;13(4):638–43.
163. Martinez VD, Buys TP, Adonis M, et al. Arsenic-related DNA copy-number alterations in lung squamous cell carcinomas. Br J Cancer. 2010;103(8):1277–1283.
164. Zhao CQ, Young MR, Diwan BA, Coogan TP, Waalkes MP. Association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Proc Natl Acad Sci U S A. 1997;94(20):10907–12.
165. Zhou X, Sun H, Ellen TP, Chen H, Costa M. Arsenite alters global histone H3 methylation. Carcinogenesis. 2008;29(9):1831–6.
166. Marsit CJ, Karagas MR, Schned A, Kelsey KT. Carcinogen exposure and epigenetic silencing in bladder cancer. Ann N Y Acad Sci. 2006;1076:810–21.
167. Cui X, Wakai T, Shirai Y, Hatakeyama K, Hirano S. Chronic oral exposure to inorganic arsenate interferes with methylation status of p16INK4a and RASSF1A and induces lung cancer in A/J mice. Toxicol Sci. 2006;91(2):372–81.
168. Chai CY, Huang YC, Hung WC, Kang WY, Chen WT. Arsenic salt-induced DNA damage and expression of mutant p53 and COX-2 proteins in SV-40 immortalized human uroepithelial cells. Mutagenesis. 2007;22(6):403–8.
169. Chen WT, Hung WC, Kang WY, Huang YC, Chai CY. Urothelial carcinomas arising in arsenic-contaminated areas are associated with hypermethylation of the gene promoter of the death-associated protein kinase. Histopathology. 2007;51(6): 785–92.
170. Mass MJ, Wang L. Arsenic alters cytosine methylation patterns of the promoter of the tumor suppressor gene p53 in human lung cells: a model for a mechanism of carcinogenesis. Mutat Res. 1997;386(3):263–77.
171. Chanda S, Dasgupta UB, Guhamazumder D, et al. DNA hypermethylation of promoter of gene p53 and p16 in arsenic-exposed people with and without malignancy. Toxicol Sci. 2006;89(2): 431–7.
172. Zhou X, Li Q, Arita A, Sun H, Costa M. Effects of nickel, chromate, and arsenite on histone 3 lysine methylation. Toxicol Appl Pharmacol. 2009;236(1):78–84.
173. Rossman TG, Uddin AN, Burns FJ. Evidence that arsenite acts as a cocarcinogen in skin cancer. Toxicol Appl Pharmacol. 2004; 198(3):394–404.
174. Li JH, Rossman TG. Mechanism of comutagenesis of sodium arsenite with n-methyl-n-nitrosourea. Biol Trace Elem Res. 1989;21:373–81.
175. Li JH, Rossman TG. Comutagenesis of sodium arsenite with ultraviolet radiation in Chinese hamster V79 cells. Biol Metals. 1991;4(4):197–200.
176. Lee TC, Huang RY, Jan KY. Sodium arsenite enhances the cytotoxicity, clastogenicity, and 6-thioguanine-resistant mutagenicity of ultraviolet light in Chinese hamster ovary cells. Mutat Res. 1985;148(1–2):83–9.
177. Wiencke JK, Yager JW. Specificity of arsenite in potentiating cytogenetic damage induced by the DNA crosslinking agent diepoxybutane. Environ Mol Mutagen. 1992;19(3):195–200.
178. Tran HP, Prakash AS, Barnard R, Chiswell B, Ng JC. Arsenic inhibits the repair of DNA damage induced by benzo(a)pyrene. Toxicol Lett. 2002;133(1):59–67.
179. Rossman TG, Uddin AN, Burns FJ, Bosland MC. Arsenite cocarcinogenesis: an animal model derived from genetic toxicology studies. Environ Health Perspect. 2002;110 Suppl 5: 749–52.
180. Chiang HC, Tsou TC. Arsenite enhances the benzo[a]pyrene diol epoxide (BPDE)-induced mutagenesis with no marked effect on repair of BPDE-DNA adducts in human lung cells. Toxicol In Vitro. 2009;23(5):897–905.
181. Chen CL, Hsu LI, Chiou HY, et al. Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan. JAMA. 2004;292(24):2984–90.

182. Ferreccio C, Gonzalez C, Milosavjlevic V, Marshall G, Sancha AM, Smith AH. Lung cancer and arsenic concentrations in drinking water in Chile. Epidemiology (Cambridge, Mass). 2000;11(6): 673–9.
183. Chen CL, Chiou HY, Hsu LI, Hsueh YM, Wu MM, Chen CJ. Ingested arsenic, characteristics of well water consumption and risk of different histological types of lung cancer in northeastern Taiwan. Environ Res. 2010;110(5):455–462.
184. Lee HL, Chang LW, Wu JP, et al. Enhancements of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) metabolism and carcinogenic risk via NNK/arsenic interaction. Toxicol Appl Pharmacol. 2008;227(1):108–14.
185. Wu JP, Chang LW, Yao HT, et al. Involvement of oxidative stress and activation of aryl hydrocarbon receptor in elevation of CYP1A1 expression and activity in lung cells and tissues by arsenic: an in vitro and in vivo study. Toxicol Sci. 2009;107(2): 385–93.
186. IARC. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC monographs on the evaluation of carcinogenic risks to human. Lyon: IARC; 1993.
187. Belinsky SA, Snow SS, Nikula KJ, Finch GL, Tellez CS, Palmisano WA. Aberrant CpG island methylation of the p16(INK4a) and estrogen receptor genes in rat lung tumors induced by particulate carcinogens. Carcinogenesis. 2002;23(2):335–9.
188. Pääkkö P, Anttila S, Kokkonen P, Kalliomäki PL. Cadmium in lung tissue as marker for smoking. Lancet. 1988;1(8583):477.
189. Misra RR, Page JE, Smith GT, Waalkes MP, Dipple A. Effect of cadmium exposure on background and anti-5 methylchrysene-1,2-dihydrodiol 3,4-epoxide-induced mutagenesis in the supF gene of pS189 in human Ad293 cells. Chem Res Toxicol. 1998;11(3):211–6.
190. Misra RR, Smith GT, Waalkes MP. Evaluation of the direct genotoxic potential of cadmium in four different rodent cell lines. Toxicology. 1998;126(2):103–14.
191. Ochi T, Ohsawa M. Participation of active oxygen species in the induction of chromosomal aberrations by cadmium chloride in cultured Chinese hamster cells. Mutat Res. 1985;143(3):137–42.
192. Price DJ, Joshi JG. Ferritin. Binding of beryllium and other divalent metal ions. J Biol Chem. 1983;258(18):10873–80.
193. Achanzar WE, Webber MM, Waalkes MP. Altered apoptotic gene expression and acquired apoptotic resistance in cadmium-transformed human prostate epithelial cells. Prostate. 2002;52(3):236–44.
194. Giaginis C, Gatzidou E, Theocharis S. DNA repair systems as targets of cadmium toxicity. Toxicol Appl Pharmacol. 2006;213(3): 282–90.
195. Mikhailova MV, Littlefield NA, Hass BS, Poirier LA, Chou MW. Cadmium-induced 8-hydroxydeoxyguanosine formation, DNA strand breaks and antioxidant enzyme activities in lymphoblastoid cells. Cancer Lett. 1997;115(2):141–8.
196. O'Connor TR, Graves RJ, de Murcia G, Castaing B, Laval J. Fpg protein of Escherichia coli is a zinc finger protein whose cysteine residues have a structural and/or functional role. J Biol Chem. 1993;268(12):9063–70.
197. Takiguchi M, Achanzar WE, Qu W, Li G, Waalkes MP. Effects of cadmium on DNA-(Cytosine-5) methyltransferase activity and DNA methylation status during cadmium-induced cellular transformation. Exp Cell Res. 2003;286(2):355–65.
198. Benbrahim-Tallaa L, Waterland RA, Dill AL, Webber MM, Waalkes MP. Tumor suppressor gene inactivation during cadmium-induced malignant transformation of human prostate cells correlates with overexpression of de novo DNA methyltransferase. Environ Health Perspect. 2007;115(10):1454–9.
199. Huang D, Zhang Y, Qi Y, Chen C, Ji W. Global DNA hypomethylation, rather than reactive oxygen species (ROS), a potential facilitator of cadmium-stimulated K562 cell proliferation. Toxicol Lett. 2008;179(1):43–7.
200. IARC. Chromium, nickel and welding. IARC monographs on the evaluation of carcinogenic risks to human. Lyon: IARC; 1990.
201. Ding M, Shi X, Castranova V, Vallyathan V. Predisposing factors in occupational lung cancer: inorganic minerals and chromium. J Environ Pathol Toxicol Oncol. 2000;19(1–2):129–38.
202. Liu K, Husler J, Ye J, et al. On the mechanism of Cr (VI)-induced carcinogenesis: dose dependence of uptake and cellular responses. Mol Cell Biochem. 2001;222(1–2):221–9.
203. Liu KJ, Shi X. In vivo reduction of chromium (VI) and its related free radical generation. Mol Cell Biochem. 2001; 222(1–2):41–7.
204. Holmes AL, Wise SS, Sandwick SJ, Wise Sr JP. The clastogenic effects of chronic exposure to particulate and soluble Cr(VI) in human lung cells. Mutat Res. 2006;610(1–2): 8–13.
205. Wise Sr JP, Wise SS, Little JE. The cytotoxicity and genotoxicity of particulate and soluble hexavalent chromium in human lung cells. Mutat Res. 2002;517(1–2):221–9.
206. O'Brien TJ, Ceryak S, Patierno SR. Complexities of chromium carcinogenesis: role of cellular response, repair and recovery mechanisms. Mutat Res. 2003;533(1–2):3–36.
207. Hirose T, Kondo K, Takahashi Y, et al. Frequent microsatellite instability in lung cancer from chromate-exposed workers. Mol Carcinog. 2002;33(3):172–80.
208. Takahashi Y, Kondo K, Hirose T, et al. Microsatellite instability and protein expression of the DNA mismatch repair gene, hMLH1, of lung cancer in chromate-exposed workers. Mol Carcinog. 2005;42(3):150–8.
209. Rodrigues CF, Urbano AM, Matoso E, et al. Human bronchial epithelial cells malignantly transformed by hexavalent chromium exhibit an aneuploid phenotype but no microsatellite instability. Mutat Res. 2009;670(1–2):42–52.
210. Ewis AA, Kondo K, Lee J, et al. Occupational cancer genetics: infrequent ras oncogenes point mutations in lung cancer samples from chromate workers. Am J Ind Med. 2001;40(1):92–7.
211. Kondo K, Hino N, Sasa M, et al. Mutations of the p53 gene in human lung cancer from chromate-exposed workers. Biochem Biophys Res Commun. 1997;239(1):95–100.
212. Schnekenburger M, Talaska G, Puga A. Chromium cross-links histone deacetylase 1-DNA methyltransferase 1 complexes to chromatin, inhibiting histone-remodeling marks critical for transcriptional activation. Mol Cell Biol. 2007;27(20): 7089–101.
213. Wei YD, Tepperman K, Huang MY, Sartor MA, Puga A. Chromium inhibits transcription from polycyclic aromatic hydrocarbon-inducible promoters by blocking the release of histone deacetylase and preventing the binding of p300 to chromatin. J Biol Chem. 2004;279(6):4110–9.
214. Sun H, Zhou X, Chen H, Li Q, Costa M. Modulation of histone methylation and MLH1 gene silencing by hexavalent chromium. Toxicol Appl Pharmacol. 2009;237(3):258–66.
215. Kondo K, Takahashi Y, Hirose Y, et al. The reduced expression and aberrant methylation of p16(INK4a) in chromate workers with lung cancer. Lung Cancer (Amsterdam, Netherlands). 2006;53(3):295–302.
216. Ali AH, Kondo K, Namura T, et al. Aberrant DNA methylation of some tumor suppressor genes in lung cancers from workers with chromate exposure. Mol Carcinog. 2011;50(2):89–99.
217. Vincent JH, Werner MA. Critical evaluation of historical occupational aerosol exposure records: applications to nickel and lead. Ann Occup Hyg. 2003;47(1):49–59.
218. Barceloux DG. Nickel. J Toxicol. 1999;37(2):239–58.
219. Patierno SR, Dirscherl LA, Xu J. Transformation of rat tracheal epithelial cells to immortal growth variants by particulate and soluble nickel compounds. Mutat Res. 1993;300(3–4): 179–93.

220. Tveito G, Hansteen IL, Dalen H, Haugen A. Immortalization of normal human kidney epithelial cells by nickel(II). Cancer Res. 1989;49(7):1829–35.
221. Fletcher GG, Rossetto FE, Turnbull JD, Nieboer E. Toxicity, uptake, and mutagenicity of particulate and soluble nickel compounds. Environ Health Perspect. 1994;102 Suppl 3:69–79.
222. Biggart NW, Costa M. Assessment of the uptake and mutagenicity of nickel chloride in salmonella tester strains. Mutat Res. 1986;175(4):209–15.
223. Kargacin B, Klein CB, Costa M. Mutagenic responses of nickel oxides and nickel sulfides in Chinese hamster V79 cell lines at the xanthine-guanine phosphoribosyl transferase locus. Mutat Res. 1993;300(1):63–72.
224. Costa M. Molecular mechanisms of nickel carcinogenesis. Annu Rev Pharmacol Toxicol. 1991;31:321–37.
225. Das KK, Buchner V. Effect of nickel exposure on peripheral tissues: role of oxidative stress in toxicity and possible protection by ascorbic acid. Rev Environ Health. 2007;22(2):157–73.
226. Das KK, Das SN, Dhundasi SA. Nickel, its adverse health effects & oxidative stress. Indian J Med Res. 2008;128(4): 412–25.
227. Higinbotham KG, Rice JM, Diwan BA, Kasprzak KS, Reed CD, Perantoni AO. GGT to GTT transversions in codon 12 of the K-ras oncogene in rat renal sarcomas induced with nickel subsulfide or nickel subsulfide/iron are consistent with oxidative damage to DNA. Cancer Res. 1992;52(17):4747–51.
228. Kawanishi S, Oikawa S, Inoue S, Nishino K. Distinct mechanisms of oxidative DNA damage induced by carcinogenic nickel subsulfide and nickel oxides. Environ Health Perspect. 2002;110 Suppl 5:789–91.
229. Sutherland JE, Costa M. Epigenetics and the environment. Ann N Y Acad Sci. 2003;983:151–60.
230. Lee YW, Klein CB, Kargacin B, et al. Carcinogenic nickel silences gene expression by chromatin condensation and DNA methylation: a new model for epigenetic carcinogens. Mol Cell Biol. 1995;15(5):2547–57.
231. Kang J, Zhang Y, Chen J, et al. Nickel-induced histone hypoacetylation: the role of reactive oxygen species. Toxicol Sci. 2003;74(2):279–86.
232. Yan Y, Kluz T, Zhang P, Chen HB, Costa M. Analysis of specific lysine histone H3 and H4 acetylation and methylation status in clones of cells with a gene silenced by nickel exposure. Toxicol Appl Pharmacol. 2003;190(3):272–7.
233. Chen H, Ke Q, Kluz T, Yan Y, Costa M. Nickel ions increase histone H3 lysine 9 dimethylation and induce transgene silencing. Mol Cell Biol. 2006;26(10):3728–37.
234. Chen H, Kluz T, Zhang R, Costa M. Hypoxia and nickel inhibit histone demethylase JMJD1A and repress Spry2 expression in human bronchial epithelial BEAS-2B cells. Carcinogenesis. 2010;31(12):2136–2144.
235. Chen H, Giri NC, Zhang R, et al. Nickel ions inhibit histone demethylase JMJD1A and DNA repair enzyme ABH2 by replacing the ferrous iron in the catalytic centers. J Biol Chem. 2010;285(10):7374–7383.
236. Govindarajan B, Klafter R, Miller MS, et al. Reactive oxygen-induced carcinogenesis causes hypermethylation of p16(Ink4a) and activation of MAP kinase. Mol Med (Cambridge, Mass). 2002;8(1):1–8.
237. Zhang J, Zhang J, Li M, et al. Methylation of RAR-beta2, RASSF1A, and CDKN2A genes induced by nickel subsulfide and nickel-carcinogenesis in rats. Biomed Environ Sci. 2011;24(2):163–171.
238. Salnikow K, Davidson T, Zhang Q, Chen LC, Su W, Costa M. The involvement of hypoxia-inducible transcription factor-1-dependent pathway in nickel carcinogenesis. Cancer Res. 2003;63(13):3524–30.
239. Chen H, Costa M. Iron- and 2-oxoglutarate-dependent dioxygenases: an emerging group of molecular targets for nickel toxicity and carcinogenicity. Biometals. 2009;22(1):191–6.
240. Kang GS, Li Q, Chen H, Costa M. Effect of metal ions on HIF-1alpha and Fe homeostasis in human A549 cells. Mutat Res. 2006;610(1–2):48–55.
241. Witkiewicz-Kucharczyk A, Bal W. Damage of zinc fingers in DNA repair proteins, a novel molecular mechanism in carcinogenesis. Toxicol Lett. 2006;162(1):29–42.
242. Brugge D, de Lemos JL, Oldmixon B. Exposure pathways and health effects associated with chemical and radiological toxicity of natural uranium: a review. Rev Environ Health. 2005;20(3): 177–93.
243. Kusiak RA, Ritchie AC, Muller J, Springer J. Mortality from lung cancer in Ontario uranium miners. Br J Ind Med. 1993;50(10): 920–8.
244. Jostes RF. Genetic, cytogenetic, and carcinogenic effects of radon: a review. Mutat Res. 1996;340(2–3):125–39.
245. Bao CY, Ma AH, Evans HH, et al. Molecular analysis of hypoxanthine phosphoribosyltransferase gene deletions induced by alpha- and X-radiation in human lymphoblastoid cells. Mutat Res. 1995;326(1):1–15.
246. Ward JF. DNA damage produced by ionizing radiation in mammalian cells: identities, mechanisms of formation, and reparability. Prog Nucleic Acid Res Mol Biol. 1988;35:95–125.
247. Richardson DB. Exposure to ionizing radiation in adulthood and thyroid cancer incidence. Epidemiology (Cambridge, Mass). 2009;20(2):181–7.
248. Richardson RB. Ionizing radiation and aging: rejuvenating an old idea. Aging. 2009;1(11):887–902.
249. Richardson D, Sugiyama H, Nishi N, et al. Ionizing radiation and leukemia mortality among Japanese atomic bomb survivors, 1950–2000. Radiat Res. 2009;172(3):368–82.
250. Richardson DB, Sugiyama H, Wing S, et al. Positive associations between ionizing radiation and lymphoma mortality among men. Am J Epidemiol. 2009;169(8):969–76.
251. Kadhim MA, Macdonald DA, Goodhead DT, Lorimore SA, Marsden SJ, Wright EG. Transmission of chromosomal instability after plutonium alpha-particle irradiation. Nature. 1992;355(6362):738–40.
252. Liu D, Momoi H, Li L, Ishikawa Y, Fukumoto M. Microsatellite instability in thorotrast-induced human intrahepatic cholangiocarcinoma. Int J Cancer. 2002;102(4):366–71.
253. Chaudhry MA. Base excision repair of ionizing radiation-induced DNA damage in G1 and G2 cell cycle phases. Cancer Cell Int. 2007;7:15.
254. Taylor JA, Watson MA, Devereux TR, Michels RY, Saccomanno G, Anderson M. p53 mutation hotspot in radon-associated lung cancer. Lancet. 1994;343(8889):86–7.
255. Hussain SP, Kennedy CH, Amstad P, Lui H, Lechner JF, Harris CC. Radon and lung carcinogenesis: mutability of p53 codons 249 and 250 to 238Pu alpha-particles in human bronchial epithelial cells. Carcinogenesis. 1997;18(1):121–5.
256. Su S, Jin Y, Zhang W, et al. Aberrant promoter methylation of p16(INK4a) and O(6)-methylguanine-DNA methyltransferase genes in workers at a Chinese uranium mine. J Occup Health. 2006;48(4):261–6.
257. Gilliland FD, Harms HJ, Crowell RE, Li YF, Willink R, Belinsky SA. Glutathione S-transferase P1 and NADPH quinone oxidoreductase polymorphisms are associated with aberrant promoter methylation of P16(INK4a) and O(6)-methylguanine-DNA methyltransferase in sputum. Cancer Res. 2002;62(8):2248–52.
258. Belinsky SA, Klinge DM, Liechty KC, et al. Plutonium targets the p16 gene for inactivation by promoter hypermethylation in human lung adenocarcinoma. Carcinogenesis. 2004;25(6):1063–7.

Lung Cancer: Genetic Susceptibility

11

Ari P. Hirvonen

Keywords
Lung cancer • Genetic susceptibility • Genome-wide association studies • Carcinogen-metabolizing genes • Work-related lung cancer • DNA repair genes • Cell-cycle genes

Individual Susceptibility to Lung Cancer

A number of occupational exposures have been shown to contribute to the development of lung cancer. These exposures include asbestos fibers, mixtures of PAHs such as coal tar, heavy metals such as hexavalent chromium and nickel, and crystalline silica [1]. Since even under very high-exposure circumstances only a small proportion of exposed workers develop lung cancer, it is plausible that genetic susceptibility factors play a role in determining individual risk of developing ill-health related to the occupational exposures [2, 3].

Gene variants that might affect individual susceptibility to lung cancer fall into three categories: rare-risk (risk of 10 or higher and prevalence of 1 % or less), moderate-risk (risk around 2–5 and prevalence of not more than 5 %), and common low-risk variants (risk of between 1.1 and 1.5 and prevalence of more than 5 %). Although family linkage studies have been able to identify the low-frequency highly penetrant susceptibility genes for lung cancer, most of the genetic risk for this malignancy is likely to involve several genes of the last two categories, i.e., moderate and low risk. Such risk variants have normally been tested on a candidate gene basis. Recently, however, the genome-wide association (GWA) studies have offered an alternative for the candidate gene studies. This chapter will introduce these two different approaches and their most promising outcomes.

A.P. Hirvonen, PhD
Finnish Institute of Occupational Health,
Topeliuksenkatu 41 a A, Helsinki 00250, Finland
e-mail: ari.hirvonen@ttl.fi

Since to date there are only a very few reports on genetic risk factors to work-related lung cancer, the present data on the most potent susceptibility factors to lung cancer in general are also summarized here; the genetic risk factors are anticipated to be similar in occupational lung cancer and, e.g., in tobacco smoking-associated lung cancer.

Candidate Gene Studies

During the last 20 years, the candidate susceptibility genes for lung cancer have been extensively studied, with most work being focused on mechanistically plausible variants in carcinogen-metabolizing and DNA repair and cell-cycle control genes. The most studied genes and their variants in these pathways are introduced below.

Carcinogen-Metabolizing Genes

CYPs

The cytochrome P450s (CYPs) catalyze detoxifying reactions involving the incorporation of an atom of molecular oxygen into the substrate, but they also activate certain chemicals to their ultimate carcinogenic form [4–6].

The first CYP polymorphism was identified for CYP2D6 based on the occurrence of adverse drug reactions to the cardiovascular drugs debrisoquine and sparteine and aptly termed the "debrisoquine/sparteine" polymorphism [7]. Individuals that are metabolically competent are referred as extensive metabolizers (EMs), and those that are incapable of metabolism of these drugs due to carriage of two defective alleles are poor metabolizers (PMs). More than ten variant

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_11,

alleles of the *CYP2D6* gene have been characterized, which are partially or totally inactive. In addition, ultrarapid metabolizers (UMs) carrying more than two copies of the functional gene exist [8, 9].

The genetically determined CYP2D6 activity is suspected to be involved in lung carcinogenesis by activating carcinogens contained in tobacco smoke. In agreement with this, the combined results of several studies carried out in various parts of the world suggest a significant but small decrease in risk of lung cancer for the individuals with *CYP2D6* PM genotype [10, 11].

The CYP1A family has two members: CYP1A1, which is predominantly expressed in extrahepatic tissues such as the lung, and CYP1A2, which is concentrated in the liver [9]. CYP1A1 is involved, e.g., in the metabolic activation of carcinogenic polycyclic aromatic hydrocarbons (PAHs) to their carcinogenic metabolites in the lung [9]. As an example, CYP1A1-dependent aryl hydrocarbon hydroxylase (AHH) activities in human lung tissue seem to be correlated to activation of benzo(a)pyrene-7,8-diol (BaP) to the ultimate carcinogen [12–14].

Increased lung cancer risks have been widely reported for the carriers of the high AHH inducibility-associated *CYP1A1*2A* and **2C* variant alleles in Asians [15–17]. Probably due to significant ethnic differences in the variant allele frequency, it has been difficult to detect such an association in Caucasian populations before being examined in recent large meta- and pooled analyses [18–23].

A significant interaction has also been observed between several *CYP1A2* genotypes affecting the CYP1A2 activity (*CYP1A2*1D*, *CYP1A2*1 F*, and *CYP1A2-T/delT* or *delT/delT*) and lung carcinogenesis [24, 25].

CYP1B1 has catalytic activities overlapping with CYP1A1 and CYP1A2 with respect to the oxidation of drugs and model CYP substrates. It is involved in the metabolic activation of PAHs and in the hydroxylation of estradiol to 4-hydroxyestradiol, a potentially genotoxic metabolite that is suggested to play a role in carcinogenesis [26].

To date seven *CYP1B1* variant alleles have been identified, which have been anticipated to cause an altered function of the enzyme thereby determining interindividual differences in susceptibility for carcinogenesis [27–30]. In agreement with this, a recent meta-analysis supported the hypothesis that the *CYP1B1* C432G, G119T, and C48G polymorphisms modify the risk of developing lung cancer [31].

CYP2A6 is an important hepatic enzyme that metabolizes approximately 3 % of therapeutic drugs, environmental toxicants, and many procarcinogens [32–35]. To date, more than 36 variant alleles of the *CYP2A6* gene have been identified [32]. Because CYP2A6 is responsible for 70–80 % of the initial metabolism of nicotine, it has been proposed to affect the lung cancer risk via modulation of smoking habits. In agreement with this, the polymorphism of *CYP2A6* has been associated with smoking behavior as well as with lung cancer risk [32, 36, 37].

CYP2E1 is a natural ethanol-inducible enzyme that is involved in the metabolic oxidation of low molecular weight carcinogens such as *N*-nitrosoamines, benzene, and vinyl chloride. Several base changes have been found in *CYP2E1* gene [38–42], and many studies have investigated associations between *CYP2E1* gene variation and lung cancer risk [43–46]. The most extensively studied SNPs of *CYP2E1* are the *Rsa*I/*Pst*I site in the 5′-flanking region, and the *Dra*I site in intron 6. Although the results from epidemiological studies have been inconsistent and controversial, in a recent meta-analysis decreased lung cancer risk was found for subjects carrying *CYP2E1 Rsa*I/*Pst*I variant alleles [47]. In addition, a protective effect against lung cancer was found for the *CYP2E1 Dra*I variant allele containing genotypes.

EPHX1

Microsomal epoxide hydrolase (EPHX1) acts coordinately with, for example, CYP1A1 and CYP1A2 to inactivate deleterious polycyclic hydrocarbon oxides and epoxides [48–53]. Thus, EPHX1 shows the same dual role of procarcinogen detoxification and activation found in some CYPs.

Interindividual differences in EPHX1 activity ranging in scale from several- to 40-fold have been reported in various human tissue types [50]. Genetic polymorphisms have been identified within exons 3 and 4 of the *EPHX1* gene [54, 55], which result in $His_{113}Tyr$ and $Arg_{139}His$ amino acid substitutions, respectively. In vitro expression analyses indicated that the corresponding EPHX1 activities are decreased by approximately 40 % (Tyr_{113}) or increased by at least 25 % (His_{139}) [55]. A genetic variation in the 5′-flanking sequence of *EPHX1* has also been observed, which may be an additional contributing factor to the range of functional EPHX1 expression existing in human populations [56].

Although the previous studies on *EPHX1* genotypes and susceptibility to lung cancer have given somewhat divergent results, data from a recent comprehensive review and meta-analysis supported a modifying role for the *EPHX1* polymorphisms in lung carcinogenesis [57, 58].

GSTs

The glutathione *S*-transferases (GSTs) are a superfamily of enzymes having broad and overlapping substrate specificities [59]. The known substrates for GSTs in cigarette smoke are those derived from in bioactivation from PAHs, namely, PAH diolepoxides. The most studied carcinogenic PAH diolepoxide, BaPDE, is a good substrate for many GST isoforms like GSTM2, GSTM3, and especially for GSTM1 and GSTP1 [59, 60].

The most studied polymorphic *GST* gene in relation to lung cancer is *GSTM1*, which is expressed in only about half of Caucasians, due to a homozygous deletion (null genotype)

of the gene in the other half [61]. In addition to the null genotype, two functional alleles denoted as *GSTM1*A* and *GSTM1*B* have been described. These alleles differ by a base substitution (C534G; Lys172Asn) in the latter, which has not been shown to affect GSTM1 activity [62].

There has been cumulating evidence that the *GSTM1* null smokers are at increased risk of lung cancer. However, several conflicting reports also exist including recent meta- and pooled analyses [63–66]. In a light of the compiled data, it has been estimated that 17 % of lung cancers may be attributable to *GSTM1* genotypes [67]. Although these values provide only a crude measure of the potential population impact of these genes, they suggest that *GSTM1* deficiency could contribute to a substantial incidence of cancer at the population level. In contrast, at the individual level the risk associated with the *GSTM1* null genotype may be smaller than has been anticipated.

GSTM3 is one of the most abundant GSTs in human lungs [68–70]. As a deviation from the wild-type *GSTM3*A* allele, the *GSTM3*B* variant allele carries a deletion of three base pairs in intron 6, which results in the generation of a recognition sequence for the YYI transcription factor [71]. The functional consequence of this is still unclear, but both negative and positive regulatory effects have been suggested [72].

People with low expression of GSTM3 were previously observed to be at an increased risk of developing adenocarcinoma of the lung [70], and subsequent genotyping studies indicated that the *GSTM3* gene polymorphism may modify the risk of lung cancer [66, 73].

The third polymorphic *GST* gene, *GSTP1*, encodes an isoform that is known to metabolize many carcinogenic compounds, among them BaPDE. Given that GSTP1 is the most abundant GST isoform in the lungs [69], it is anticipated to be of particular importance in the detoxification of inhaled carcinogens.

Two *GSTP1* variant alleles, *GSTP1*B* and *GSTP1*C*, have been detected in addition to the wild-type allele *GSTP1*A*. As compared to *GSTP1*A*, proteins encoded by *GSTP1*B* and *GSTP1*C* have been shown to have decreased enzyme activity [74–76], and individuals homozygous for the *GSTP1* low activity alleles have been suggested to pose an increased risk of lung cancer [66, 73, 77–80].

A deletion polymorphism similar to that observed for *GSTM1* has also been discovered for the *GSTT1* gene [81]. GSTT1 participates in detoxification of potentially carcinogenic monohalomethanes and of reactive epoxide metabolites of butadiene [82], both of which are constituents of tobacco smoke. Similarly to the above introduced other at-risk *GST* genotypes, the *GSTT1* null genotype has been associated with increased risk of lung cancer in several studies [15, 80].

MnSOD and MPO

Manganese superoxide dismutase (MnSOD), located in the mitochondrial matrix, provides an initial defense against reactive oxygen species (ROS) [83, 84]. A polymorphism in the second exon of the *MnSOD* gene results in an Ala16Val amino acid change [85]. This substitution may change the structural conformation and thereby mitochondrial transport of MnSOD [86, 87]. Consequently, the *MnSOD 16Ala* allele encodes a protein with 30–40 % more activity than the protein encoded by the *16Val* allele [87].

Myeloperoxidase (MPO), in turn, is the most abundant protein in neutrophils. The recruitment of neutrophils due to pulmonary inflammation initiates the local release and activation of MPO [88, 89]. Once MPO is released at the sites of inflammation, the process of metabolic biotransformation and oxidation is initiated. The *MPO* gene contains a functional polymorphism (−463G>A) in an untranslated region of the gene [90].

The studies on *MnSOD* Ala16Val polymorphism and lung cancer risk have given somewhat contradictory results [91–94], whereas the *MPO* −463G>A polymorphism has been associated with lung cancer risk in several studies [95].

NATs

Human *N*-acetyltransferases (NATs) catalyze conjugation of an acetyl motif, usually from acetyl coenzyme A (AcCoA), to the exocyclic amine (*N*-acetylation) or hydroxyl (*O*-acetylation) of substrates. *N*-Acetylation of the exocyclic amine usually results in their detoxification [96]. However, following *N*-oxidation, the *N*-hydroxyl metabolite undergoes *O*-acetylation (usually activation).

The human genome contains two functional *NAT* genes, which code for NAT1 and NAT2 enzymes [97–99]. A number of genetic polymorphisms with functional consequences have been observed in both *NAT1* and *NAT2* [96, 100, 101]. These polymorphisms cause individual variations in biotransformation of various xenobiotics with a primary aromatic amine or a hydrazine structure [102–105].

The *NAT2* polymorphisms are well established as the basis of rapid, intermediate, and slow acetylation phenotypes. Excellent *NAT2* genotype/phenotype correlations have been reported [106–110], whereas the functional effects of *NAT1* alleles, genotypes, and haplotypes are yet not fully understood [111–113].

Previous phenotyping studies as well as subsequent genotyping studies have suggested a modifying role for *NAT* genotypes in all major cancer sites including lung [114–117]. However, the most recent studies indicate no substantial effect for the *NAT2* genotypes, whereas the NAT1 fast acetylator phenotype-associated genotypes remained significantly associated with increased lung cancer risk [117–119].

DNA Repair and Cell-Cycle Genes

The DNA repair system maintains the integrity of the human genome. Interindividual differences in capacity to repair DNA damage may therefore contribute to individual variability

in susceptibility to environmental or occupational cancer; individuals who have lowered or negligible DNA repair capacity may accumulate mutations that modulate the cancer risk [120].

The activation of cell-cycle checkpoints is also a critical component of the cellular response to DNA damage, and numerous enzymes play a role in keeping the cell cycle in check [121]. Therefore, variation in relevant cell-cycle control pathway genes could magnify or attenuate cumulative effects from deficiencies in DNA repair.

Five main mechanisms are involved in repair of specific types of DNA damage. Base excision repair (BER) operates on small lesions, nucleotide excision repair (NER) repairs bulk lesions, mismatch repair (MMR) corrects replication errors, double-strand break repair (DSBR) corrects double-strand breaks through two different pathways (homologous recombination and non-homologous end rejoining), and direct repair corrects methylated bases [122].

The few most promising DNA repair and cell-cycle control genes as candidates for modifiers of lung cancer risk, based on the recent meta- and pooled analyses, are introduced below.

ATM

The highly polymorphic ataxia-telangiectasia-mutated (ATM) gene is known to be involved in both DNA repair and cell-cycle checkpoint activation [123, 124], and therefore, functional polymorphisms in *ATM* gene may have crucial effects in cancer risk. In agreement with this, the recent meta-analyses indicate that two of the *ATM* SNPs modify individual's susceptibility to lung cancer; the IVS34+60G>A base change was associated with increased lung cancer risk, whereas the IVS 22–77 T>C base change was associated with decreased lung cancer risk [125, 126].

APEX1

AP endonuclease 1 (APEX1) is a multifunctional protein that plays a central role in the BER pathway through hydrolyzing the phosphodiester backbone immediately 5′ to the AP site [127, 128]. A total of 18 SNPs in *APEX1* gene have been identified [129], of which two functional SNPs, −656T>G and 1349T>G, have been most widely investigated.

Recent meta-analyses suggested that the *APEX1* −656T>G base change has a possible protective effect on lung cancer risk [130] and that the 1349T>G base change contributes to the lung cancer risk among smokers [131].

ERCC1 and ERCC2

Excision repair cross-complimentary groups 1 (ERCC1) and 2 (ERCC2) play an essential role in the NER pathway; ERCC2 is also named as xeroderma pigmentosum complementary group D (XPD) gene [122].

Several common and putatively functional SNPs of *ERCC1* and *ERCC2* genes have been identified, of which *ERCC1* 19007T>C and 8092C>A SNPs have been reported to have some effects on *ERCC1* mRNA expression [132, 133], whereas *ERCC2* Asp312Asn and Lys751Gln SNPs are associated with a suboptimal DNA repair capacity [134, 135].

In addition to the previously mentioned *ERCC1* 19007T>C and 8092C>A SNPs, a 17677A>C SNP has been in the focus of the previous studies on *ERCC1* genotypes and cancer susceptibility. Based on recent meta-analyses, the 8092C>A SNP does not appear to have an effect on individual cancer proneness [136]. Although the 17677A>C SNP seemed to modify individual susceptibility to cancer in general, the data was too limited to perform stratified analyses by the cancer type. A significant association with lung cancer risk was, however, found for the *ERCC1* 19007T>C SNP [136].

As for *ERCC2*, recent meta- and pooled analyses indicated slightly elevated lung cancer risk for carriers of the homozygous variant Gln751Gln genotype, whereas no significant association was found for the Asp312Asn genotypes [137, 138].

XPA and XPC

Xeroderma pigmentosum complementary group C (XPC) is one of the core enzymes in the NER pathway; the binding of XPC to damaged DNA is the rate-limiting step for NER [139, 140]. XPA protein, in turn, is involved in damage recognition following the initial damage recognition [141, 142].

The most studied *XPA* gene polymorphism is −4G>A (A23G) located four nucleotides upstream of the start codon [143]. To date, a number of molecular epidemiological studies have evaluated the possible role of the *XPA* −4G>A SNP in lung cancer proneness with inconsistent or even contradictory results [144].

Among all identified SNPs in the *XPC* gene, three are commonly studied, i.e., PAT−/+, Lys939Gln, and Ala499Val. The PAT−/+ and Lys939Gln polymorphisms have been demonstrated to affect the DNA repair capacity [145, 146], whereas the impact of the non-synonymous Ala499Val polymorphism on the protein function is yet unknown. Similarly to the *XPA* −4G>A SNP, a number of molecular epidemiological studies have been conducted to explore the association of *XPC* polymorphisms with cancer risk with contradictory results [147].

The potential reasons for the divergent findings on *XPA* and *XPC* polymorphisms and lung cancer risk are, e.g., insufficient power of the individual studies and different ethnicities of the study populations. In agreement with this, a recent large meta-analysis and pooled analysis suggested that the homozygous carriage of the *XPA* −4A variant allele poses an increased risk of lung cancer among Asians [144]. Similarly, another recent meta-analysis concluded that the homozygous carriers of the *XPC* 939Gln allele are at increased risk of lung cancer [147].

XRCC1

X-ray repair cross-complementing group 1 (XRCC1) protein is an important component in the BER pathway. XRCC1 fixes base damage and DNA single-strand breaks caused by ionizing radiation and alkylating agents by directly interacting with polymerase beta, DNA ligase III, and poly (ADP-ribose) polymerase (PARP) [148].

Among the great number of non-synonymous coding SNPs in *XRCC1* gene, three are common and lead to amino acid substitutions in codons 194 (Arg194Trp), 280 (Arg280His), and 399 (Arg399Gln). In addition, a −77T>C SNP in the 5′-untranslated region (UTR) of *XRCC1* has been widely studied. The *XRCC1* Arg399Gln and −77 T>C polymorphisms have been shown to have clear functional effects [134, 149–153], whereas the functional significance of the Arg194Trp and Arg280His polymorphisms is yet unclear.

In a recent meta-analysis, the *XRCC1* Arg194Trp and −77T>C polymorphisms appeared as significant modifiers of individual lung cancer risk, whereas no associations were found for the Arg280His and Arg399Gln polymorphisms [154].

Genome-Wide Association Studies

An alternative to candidate gene studies is the recent development of GWA studies, which do not require prior knowledge of the functional significance of the variants studied [155]. By the end of 2009, more than 80 common variants independently associated with different cancer sites were identified by the GWA studies [156] including three separate studies on lung cancer [157–159]. All of the three studies on lung cancer provided strong evidence of a susceptibility region in 15q25.1. Subsequent GWA studies have supported these findings [160, 161]. A SNP in chromosome 6p21 affecting lung cancer risk was also reported in one of the studies [157]. Evidence for an association with the 6p21 SNP, situated in the *HLA* (human leukocyte antigen) gene region, has been supported in additional studies [162] although contrasting findings also exist [161].

A third gene region in chromosome 5p has subsequently been confirmed to be a susceptibility locus for lung cancer [162, 163]. This locus includes *TERT* (human telomerase reverse transcriptase) and *CLPTM1L* (cleft lip and palate transmembrane-1-like) genes [163].

Two further large and partly overlapping GWA studies of lung cancer have recently been reported which did not observe any additional susceptibility loci [160, 161]. Moreover, a large GWA study of lung cancer among never-smokers provided preliminary evidence for a susceptibility locus in region 13q31.3, with additional gene-expression data suggesting possible involvement of the *GPC5* gene [164]. However, the association was not statistically significant and additional data to confirm this effect are needed.

The potential modifiers of the lung cancer risk in the 15q25 susceptibility region include three cholinergic nicotine receptor genes (*CHRNA3*, *CHRNA5*, and *CHRNB4*), encoding nicotine acetylcholine receptors (nAChRs). The risk variants were identified either directly via their association with lung cancer risk [157, 158] or by an association with the same genetic region and smoking quantity, leading to a conclusion that the variant alleles increase lung cancer risk indirectly through smoking [159]; since nAChRs mediate sensitivity to nicotine, it has been proposed that variant receptors might increase addiction to tobacco and, therefore, exposure to tobacco carcinogens.

The susceptibility locus at 5p15.33 contains two biologically relevant genes for lung cancer, *TERT* and *CLPTM1L*, variants of which have been reported to be associated with lung cancer risk [162, 163]. This association was further clarified by an international coordinated analysis [165]. Current knowledge of the functions of *TERT* and *CLPTM1L* implicate *TERT* as the more plausible lung cancer gene candidate. *TERT* is the reverse transcriptase component of telomerase that is essential for telomerase enzymatic activity and maintenance of telomeres [166]; up to 90 % of human tumor samples (including lung cancer) show telomerase activity, suggesting that regeneration of telomeres is a vital step for most forms of carcinogenesis [167]. The functions of *CLPTM1L*, on the other hand, are poorly understood and a possible role in cancer is a matter of speculation.

Genetic Factors and Work-Related Lung Cancer

As stated earlier, to date there are only a limited number of reports on the potential role of the above introduced genetic risk factors and work-related lung cancer. The present data are summarized below.

In contrast to other *XME* gene polymorphisms, a reasonable data exists on the potential role of *GSTM1* and *GSTT1* genotypes and occupationally induced lung cancer; the studies that included information on metabolic polymorphisms and occupational exposures were selected to a pooled analysis from the international database on Genetic Susceptibility and Environmental Carcinogens (GSEC) [168]. Adequate data were available for asbestos exposure and *GSTM1* (five studies) and *GSTT1* (three studies) polymorphisms.

For *GSTM1*, the pooled analysis included 651 cases and 983 controls. The lung cancer risk was twofold (OR 2.0, 95 % CI 1.4–2.7) for asbestos exposure, but no effect was observed for the *GSTM1* null genotype (OR 1.1, 95 % CI 0.9–1.4).

The case-only approach, which was based on 869 lung cancer cases and had an 80 % power to detect an OR of interaction of 1.56, also provided lack of evidence of interaction.

Similarly, the analysis of possible interaction between *GSTT1* polymorphism and asbestos exposure in relation to lung cancer, based on 619 cases, revealed no significant interaction; the prevalence OR of *GSTT1* null genotype and asbestos exposure was 1.1 (95 % CI 0.6–2.0).

The results do therefore not support the hypothesis that the risk of lung cancer after asbestos exposure differs according to *GSTM1* genotype. As for *GSTT1*, the low statistical power of the pooled analysis for *GSTT1* genotypes hampered any firm conclusion. No adequate data were available to assess other interactions between occupational exposures and metabolic polymorphisms.

Recently similar results were observed; no association was found in the analysis of the interaction between *GSTM1* present/null, *GSTT1* present/null, and *GSTP1* Ile105Val polymorphisms and occupation in lung cancer risk (each gene analyzed separately with occupation) [169]. In addition, Nazar-Stewart et al. [170] evaluated the occupational exposure to arsenic, asbestos, and welding or diesel products as potential effect modifiers for the *GSTM1* present/null, *GSTT1* present/null, and *GSTP1* Ile105Val polymorphisms but found no association. Moreover, Jourenkova-Mironova et al. [171], Reszka et al. [172], and Risch et al. [173] used occupational exposure as a confounding variable, and Yin et al. [174] used occupation as matching variable.

Aside the *GST* genotypes, very scarce data is available for the other *XME* genotypes and work-related lung cancer. In one study the *CYP1A1*2C* variant allele was found to be associated with occupations (OR 2.20, 95 % CI 1.11–4.35) known to be associated with increased risk of developing lung cancer [169]. Examples of such occupations were arsenic, uranium, iron-ore, asbestos, and talc miners; ceramic and pottery workers; coke plant and gas production workers; insulators, roofers and asphalt workers; and painters.

Studies in asbestos-exposed populations, in turn, have provided evidence of the effect of functional polymorphism of *MnSOD* (Ala16Val) and *MPO* (−463G>A) in susceptibility to lung cancer in the asbestos-exposed workers [88, 95].

Conclusion

It is clear from the above that genetic differences underlie individual susceptibility to lung cancer, whether caused by exposure to tobacco smoke or to occupational carcinogens. However, very few studies on genetic variants in the genes reviewed here have been able to take occupation into account, supposedly because of the difficulty to compile that information. Therefore, while the above discussed carcinogen-related association between the gene polymorphisms and lung cancer risk is anticipated to be at least partly generalized to, e.g., occupational PAH exposures, majority of the potential associations between genetic polymorphisms and occupational cancer remain to be elucidated.

References

1. Spyratos D, Zarogoulidis P, Porpodis K, Tsakiridis K, Machairiotis N, Katsikogiannis N, Katsokogiannis N, Kougioumzi I, Dryllis G, Kallianos A, Rapti A, Li C, Zarogouldis K. Occupational exposure and lung cancer. J Thorac Dis. 2013;5:S440–5.
2. Smith G, Stanley LA, Sim E, Strange R, Wolf CR. Metabolic polymorphisms and cancer susceptibility. Cancer Surv. 1995;25:27–65.
3. Nebert DW, Mckinnon RA, Puga A. Human drug-metabolizing enzyme polymorphisms: effects on risk of toxicity and cancer. DNA Cell Biol. 1996;15:273–80.
4. Guengerich FP. Catalytic selectivity of human cytochrome P450 enzymes: relevance to drug metabolism and toxicity. Toxicol Lett. 1994;70:133–8.
5. Gonzalez FJ, Aoyama T, Gelboin HV. Activation of promutagens by human cDNA expressed cytochrome P450s. Prog Clin Biol Res. 1990;340B:77–86.
6. Eaton DL, Gallagher EP, Bammler TK, Kunze KL. Role of cytochrome P4501A2 in chemical carcinogenesis: implications for human variability in expression and enzyme activity. Pharmacogenetics. 1995;5:259–74.
7. Gonzalez FJ. The CYP2D6 subfamily. In: Ioannides C, editor. Cytochromes P450s: metabolic and toxicologic aspects. Boca Raton: CRC Press; 1996. p. 183–210.
8. Daly AK, Brockmoller J, Broly F, Eichelbaum M, Evans WE, Gonzalez FJ, Huang J-D, Idle JR, Ingelman-sundberg M, Ishizaki T, Jacqz-Aigrain E, Meyer UA, Nebert DW, Steen VM, Wolf CR, Zanger UM. Nomenclature for human *CYP2D6* alleles. Pharmacogenetics. 1996;6:193–201.
9. Nelson DR, Koymans L, Kamataki T, Stegeman JJ, Feyereisen R, Waxman DJ, Waterman MR, Gotoh O, Coon MJ, Astabrook RW, Gunsalus IC, Nebert DE. P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics. 1996;6:1–42.
10. Rostami-Hodjegan A, Lenard MS, Woods HE, Tucker GT. Meta-analysis of studies of the CYP2D6 polymorphism in relation to lung cancer and Parkinson's disease. Pharmacogenetics. 1998;8:227–38.
11. Agundez JA. Cytochrome P450 gene polymorphism and cancer. Curr Drug Metab. 2004;5:211–24.
12. Rojas M, Camus AM, Alexandrov K, Husgafvel-Pursiainen K, Anttila S, Vainio H, Bartsch H. Stereoselective metabolism of (−)-benzoapyrene-7,8-diol by human lung microsomes and peripheral blood lymphocytes: effects of smoking. Carcinogenesis. 1992;13:929–33.
13. Shou M, Krausz KW, Gonzalez FJ, Gelboin HV. Metabolic activation of the potent carcinogen dibenzo(a)pyrene by human recombinant cytochromes P450, lung and liver microsomes. Carcinogenesis. 1996;17:2429–33.
14. Bartsch H, Rojas M, Alexandrov K, Camus A-M, Castegnaro M, Malaveille C, Anttila S, Hirvonen A, Husgafvel-Pursiainen K, Hietanen E, Vainio H. Metabolic polymorphism affecting DNA binding and excretion of carcinogens in humans. Pharmacogenetics. 1995;5:S84–90.
15. Okazaki I, Sugita M, Matsuki H, Billah SM, Watanabe T. Additional candidates to conventional genes susceptible for lung cancer and changing trend in Japan. Oncol Rep. 2010;23:1493–500.
16. Hecht SS. Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. Lancet Oncol. 2002;3:461–9.
17. Brockmoeller J, Cascorbi I, Kerb R, Sachse C, Roots I. Polymorphisms in xenobiotic conjugation and disease predisposition. Toxicol Lett. 1998;102–103:173–83.
18. Vineis P, Veglia F, Benhamou S, Butkiewicz D, Cascorbi I, Clapper ML, Dolzan V, Haugen A, Hirvonen A, Ingelman-Sundberg M, Kihara M, Kiyohara C, Kremers P, Le Marchand L, Ohshima S, Pastorelli R, Rannug A, Romkes M, Schoket B,

Shields P, Strange RC, Stucker I, Sugimura H, Garte S, Gaspari L, Taioli E. CYP1A1 T3801 C polymorphism and lung cancer: a pooled analysis of 2,451 cases and 3,358 controls. Int J Cancer. 2003;104:650–7.
19. Vineis P, Anttila S, Benhamou S, Spinola M, Hirvonen A, Kiyohara C, Garte SJ, Puntoni R, Rannug A, Strange RC, Taioli E. Evidence of gene-gene interactions in lung carcinogenesis in a large pooled analysis. Carcinogenesis. 2007;28:1902–5.
20. Houlston RS. CYP1A1 polymorphisms and lung cancer risk: a meta-analysis. Pharmacogenetics. 2000;10:105–14.
21. Hung RJ, Boffetta P, Brockmoller J, Butkiewicz D, Cascorbi I, Clapper ML, Garte S, Haugen A, Hirvonen A, Anttila S, Kalina I, Le Marchand L, London SJ, Rannug A, Romkes M, Salagovic J, Schoket B, Gaspari L, Taioli E. CYP1A1 and GSTM1 genetic polymorphisms and lung cancer risk in Caucasian non-smokers: a pooled analysis. Carcinogenesis. 2003;24:875–82.
22. Vineis P, Veglia F, Anttila S, Benhamou S, Clapper ML, Dolzan V, Ryberg D, Hirvonen A, Kremers P, Le Marchand L, Pastorelli R, Rannug A, Romkes M, Schoket B, Strange RC, Garte S, Taioli E. CYP1A1, GSTM1 and GSTT1 polymorphisms and lung cancer: a pooled analysis of gene-gene interactions. Biomarkers. 2004;9: 298–305.
23. Le Marchand L, Guo C, Benhamou S, Bouchardy C, Cascorbi I, Clapper ML, Garte S, Haugen A, Ingelman-Sundberg M, Kihara M, Rannug A, Ryberg D, Stücker I, Sugimura H, Taioli E. Pooled analysis of the CYP1A1 exon 7 polymorphism and lung cancer (United States). Cancer Causes Control. 2003;14:339–46.
24. Pavanello S, B'chir F, Pulliero A, Saguem S, Ben Fraj R, El Aziz HA, Clonfero E, Mastrangelo G. Interaction between CYP1A2-T2467DELT polymorphism and smoking in adenocarcinoma and squamous cell carcinoma of the lung. Lung Cancer. 2007;57:266–72.
25. Singh AP, Pant MC, Ruwali M, Shah PP, Prasad R, Mathur N, Parmar D. Polymorphism in cytochrome P450 1A2 and their interaction with risk factors in determining risk of squamous cell lung carcinoma in men. Cancer Biomark. 2010;8:351–9.
26. Roos PH, Bolt HM. Cytochrome P450 interactions in human cancers: new aspects considering CYP1B1. Expert Opin Drug Metab Toxicol. 2005;1:187–202.
27. Watanabe J, Shimada T, Gillam EM, Ikuta T, Suemasu K, Higashi Y, Gotoh O, Kawajiri K. Association of CYP1B1 genetic polymorphism with incidence to breast and lung cancer. Pharmacogenetics. 2005;10:25–33.
28. Liang G, Pu Y, Yin L. Rapid detection of single nucleotide polymorphisms related with lung cancer susceptibility of Chinese population. Cancer Lett. 2005;223:265–74.
29. Timofeeva MN, Kropp S, Sauter W, Beckmann L, Rosenberger A, Illig T, Jäger B, Mittelstrass K, Dienemann H, LUCY-Consortium, Bartsch H, Bickeböller H, Chang-Claude JC, Risch A, Wichmann HE. CYP450 polymorphisms as risk factors for early-onset lung cancer: gender-specific differences. Carcinogenesis. 2009;30: 1161–9.
30. Rotunno M, Yu K, Lubin JH, Consonni D, Pesatori AC, Goldstein AM, Goldin LR, Wacholder S, Welch R, Burdette L, Chanock SJ, Bertazzi PA, Tucker MA, Caporaso NE, Chatterjee N, Bergen AW, Landi MT. Phase I metabolic genes and risk of lung cancer: multiple polymorphisms and mRNA expression. PLoS One. 2009;4:e5652.
31. Xu W, Zhou Y, Hang X, Shen D. Current evidence on the relationship between CYP1B1 polymorphisms and lung cancer risk: a meta-analysis. Mol Biol Rep. 2012;39:2821–9.
32. Di YM, Chow VD, Yang LP, Zhou SF. Structure, function, regulation and polymorphism of human cytochrome P450 2A6. Curr Drug Metab. 2009;10:754–80.
33. Fernandez-Salguero P, Gonzalez FJ. The *CYP2A* gene subfamily: species differences, regulation, catalytic activities and role in chemical carcinogenesis. Pharmacogenetics. 1995;5:S123–8.
34. Fernandez-Salguero P, Hoffman SMG, Cholerton S, Mohrenweiser H, Raunio H, Rautio A, Pelkonen O, Huang J, Evans WE, Idle JR, Gonzalez FJ. A genetic polymorphism in coumarin 7-hydroxylation: sequence of the human *CYP2A* genes and identification of variant *CYP2A6* alleles. Am J Hum Genet. 1995;57: 651–60.
35. Cholerton S, Idle ME, Vas A, Gonzalez FJ, Idle JR. Comparison of a novel thin layer chromatographic-fluorescence detection method with a spectrofluoromethric method for the determination of 7-hydrocoumarin in human urine. J Chromatogr. 1992;575:325–30.
36. Tamaki Y, Arai T, Sugimura H, Sasaki T, Honda M, Muroi Y, Matsubara Y, Kanno S, Ishikawa M, Hirasawa N, Hiratsuka M. Association between cancer risk and drug-metabolizing enzyme gene (CYP2A6, CYP2A13, CYP4B1, SULT1A1, GSTM1, and GSTT1) polymorphisms in cases of lung cancer in Japan. Drug Metab Pharmacokinet. 2011;26:516–22.
37. Wassenaar CA, Dong Q, Wei Q, Amos CI, Spitz MR, Tyndale RF. Relationship between CYP2A6 and CHRNA5-CHRNA3-CHRNB4 variation and smoking behaviors and lung cancer risk. J Natl Cancer Inst. 2011;103:1342–6.
38. Uematsu F, Kikuchi H, Ohmachi T, Sagami I, Motomiya M, Kamataki T, Komori M, Watanabe M. Two common RFLPs of the human *CYP2E1* gene. Nucl Acid Res. 1991;19:2803.
39. Uematsu F, Kikuchi H, Motomiya M, Abe T, Sagami I, Ohmachi T, Wakui A, Kanamaru R, Watanabe M. Association between restriction fragment length polymorphism of the human cytochrome P450IIE1 gene and susceptibility to lung cancer. Jpn J Cancer Res. 1991;82:254–6.
40. Uematsu F, Kikuchi H, Abe T, Motomiya M, Ohmachi T, Sagami I, Watanabe M. Msp I polymorphism of the human *CYP2E1* gene. Nucl Acids Res. 1991;19:5797.
41. Hayashi S, Watanabe J, Kawajiri K. Genetic polymorphisms in the 5′-flanking region change transcriptional regulation of the human cytochrome P450IIE1 gene. J Biochem. 1991;110:559–65.
42. Liu Y, Meng XW, Zhou LY, Zhang PY, Sun X, Zhang P. Genetic polymorphism and mRNA levels of cytochrome P450IIE1 and glutathione S-transferase P1 in patients with alcoholic liver disease in different nationalities. Hepatobiliary Pancreat Dis Int. 2009;8:162–7.
43. Uematsu F, Kikuchi H, Motomiya M, Abe T, Ishioka C, Kanamaru R, Sagami I, Watanabe M. Human cytochrome P450IIE1 gene: *Dra*I polymorphism and susceptibility to cancer. Tohoku J Exp Med. 1992;168:113–7.
44. Uematsu F, Ikawa S, Sagami I, Kanamaru R, Abe T, Satoh K, Motomiya M, Watanabe M. Restriction fragment length polymorphism of the human *CYP2E1* (cytochrome P450IIE1) gene and susceptibility to lung cancer: possible relevance to low smoking exposure. Pharmacogenetics. 1994;4:58–63.
45. Hirvonen A, Husgafvel-Pursiainen K, Anttila S, Karjalainen A, Vainio H. The human *CYP2E1* gene and lung cancer: *Dra*I and *Rsa*I restriction fragment length polymorphisms in a Finnish study population. Carcinogenesis. 1993;14:85–8.
46. Rannug A, Alexandrie AK, Persson I, Ingelman-Sundberg M. Genetic polymorphism of cytochromes P450 1A1, 2D6 and 2E1: regulation and toxicological significance. J Occup Environ Med. 1995;37:25–36.
47. Wang Y, Yang H, Li L, Wang H, Zhang C, Yin G, Zhu B. Association between CYP2E1 genetic polymorphisms and lung cancer risk: a meta-analysis. Eur J Cancer. 2010;46:758–64.
48. Oesch F. Mammalian epoxide hydrolases: inducible enzymes catalyzing the inactivation of carcinogenic and cytotoxic metabolites derived from aromatic and olefinic compounds. Xenobiotica. 1973;3:305–40.
49. Oesch F, Glatt H, Schimassmann H. The apparent ubiquity of epoxide hydrolase in rat organs. Biochem Pharmacol. 1977;26: 603–7.

50. Seidegård J, Ekström G. The role of human glutathione transferases and epoxide hydrolases in the metabolism of xenobiotics. Environ Health Perspect. 1997;105:791–9.
51. Omiecinski CJ, Aicher L, Holubkov R, Checkoway H. Human peripheral lymphocytes as indicators of microsomal epoxide hydrolase activity in liver and lung. Pharmacogenetics. 1993;3: 150–8.
52. Etter H, Richter C, Ohta Y, Winterhalter KH, Sasabe H, Kawato S. Rotation and interaction with epoxide hydrolase of P-450 in proteoliposomes. J Biol Chem. 1991;266:18600–5.
53. Sims P, Grover PL, Swaisland A, Pal K, Hewer A. Metabolic activation of benzo(a)pyrene proceeds by a diol epoxide. Nature. 1974;252:326–8.
54. Hasset C, Robinson KB, Beck NB, Omiecinski CJ. The human microsomal epoxide hydrolase gene (*EPHX1*): complete nucleotide sequence and structural characterization. Genomics. 1994;23:433–42.
55. Hasset C, Aicher L, Sidhu JS, Omiecinski CJ. Human microsomal epoxide hydrolase: genetic polymorphism and functional expression *in vitro* of amino acid variants. Hum Mol Genet. 1994;3:421–8.
56. Raaka S, Hasset C, Omiecinski CJ. Human microsomal epoxide hydrolase: 5′-flanking region genetic polymorphism. Carcinogenesis. 1998;19:387–93.
57. Kiyohara C, Yoshimasu K, Takayama K, Nakanishi Y. EPHX1 polymorphisms and the risk of lung cancer: a HuGE review. Epidemiology. 2006;17:89–99.
58. Li X, Hu Z, Qu X, Zhu J, Li L, Ring BZ, Su L. Putative EPHX1 enzyme activity is related with risk of lung and upper aerodigestive tract cancers: a comprehensive meta-analysis. PLoS One. 2011;6:e14749.
59. Hayes JD, Pulford DJ. The glutathione *S*-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit Rev Biochem Mol Biol. 1995;30:445–600.
60. Coles B, Ketterer B. The role of glutathione and glutathione transferases in chemical carcinogenesis. Crit Rev Biochem Mol Biol. 1990;25:47–70.
61. Seidegård J, Vorachek WR, Pero RW, Pearson WR. Hereditary differences in the expression of the human glutathione transferase active on trans-stilbene oxide are due to a gene deletion. Proc Natl Acad Sci. 1988;85:7293–7.
62. Widersten M, Pearson WR, Engstrom A, Mannervik B. Heterologous expression of the allelic variant mu-class glutathione transferases mu and psi. Biochem J. 1991;276:519–24.
63. Gemignani F, Landi S, Szeszenia-Dabrowska N, Zaridze D, Lissowska J, Rudnai P, Fabianova E, Mates D, Foretova L, Janout V, Bencko V, Gaborieau V, Gioia-Patricola L, Bellini I, Barale R, Canzian F, Hall J, Boffetta P, Hung RJ, Brennan P. Development of lung cancer before the age of 50: the role of xenobiotic metabolizing genes. Carcinogenesis. 2007;28:1287–93.
64. Carlsten C, Sagoo GS, Frodsham AJ, Burke W, Higgins JP. Glutathione S-transferase M1 (GSTM1) polymorphisms and lung cancer: a literature-based systematic HuGE review and meta-analysis. Am J Epidemiol. 2008;167:759–74.
65. Lee KM, Kang D, Clapper ML, Ingelman-Sundberg M, Ono-Kihara M, Kiyohara C, Min S, Lan Q, Le Marchand L, Lin P, Lung ML, Pinarbasi H, Pisani P, Srivatanakul P, Seow A, Sugimura H, Tokudome S, Yokota J, Taioli E. CYP1A1, GSTM1, and GSTT1 polymorphisms, smoking, and lung cancer risk in a pooled analysis among Asian populations. Cancer Epidemiol Biomarkers Prev. 2008;17:1120–6.
66. Langevin SM, Ioannidis JP, Vineis P, Taioli E, Genetic Susceptibility to Environmental Carcinogens group (GSEC). Assessment of cumulative evidence for the association between glutathione S-transferase polymorphisms and lung cancer: application of the Venice interim guidelines. Pharmacogenet Genomics. 2010;20:586–97.
67. McWilliams JE, Sanderson BJ, Harris EL, Richert-Boe KE, Henner WD. Glutathione *S*-transferase M1 (GSTM1) deficiency and lung cancer risk. Cancer Epidemiol Biomarkers Prev. 1995;4(6):589–94.
68. Inskip A, Elexpuru-Camiruaga J, Buxton N, Dias PS, Macintosh J, Campbell D, Jones PW, Yengi L, Talbot JA, Strange RC, Fryer AA. Identification of polymorphism at the glutathione *S*-transferase, *GSTM3* locus: evidence for linkage with *GSTM1***A*. Biochem J. 1995;312:713–6.
69. Anttila S, Hirvonen A, Vainio H, Husgafvel-Pursiainen K, Hayes JD, Ketterer B. Immunohistochemical localization of glutathione *S*-transferases in human lung. Cancer Res. 1993;53:5643–8.
70. Anttila S, Luostarinen L, Hirvonen A, Elovaara E, Karjalainen A, Nurminen T, Hayes JD, Vainio H, Ketterer B. Pulmonary expression of glutathione *S*-transferase M3 in lung cancer patients: association with *GSTM1* polymorphism, smoking, and asbestos exposure. Cancer Res. 1995;55:3305–9.
71. Yengi L, Inskip A, Gilford J, Alldersea J, Bailey L, Smith A, Lear JT, Heagerty AH, Bowers B, Hand P, Hayes JD, Jones PW, Strange RC, Fryer AA. Polymorphism at the glutathione *S*-transferase locus *GSTM3*: interactions with cytochrome P450 and glutathione *S*-transferase genotypes as risk factors for multiple cutaneous basal cell carcinoma. Cancer Res. 1996;56:1974–7.
72. Matthias C, Bockműhl U, Jahnke V, Jones PW, Hayes JD, Alldersea J, Gilford J, Bailey L, Bath J, Worrall SF, Hand P, Fryer AA, Strange R. Polymorphism in cytochrome P450 CYP2D6, CYP1A1, CYP2E1 and glutathione *S*-transferase, GSTM1, GSTM3, GSTT1 and susceptibility to tobacco-related cancers: studies in upper aerodigestive tract cancers. Pharmacogenetics. 1998;8:91–100.
73. Jourenkova-Mirnova N, Wikman H, Bouchardy C, Voho A, Dayer P, Benhamou S, Hirvonen A. Role of glutathione S-transferase GSTM1, GSTM3, GSTP1, and GSTT1 genotypes in modulating susceptibility to smoking related lung cancer. Pharmacogenetics. 1998;8:495–502.
74. Ali-Osman F, Akande N, Mao J. Molecular cloning, characterization, and expression in Escherichia coli of full-length cDNAs of three human glutathione *S*-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. J Biol Chem. 1997;272:10004–12.
75. Zimniak P, Nanduri B, Pilula S, Bandorowicz-Pikula J, Singhal S, Srivastava SK, Awasthi S, Awasrhi JC. Naturally occurring human glutathione *S*-transferase GSTP1.1 isoforms with isoleucine and valine at position 104 differ in enzymatic properties. Eur J Biochem. 1994;224:893–9.
76. Ryberg D, Skaug V, Hewer A, Phillips DH, Harries LW, Wolf CR, Øgreid D, Ulvik A, Vu P, Haugen A. Genotypes of glutathione transferase M1 and P1 and their significance for lung DNA adduct levels and cancer risk. Carcinogenesis. 1997;18:1285–9.
77. Jaskula-Sztul R, Reinikainen M, Husgafvel-Pursiainen K, Szmeja Z, Szyfter W, Szyfter K, Hirvonen A. Glutathione *S*-transferase M1 and T1 genotypes as and susceptibility to smoking-related larynx cancer. Biomarkers. 1998;3:149–55.
78. Harris MJ, Coggan M, Langton L, Wilson SR, Board PG. Polymorphism of the Pi class glutathione S-transferase in normal populations and cancer patients. Pharmacogenetics. 1998;8:27–31.
79. Cote ML, Chen W, Smith DW, Benhamou S, Bouchardy C, Butkiewicz D, Fong KM, Gené M, Hirvonen A, Kiyohara C, Larsen JE, Lin P, Raaschou-Nielsen O, Povey AC, Reszka E, Risch A, Schneider J, Schwartz AG, Sorensen M, To-Figueras J, Tokudome S, Pu Y, Yang P, Wenzlaff AS, Wikman H, Taioli E. Meta- and pooled analysis of GSTP1 polymorphism and lung cancer: a HuGE-GSEC review. Am J Epidemiol. 2009;169:802–14.
80. Ye Z, Song H, Higgins JP, Pharoah P, Danesh J. Five glutathione s-transferase gene variants in 23,452 cases of lung cancer and 30,397 controls: meta-analysis of 130 studies. PLoS Med. 2006;3:e91.

81. Pemble S, Schroeder KR, Spencer SR, Meyer DJ, Hallier E, Bolt HM, Ketterer B, Taylor JB. Human glutathione *S*-transferase theta (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. Biochem J. 1994;300:271–6.
82. Schröder KR, Hallier E, Peter H, Bolt HM. Dissociation of a new glutathione *S*-transferase activity in human erythrocytes. Biochem Pharmacol. 1992;43:1671–4.
83. Church SL. Manganese superoxide dismutase: nucleotide and deduced amino acid sequence of a cDNA encoding a new human transcript. Biochim Biophys Acta. 1990;1087:250–2.
84. Church SL, Grant JW, Ridnour LA, Oberley LW, Swanson PE, Meltzer PS, Trent JM. Increased manganese superoxide dismutase expression suppresses the malignant phenotype of human melanoma cells. Proc Natl Acad Sci. 1993;90:3113–7.
85. Shimoda-Matsubayashi S, Matsumine H, Kobayashi T, Nakagawa-Hattori Y, Shimizu Y, Mizuno Y. Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene. A predictive evidence for conformational change to influence mitochondrial transport and a study of allelic association in Parkinson's disease. Biochem Biophys Res Commun. 1996;226:561–5.
86. Rosenblum JS, Gilula NB, Lerner RA. On signal sequence polymorphisms and diseases of distribution. Proc Natl Acad Sci. 1996;93:4471–3.
87. Sutton A, Khoury H, Prip-Buus C, Cepanec C, Pessayre D, Degoul F. The Ala16Val genetic dimorphism modulates the import of human manganese superoxide dismutase into rat liver mitochondria. Pharmacogenetics. 2003;13:145–57.
88. Schmekel B, Venge P. The distribution of myeloperoxidase, eosinophil cationic protein, albumin and urea in sequential bronchoalveolar lavage. Eur Respir J. 1991;4:517–23.
89. Schmekel B, Karlsson SE, Linden M, Sundström C, Tegner H, Venge P. Myeloperoxidase in human lung lavage. I. A marker of local neutrophil activity. Inflammation. 1990;14:447–54.
90. Piedrafita FJ, Molander RB, Vansant G, Orlova EA, Pfahl M, Reynolds WF. An Alu element in the myeloperoxidase promoter contains a composite SP1-thyroid hormone-retinoic acid response element. J Biol Chem. 1996;271:14412–20.
91. Wang LI, Neuberg D, Christiani DC. Asbestos exposure, manganese superoxide dismutase (MnSOD) genotype, and lung cancer risk. J Occup Environ Med. 2004;46:556–64.
92. Wang LI, Miller DP, Sai Y, Liu G, Su L, Wain JC, Lynch TJ, Christiani DC. Manganese superoxide dismutase alanine-to-valine polymorphism at codon 16 and lung cancer risk. J Natl Cancer Inst. 2001;93(23):1818–21.
93. Lin P, Hsueh YM, Ko JL, Liang YF, Tsai KJ, Chen CY. Analysis of NQO1, GSTP1, and MnSOD genetic polymorphisms on lung cancer risk in Taiwan. Lung Cancer. 2003;40:123–9.
94. Zejnilovic J, Akev N, Yilmar H, Isbir T. Association between manganese superoxide dismutase polymorphism and risk of lung cancer. Cancer Genet Cytogenet. 2009;189:1–4.
95. Schabath MB, Spitz MR, Delclos GL, Gunn GB, Whitehead LW, Wu X. Association between asbestos exposure, cigarette smoking, myeloperoxidase (MPO) genotypes, and lung cancer risk. Am J Ind Med. 2002;42:29–37.
96. Hein DW. N-acetyltransferase SNPs: emerging concepts serve as a paradigm for understanding complexities of personalized medicine. Expert Opin Drug Metab Toxicol. 2009;5:353–66.
97. Husain A, Zhang X, Doll MA, States JC, Barker DF, Hein DW. Functional analysis of the human N-acetyltransferase 1 major promoter: quantitation of tissue expression and identification of critical sequence elements. Drug Metab Dispos. 2007;35:1649–56.
98. Sim E, Payton M, Noble M, Minchin R. An update on genetic, structural and functional studies of arylamine N-acetyltransferases in eucaryotes and procaryotes. Hum Mol Genet. 2000;9: 2435–41.
99. Smelt VA, Upton A, Adjaye J, Payton MA, Boukouvala S, Johnson N, Mardon HJ, Sim E. Expression of arylamine N-acetyltransferases in pre-term placentas and in human pre-implantation embryos. Hum Mol Genet. 2000;9:1101–7.
100. Sim E, Lack N, Wang CJ, Long H, Westwood I, Fullam E, Kawamura A. Arylamine N-acetyltransferases: structural and functional implications of polymorphisms. Toxicology. 2008;254:170–83.
101. Butcher NJ, Tiang J, Minchin RF. Regulation of arylamine N-acetyltransferases. Curr Drug Metab. 2008;9:498–504.
102. Evans DA. *N*-acetyltransferase. In: Kalow W, editor. Pharmacogenetics of drug metabolism. New York: Pergamon Press; 1992. p. 95–178.
103. Hein DW, Doll MA, Rustan TD, Gray K, Feng Y, Ferguson RJ, Grant DM. Metabolic activation and deactivation of arylamine carcinogens by recombinant human NAT1 and polymorphic NAT2 acetyltransferases. Carcinogenesis. 1993;14:1633–8.
104. Vatsis KP, Weber WW, Bell DA, Dupret J-M, Evans DAP, Grant DM, Hein DW, Lin HJ, Meyer UA, Relling MV, Sim E, Suzuki T, Yamazoe Y. Nomenclature for *N*-acetyltransferases. Pharmacogenetics. 1995; 5:1–17.
105. Hein DW, Boukouvala S, Grant DM, Minchin RF, Sim E. Changes in consensus arylamine N-acetyltransferase gene nomenclature. Pharmacogenet Genomics. 2008;18:367–8.
106. Chen B, Zhang WX, Cai WM. The influence of various genotypes on the metabolic activity of NAT2 in a Chinese population. Eur J Clin Pharmacol. 2006;62:355–9.
107. Ma JJ, Liu CG, Li JH, Cao XM, Sun SL, Yao X. Effects of NAT2 polymorphism on SASP pharmacokinetics in Chinese population. Clin Chim Acta. 2009;407:30–5.
108. Doll MA, Zang Y, Moeller T, Hein DW. Codominant expression of N-acetylation and O-acetylation activities catalyzed by N-acetyltransferase 2 in human hepatocytes. J Pharmacol Exp Ther. 2010;334:540–4.
109. Walraven JM, Zang Y, Trent JO, Hein DW. Structure/function evaluations of single nucleotide polymorphisms in human N-acetyltransferase 2. Curr Drug Metab. 2008;9:471–86.
110. Hein DW. N-acetyltransferase 2 genetic polymorphism: effects of carcinogen and haplotype on urinary bladder cancer risk. Oncogene. 2006;25:1649–58.
111. Walraven JM, Trent JO, Hein DW. Structure-function analyses of single nucleotide polymorphisms in human N-acetyltransferase 1. Drug Metab Rev. 2008;40:169–84.
112. Zhu Y, States C, Wang Y, Hein DW. Functional effects of genetic polymorphisms in the N-acetyltransferase 1 coding and 3′ untranslated regions. Birth Defects Res A Clin Mol Teratol. 2011;91:77–84.
113. Zhu Y, Hein DW. Functional effects of single nucleotide polymorphisms in the coding region of human N-acetyltransferase 1. Pharmacogenomics J. 2008;8:339–48.
114. Hirvonen A. Polymorphic *NATs* and cancer proneness. In: Boffetta P, Caporaso N, Cuzick J, Lang M, Vineis P, editors. Metabolic polymorphisms and cancer. Lyon: IARC Scientific Publications; 1998.
115. Martínez C, Agúndez JAG, Olivera M, Martín R, Ladero JM, Benítez J. Lung cancer and mutations at the polymorphic *NAT2* gene locus. Pharmacogenetics. 1995;5:207–14.
116. Cascorbi I, Brockmöller J, Mrozikiewicz PM, Bauer S, Loddenkemper R, Roots I. Homozygous rapid arylamine *N*-acetyltransferase (*NAT2*) genotype as a susceptibility factor for lung cancer. Cancer Res. 1996;56:3961–6.
117. McKay JD, Hashibe M, Hung RJ, Wakefield J, Gaborieau V, Szeszenia-Dabrowska N, Zaridze D, Lissowska J, Rudnai P, Fabianova E, Mates D, Foretova L, Janout V, Bencko V, Chabrier A, Hall J, Boffetta P, Canzian F, Brennan P. Sequence variants of NAT1 and NAT2 and other xenometabolic genes and risk of lung and aerodigestive tract cancers in Central Europe. Cancer Epidemiol Biomarkers Prev. 2008;17:141–7.

118. Bouchardy C, Mitrunen K, Wikman H, Husgafvel-Pursiainen K, Dayer P, Benhamou S, Hirvonen A. *N*-acetyltransferase *NAT1* and *NAT2* genotypes and lung cancer risk. Pharmacogenetics. 1998;8:291–8.
119. Zienolddiny S, Campa D, Lind H, Ryberg D, Skaug V, Stangeland LB, Canzian F, Haugen A. A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of non-small cell lung cancer in smokers. Carcinogenesis. 2008;29: 1164–9.
120. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature. 2001;411:366–74.
121. Kastan MB, Bartek J. Cell-cycle checkpoints and cancer. Nature. 2004;423:316–23.
122. Wood RD, Mitchell M, Lindahl T. Human DNA repair genes. Mutat Res. 2005;577:275–83.
123. Lavin MF, Kozlov S. ATM activation and DNA damage response. Cell Cycle. 2007;6:931–42.
124. Kastan MB, Derheimer DA. Multiple roles of ATM in monitoring and maintaining DNA integrity. Febs Lett. 2010;584:3675–81.
125. Shen L, Yin Z-H, Wan Y, Zhang Y, Li K, Zhou B-S. Association between ATM polymorphisms and cancer risk: a meta-analysis. Mol Biol Rep. 2012;39:5719–25.
126. Zhao L, Gu A, Guixiang J, Zhou P, Zhao P, Lu A. The association between ATM IVS 22–77 T>C and cancer risk: a meta-analysis. PLoS One. 2012;6:e29479.
127. Barzilay G, Hickson ID. Structure and function of apurinic/apyrimidinic endonucleases. Bioessays. 1995;17:713–9.
128. Tell G, Quadrifoglio F, Tribelli C, Kelley MR. Many functions of APE1/ref-1: not only DNA repair enzyme. Antioxid Redox Signal. 2009;11:601–20.
129. Xi T, Jones IM, Mohrenweiser HW. Many amino acid substitution variants identified in DNA repair genes during human population screenings are predicted to impact protein function. Genomics. 2004;83:970–9.
130. Zhou B, Shan H, Su Y, Xia K, Shao X, Mao W, Shao Q. The association of APE1–656T>G and 1349T>G polymorphism and cancer risk: a meta-analysis based on 37 case-control studies. BMC Cancer. 2011;11:521.
131. Ji Y-N, Zhan P, Wang J, Qiu L-X, Yu L-K. APE1 Asp148Glu gene polymorphism and lung cancer risk: a meta-analysis. Mol Biol Rep. 2011;38:4537–43.
132. Ma H, Xu L, Yan J, Shao M, Hu Wang F, Wang Y, Yuan W, Qian J, Wang Y, Xun P, Liu H, Chen W, Yang L, Jin G, Huo X, Chen F, Shugart YY, Jin L, Wei Q, Wu T, Shen H, Huang W, Lu D. Tagging single nucleotide polymorphisms in excision repair cross-complementing group 1 (ERCC1) and risk of primary lung cancer in a Chinese population. Pharmacogenet Genomics. 2007;17:417–23.
133. Yu JJ, Lee KB, Mu C, Li Q, Abernathy TV, Bostick-Bruton F, Reed E. Comparison of two human ovarian carcinoma cell lines (A2780/CP70 and MCAS) that are equally resistant to platinum, but differ at codon 118 of the ERCC1 gene. Int J Oncol. 2000;16:555–60.
134. Duell EJ, Wiencke JK, Cheng TJ, Varkonyi A, Zuo ZF, Ashok TD, Mark EJ, Wain JC, Christiani DC, Kelsey KT. Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. Carcinogenesis. 2000;21:965–671.
135. Lunn RM, Helzlsouer KJ, Parshad R, Umbach DM, Harris EL, Sanford KK, Bell DA. XPD polymorphisms: effects on DNA repair proficiency. Carcinogenesis. 2000;21:551–5.
136. Zhang L, Wang J, Xu L, Zhou J, Guan X, Jiang F, Wu Y, Fan W. Nucleotide excision repair gene ERCC1 polymorphisms contribute to cancer susceptibility: a meta analysis. Mutagenesis. 2011;27:67–76.
137. Kiyohara C, Yoshimasu K. Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. Int J Med Sci. 2007;4:59–71.
138. Hung RJ, Christiani DC, Risch A, Popanda O, Haugen A, Zienolddiny S, Benhamou S, Bouchardy C, Lan Q, Spitz MR, Wichmann HE, LeMarchand L, Vineis P, Matullo G, Kiyohara C, Zhang ZF, Pezeshki B, Harris C, Mechanic L, Seow A, Ng DP, Szeszenia-Dabrowska N, Zaridze D, Lissowska J, Rudnai P, Fabianova E, Mates D, Foretova L, Janout V, Bencko V, Caporaso N, Chen C, Duell EJ, Goodman G, Field JK, Houlston RS, Hong YC, Landi MT, Lazarus P, Muscat J, McLaughlin J, Schwartz AG, Shen H, Stucker I, Tajima K, Matsuo K, Thun M, Yang P, Wiencke J, Andrew AS, Monnier S, Boffetta P, Brennan P. International Lung Cancer Consortium: pooled analysis of sequence variants in DNA repair and cell cycle pathways. Cancer Epidemiol Biomarkers Prev. 2008;17:3081–9.
139. Janićijević A, Sugasawa K, Shimizu Y, Hanaoka F, Wijgers N, Djurica M, Hoeijmakers JH, Wyman C. DNA bending by the human damage recognition complex XPC-HR23B. DNA Repair (Amst). 2003;2:325–36.
140. Tapias A, Auriol J, Forget D, Enzlin JH, Schärer OD, Coin F, Coulombe B, Egly JM. Ordered conformational changes in damaged DNA induced by nucleotide excision repair factors. J Biol Chem. 2004;279:19074–83.
141. Rademakers S, Volker M, Hoogstraten D, Nigg AL, Moné MJ, Van Zeeland AA, Hoeijmakers JH, Houtsmuller AB, Vermeulen W. Xeroderma pigmentosum group A protein loads as a separate factor onto DNA lesions. Mol Cell Biol. 2003;23:5755–67.
142. Batty DP, Wood RD. Damage recognition in nucleotide excision repair of DNA. Gene. 2000;241:193–204.
143. Kozak M. Interpreting cDNA sequences: some insights from studies on translation. Mamm Genome. 1996;7:563–74.
144. Ding D, Zhang Y, Yu H, Guo Y, Jiang L, He X, Ma W, Zheng W. Genetic variation of XPA gene and risk of cancer: a systematic review and pooled analysis. Int J Cancer. 2012;131:488–96.
145. Qiao Y, Spitz MR, Shen H, Guo Z, Shete S, Hedayati M, Grossman L, Mohrenweiser H, Wei Q. Modulation of repair of ultraviolet damage in the host-cell reactivation assay by polymorphic XPC and XPD/ERCC2 genotypes. Carcinogenesis. 2002;23:295–9.
146. Vodicka P, Kumar R, Stetina R, Sanyal S, Soucek P, Haufroid V, Dusinska M, Kuricova M, Zamecnikova M, Musak L, Buchancova J, Norppa H, Hirvonen A, Vodickova L, Naccarati A, Matousu Z, Hemminki K. Genetic polymorphisms in DNA repair genes and possible links with DNA repair rates, chromosomal aberrations and single-strand breaks in DNA. Carcinogenesis. 2004;25:757–63.
147. Qiu L, Wang Z, Shi X, Wang Z. Association between XPC polymorphisms and risk of cancers: a meta-analysis. Eur J Cancer. 2008;44:2241–52.
148. Masson M, Niedergang C, Schreiber V, Muller S, Menissier-de Murcia J, de Murcia G. XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Mol Cell Biol. 1998;18:3563–71.
149. Abdel-Rahman SZ, Soliman AS, Bondy ML, Omar S, El-Badawy SA, Khaled HM, Seifeldin IA, Levin B. Inheritance of the 194Trp and the 399Gln variant alleles of the DNA repair gene XRCC1 are associated with increased risk of early-onset colorectal carcinoma in Egypt. Cancer Lett. 2000;159:79–86.
150. Lunn RM, Langlois RG, Hsieh LL, Thompson CL, Bell DA. XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. Cancer Res. 1999;59:2557–61.
151. Hu JJ, Smith TR, Miller MS, Mohrenweiser HW, Golden A, Case LD. Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. Carcinogenesis. 2001;22:917–1022.
152. Hao B, Miao X, Li Y, Zhang X, Sun T, Liang G, Zhao Y, Zhou Y, Wang H, Chen X, Zhang L, Tan W, Wei Q, Lin D, He F. A novel T-77C polymorphism in DNA repair gene XRCC1 contributes to diminished promoter activity and increased risk of non-small cell lung cancer. Oncogene. 2006;25:3613–20.
153. Hao B, Wang H, Zhou K, Li Y, Chen X, Zhou G, Zhu Y, Miao X, Tan W, Wei Q, Lin D, He F. Identification of genetic variants in base excision repair pathway and their associations with risk of esophageal squamous cell carcinoma. Cancer Res. 2004;64:4378–84.

154. Dai L, Duan F, Wang P, Song C, Wang K, Zhang J. XRCC1 gene polymorphisms and lung cancer susceptibility: a meta-analysis of 44 case-control studies. Mol Biol Rep. 2012;39:9535–47.[Epub ahead of print]. PMID: 22729882.
155. Spencer CC, Su Z, Donnelly P, Marchini J. Designing genome-wide association studies: sample size, power, imputation, and the choice of genotyping chip. PLoS Genet. 2009;5:1000477.
156. Orr N, Chanock S. Common genetic variation and human disease. Adv Genet. 2008;62:1–32.
157. Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, Chen C, Goodman G, Field JK, Liloglou T, Xinarianos G, Cassidy A, McLaughlin J, Liu G, Narod S, Krokan HE, Skorpen F, Elvestad MB, Hveem K, Vatten L, Linseisen J, Clavel-Chapelon F, Vineis P, Bueno-de-Mesquita HB, Lund E, Martinez C, Bingham S, Rasmuson T, Hainaut P, Riboli E, Ahrens W, Benhamou S, Lagiou P, Trichopoulos D, Holcátová I, Merletti F, Kjaerheim K, Agudo A, Macfarlane G, Talamini R, Simonato L, Lowry R, Conway DI, Znaor A, Healy C, Zelenika D, Boland A, Delepine M, Foglio M, Lechner D, Matsuda F, Blanche H, Gut I, Heath S, Lathrop M, Brennan P. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature. 2008;452:633–7.
158. Amos CI, Wu X, Broderick P, Gorlov IP, Gu J, Eisen T, Dong Q, Zhang Q, Gu X, Vijayakrishnan J, Sullivan K, Matakidou A, Wang Y, Mills G, Doheny K, Tsai YY, Chen WV, Shete S, Spitz MR, Houlston RS. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet. 2008;40:616–22.
159. Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, Manolescu A, Thorleifsson G, Stefansson H, Ingason A, Stacey SN, Bergthorsson JT, Thorlacius S, Gudmundsson J, Jonsson T, Jakobsdottir M, Saemundsdottir J, Olafsdottir O, Gudmundsson LJ, Bjornsdottir G, Kristjansson K, Skuladottir H, Isaksson HJ, Gudbjartsson T, Jones GT, Mueller T, Gottsäter A, Flex A, Aben KK, de Vegt F, Mulders PF, Isla D, Vidal MJ, Asin L, Saez B, Murillo L, Blondal T, Kolbeinsson H, Stefansson JG, Hansdottir I, Runarsdottir V, Pola R, Lindblad B, van Rij AM, Dieplinger B, Haltmayer M, Mayordomo JI, Kiemeney LA, Matthiasson SE, Oskarsson H, Tyrfingsson T, Gudbjartsson DF, Gulcher JR, Jonsson S, Thorsteinsdottir U, Kong A, Stefansson K. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature. 2008;452:638–42.
160. Broderick P, Wang Y, Vijayakrishnan J, Matakidou A, Spitz MR, Eisen T, Amos CI, Houlston RS. Deciphering the impact of common genetic variation on lung cancer risk: a genome-wide association study. Cancer Res. 2009;69:6633–41.
161. Landi MT, Chatterjee N, Yu K, Goldin LR, Goldstein AM, Rotunno M, Mirabello L, Jacobs K, Wheeler W, Yeager M, Bergen AW, Li Q, Consonni D, Pesatori AC, Wacholder S, Thun M, Diver R, Oken M, Virtamo J, Albanes D, Wang Z, Burdette L, Doheny KF, Pugh EW, Laurie C, Brennan P, Hung R, Gaborieau V, McKay JD, Lathrop M, McLaughlin J, Wang Y, Tsao MS, Spitz MR, Wang Y, Krokan H, Vatten L, Skorpen F, Arnesen E, Benhamou S, Bouchard C, Metspalu A, Vooder T, Nelis M, Välk K, Field JK, Chen C, Goodman G, Sulem P, Thorleifsson G, Rafnar T, Eisen T, Sauter W, Rosenberger A, Bickeböller H, Risch A, Chang-Claude J, Wichmann HE, Stefansson K, Houlston R, Amos CI, Fraumeni Jr JF, Savage SA, Bertazzi PA, Tucker MA, Chanock S, Caporaso NE. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet. 2009;85:679–91.
162. Wang Y, Broderick P, Webb E, Wu X, Vijayakrishnan J, Matakidou A, Qureshi M, Dong Q, Gu X, Chen WV, Spitz MR, Eisen T, Amos CI, Houlston RS. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet. 2008;40:1407–9.
163. McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, Byrnes G, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, McLaughlin J, Shepherd F, Montpetit A, Narod S, Krokan HE, Skorpen F, Elvestad MB, Vatten L, Njølstad I, Axelsson T, Chen C, Goodman G, Barnett M, Loomis MM, Lubiński J, Matyjasik J, Lener M, Oszutowska D, Field J, Liloglou T, Xinarianos G, Cassidy A, Study EPIC, Vineis P, Clavel-Chapelon F, Palli D, Tumino R, Krogh V, Panico S, González CA, Ramón Quirós J, Martínez C, Navarro C, Ardanaz E, Larrañaga N, Kham KT, Key T, Bueno-de-Mesquita HB, Peeters PH, Trichopoulou A, Linseisen J, Boeing H, Hallmans G, Overvad K, Tjønneland A, Kumle M, Riboli E, Zelenika D, Boland A, Delepine M, Foglio M, Lechner D, Matsuda F, Blanche H, Gut I, Heath S, Lathrop M, Brennan P. Lung cancer susceptibility locus at 5p15.33. Nat Genet. 2008;40:1404–6.
164. Li Y, Sheu CC, Ye Y, de Andrade M, Wang L, Chang SC, Aubry MC, Aakre JA, Allen MS, Chen F, Cunningham JM, Deschamps C, Jiang R, Lin J, Marks RS, Pankratz VS, Su L, Li Y, Sun Z, Tang H, Vasmatzis G, Harris CC, Spitz MR, Jen J, Wang R, Zhang ZF, Christiani DC, Wu X, Yang P. Genetic variants and risk of lung cancer in never smokers: a genome-wide association study. Lancet Oncol. 2010;11:321–30.
165. Truong T, Hung RJ, Amos CI, Wu X, Bickeböller H, Rosenberger A, Sauter W, Illig T, Wichmann HE, Risch A, Dienemann H, Kaaks R, Yang P, Jiang R, Wiencke JK, Wrensch M, Hansen H, Kelsey KT, Matsuo K, Tajima K, Schwartz AG, Wenzlaff A, Seow A, Ying C, Staratschek-Jox A, Nürnberg P, Stoelben E, Wolf J, Lazarus P, Muscat JE, Gallagher CJ, Zienolddiny S, Haugen A, van der Heijden HF, Kiemeney LA, Isla D, Mayordomo JI, Rafnar T, Stefansson K, Zhang ZF, Chang SC, Kim JH, Hong YC, Duell EJ, Andrew AS, Lejbkowicz F, Rennert G, Müller H, Brenner H, Le Marchand L, Benhamou S, Bouchardy C, Teare MD, Xue X, McLaughlin J, Liu G, McKay JD, Brennan P, Spitz MR. Replication of lung cancer susceptibility loci at chromosomes 15q25, 5p15, and 6p21: a pooled analysis from the International Lung Cancer Consortium. J Natl Cancer Inst. 2010;102:959–71.
166. Lansdorp PM. Telomeres and disease. EMBO J. 2009;28: 2532–40.
167. Fernandez-Garcia I, Ortiz-de-Solorzano C, Montuenga LM. Telomeres and telomerase in lung cancer. J Thorac Oncol. 2008; 3:1085–8.
168. Stücker I, Boffetta P, Anttila S, Benhamou S, Hirvonen A, London S, Taioli E. Lack of interaction between asbestos exposure and glutathione S-transferase M1 and T1 genotypes in lung carcinogenesis. Cancer Epidemiol Biomarkers Prev. 2001;10:1253–8.
169. López-Cima MF, Alvarez-Avellón SM, Pascual T, Fernández-Somoano A, Tardón A. Genetic polymorphisms in CYP1A1, GSTM1, GSTP1 and GSTT1 metabolic genes and risk of lung cancer in Asturias. BMC Cancer. 2012;12:433.
170. Nazar-Stewart V, Vaughan TL, Stapleton P, Van Loo J, Nicol-Blades B, Eaton DL. A population-based study of glutathione S-transferase M1, T1 and P1 genotypes and risk for lung cancer. Lung Cancer. 2003;40:247–58.
171. Jourenkova-Mironova N, Wikman H, Bouchardy C, Voho A, Dayer P, Benhamou S, Hirvonen A. Role of glutathione S-transferase GSTM1, GSTM3, GSTP1 and GSTT1 genotypes in modulating susceptibility to smoking-related lung cancer. Pharmacogenetics. 1998;8:495–502.
172. Reszka E, Wasowicz W. Significance of genetic polymorphisms in glutathione S-transferase multigene family and lung cancer risk. Int J Occup Med Environ Health. 2001;14:99–113.
173. Risch A, Wikman H, Thiel S, Schmezer P, Edler L, Drings P, Dienemann H, Kayser K, Schulz V, Spiegelhalder B, Bartsch H. Glutathione-S-transferase M1, M3, T1 and P1 polymorphisms and susceptibility to non-small-cell lung cancer subtypes and hamartomas. Pharmacogenetics. 2001;11:757–64.
174. Yin L, Pu Y, Liu TY, Tung YH, Chen KW, Lin P. Genetic polymorphisms of NAD(P)H quinone oxidoreductase, CYP1A1 and microsomal epoxide hydrolase and lung cancer risk in Nanjing, China. Lung Cancer. 2001;33:133–41.

Lung Cancer: Molecular Markers

12

Penny E.H. Nymark and Sisko Anttila

Keywords
Occupational lung cancer • Molecular markers • Biomarkers • Chromosomal aberrations • Gene expression profiling • Genomics • Epigenetic changes • Gene copy number profiling • Asbestos

Introduction

Lung cancer is the most frequent and one of the most devastating occupational cancers [1]. Therefore, early detection is a major focus area and could be improved by the use of molecular markers. Specific molecular markers are also crucial in the development of molecular diagnosis and molecular targeted treatments. Molecular markers can reflect either the early effects of exposure or the secondary effects of the exposure-related early effects, which are more closely related to the actual disease process. Although early effects may be reversible or have a very low probability of causing the development of a tumor, they can also be closely related to the disease process. To make a molecular marker relevant in disease prevention, it should measure an event in the disease process. Furthermore, it should be able to accommodate individual differences in exposure and susceptibility, be readily detectable, and show a dose-response to the exposure level [2].

P.E.H. Nymark, PhD
Department of Toxicogenomics, Maastricht University, Maastricht, Netherlands

S. Anttila, MD, PhD (✉)
Jorvi Hospital Laboratory of Pathology, Helsinki University Central Hospital, Hospital District of Helsinki and Uusimaa, Laboratory Services, HUSLAB, Helsinki, Finland

Health and Work Ability, Finnish Institute of Occupational Health, Helsinki, Finland
e-mail: sisko.l.anttila@hus.fi

It has, however, been difficult to identify exposure-specific molecular markers for occupationally derived lung cancer due to several confounding factors, such as tobacco smoking and other environmental exposures. Further difficulties include collecting proper samples and characterization of the study population, such as obtaining detailed occupational histories. In addition, the potential for interaction between occupational and environmental exposures, such as the well-known synergism between tobacco smoke and asbestos (see Chap. 10 for a more in-depth discussion), further complicates the identification of exposure-specific molecular markers and the use of these as markers of attribution in medicolegal connection. Nevertheless, some efforts have been made, and a basis for the development of such markers has been laid. For example, asbestos exposure-related chromosomal aberrations and alterations in microRNA expression have been described in lung cancer. However, none of these have been implicated in clinical use so far [3].

Disease-specific markers can be detected as gene products either in target tissues, such as lung or tumor tissue, or in surrogate tissues obtained with less invasive operations, such as blood, effusion fluid, and bronchoalveolar lavage fluid, or in the best of cases in exhaled breath condensate (EBC) [1]. The use of tissues that can be obtained with non-invasive techniques is important especially in the surveillance and screening of healthy people for cancer prevention or early detection. Gessner et al. showed that EBC contains DNA suitable for amplification [4]. *TP53* gene mutations were detected in the EBC of lung cancer patients, while no mutation was found in healthy volunteers [5]. Furthermore, microsatellite DNA alterations specific to lung cancer have also been detected in EBC [6, 7].

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_12,

Table 12.1 Alterations in chromosomes, genes, and pathways associated with occupational exposures to asbestos in lung cancer

Alteration	Consequence or carcinogenic association	Type of study	References
AI and loss at 2p16		Lung cancer of asbestos-exposed individuals	[10]
LOH at 3p14	*FHIT* exon loss	Lung cancer of asbestos-exposed individuals	[11, 12]
LOH at 3p21	Possible downregulation of tumor suppressors	Lung cancer of asbestos-exposed individuals	[13, 14]
LOH/homozygous deletion at 9p21.3	Loss of *P16/CDKN2A*	Lung cancer of asbestos-exposed individuals	[15]
CNA at 9q33.1		Lung cancer of asbestos-exposed individuals	[16]
Break at the centromere of chromosome 9		In vitro	[17]
Monosomy of chromosome 19	Possible downregulation of tumor suppressors	In vitro	[18]
AI and loss at 19p13	Possible downregulation of tumor suppressors	In vitro; lung cancer of asbestos-exposed individuals	[19]
Polyploidy	Aneuploidy and CIN	In vitro; lung cancer of asbestos-exposed individuals	[16, 20]
Upregulation of *TP53*	Decreased or abnormal tumor suppressor activity possibly due to mutations	In vitro; lung cancer of asbestos-exposed individuals	[21–27] and reviewed in [3, 28]
Serum Ras (p21)	Upregulation due to mutations	Lung cancer of asbestos-exposed individuals	[29] and reviewed in [1]
KRAS	Specific mutations	Lung cancer of asbestos-exposed individuals	[30, 31]

It has been proposed that combinations of several markers, rather than single molecular markers alone, are able to improve diagnosis [8, 9]. For example, serum biomarkers (e.g., p53, anti-p53, Ras also called p21, EGFR) have shown to have high specificities in indicating occupationally derived lung cancer but very low sensitivities, and they are not presently recommended for clinical use. However, they could possibly be used in a panel of tumor-specific molecular markers, i.e., a combination of different markers in the form of molecular assays. Nevertheless, methods must be standardized and those used validated, before such molecular assays can be applied in clinical practice [1].

In the following, we discuss molecular markers in relation to asbestos exposure and touch a few relevant other exposures, such as tobacco smoking. Table 12.1 presents a summary of molecular markers associated with asbestos exposure in lung cancer patients.

Occupational Exposures and Tobacco Smoking

Lung cancer of never smokers (~25 % of all lung cancers) has molecularly been considered a completely different disease to that of smokers [32]. Some of the molecular alterations in the lung cancer of never smokers may be due to other types of environmental exposures (including occupational exposures). Therefore, studies on lung cancer in never smokers may provide insights into the molecular alterations involved in occupationally derived lung cancer, especially since the majority of patients with occupationally derived lung cancer are also smokers (up to 70 % in certain asbestos worker populations [33]), which confounds the analysis on specific molecular alteration related to other exposures. Some of the typical alterations associated with never smoking in lung cancer are the *EML4-ALK* fusion gene caused by an inversion in chromosome 2, hypermethylation of *MGMT*, mutation of *EGFR*, specific mutations in *TP53* (G:C to A:T at non-CpG sites) [32], and allelic loss of *FHIT* [32, 34]. Interestingly, a combination of *TP53* mutations and allelic loss of *FHIT* is typical for adenocarcinoma (AC) in never smokers [32], and loss of *FHIT* has also been associated with asbestos exposure in lung cancer patients [11].

Specific mutations in *TP53* (especially G to T transversions) have been linked to tobacco smoking, and these are rarely found in cancers of organs other than the lung, indicating that other types of mutations are related to other exposures [35]. For example, deletion mutations in the gene have only been found in ex-smokers or nonsmokers exposed to ETS (environmental tobacco smoke) [36].

Nonetheless, in most cases, tobacco smoke greatly enhances the carcinogenic effect of an occupational exposure, such as asbestos, radon, and arsenic. Thus, the molecular alterations in the lung cancer of smoking patients with a history of occupational lung carcinogen exposure may be specific to the combinatorial exposure. However, it is also likely that cells with molecular alterations caused by one of the carcinogens are allowed to proliferate and clonally expand due to alterations caused by the other carcinogen. For example, asbestos exposure is known to induce cell proliferation at low doses, thereby possibly leading to the clonal expansion of

cells with heritable tobacco carcinogen-induced alterations in critical genes (reviewed in [8]). In this case, it may be impossible to identify molecular markers associated with occupational exposures, even if the exposure has played a relevant role in driving the disease.

Asbestos

Several different types of genetic, epigenetic, and gene expression alterations have been reported as being associated with asbestos exposure in lung cancer. Here we discuss the alterations that could possibly be useful in clinical settings. Furthermore, we will emphasize findings that have also been detected in malignant mesothelioma, another asbestos-related cancer. Similar alterations in these two cancers may be considered more strongly asbestos-related. The reader is referred to Chaps. 2 and 3 for a description of the terminology and basic biological mechanisms, and Chap. 19 for a detailed discussion on the molecular markers in malignant mesothelioma. Chapter 19 also introduces the methods used for identifying genetic changes, which too apply largely to asbestos-related lung cancer.

Gene Copy Number Markers

Asbestos-specific chromosomal and genetic alterations in lung cancer have been described in several chromosomes, e.g., 2p, 3p, 9, and 19p. Two studies have shown that a common early alteration in lung cancer, namely loss of 3p21, occurs more frequently in the tumors of asbestos-exposed than non-exposed patients. First, Marsit et al. found that frequent allelic imbalance (AI) in 3p21.3 was associated with occupational asbestos exposure as well as with *TP53* mutations and better patient survival [13]. Later in another study, 3p21.3 was found to be one of the most significant regions differing in copy number between the lung tumors of asbestos-exposed and non-exposed patients [14]. This study identified 18 asbestos-related copy number alterations (CNA), 6 of which were also associated with asbestos-related gene expression changes, by using a whole-genome CNA and gene expression screening on two groups of cancer patients, asbestos-exposed and non-exposed, matched for age, gender, smoking status, and cancer histology (Fig. 12.1) [14, 37]. Interestingly, loss of 3p21.3 and promoter hypermethylation of the gene *RASSF1A*, located in this region, has also shown to be frequent in malignant

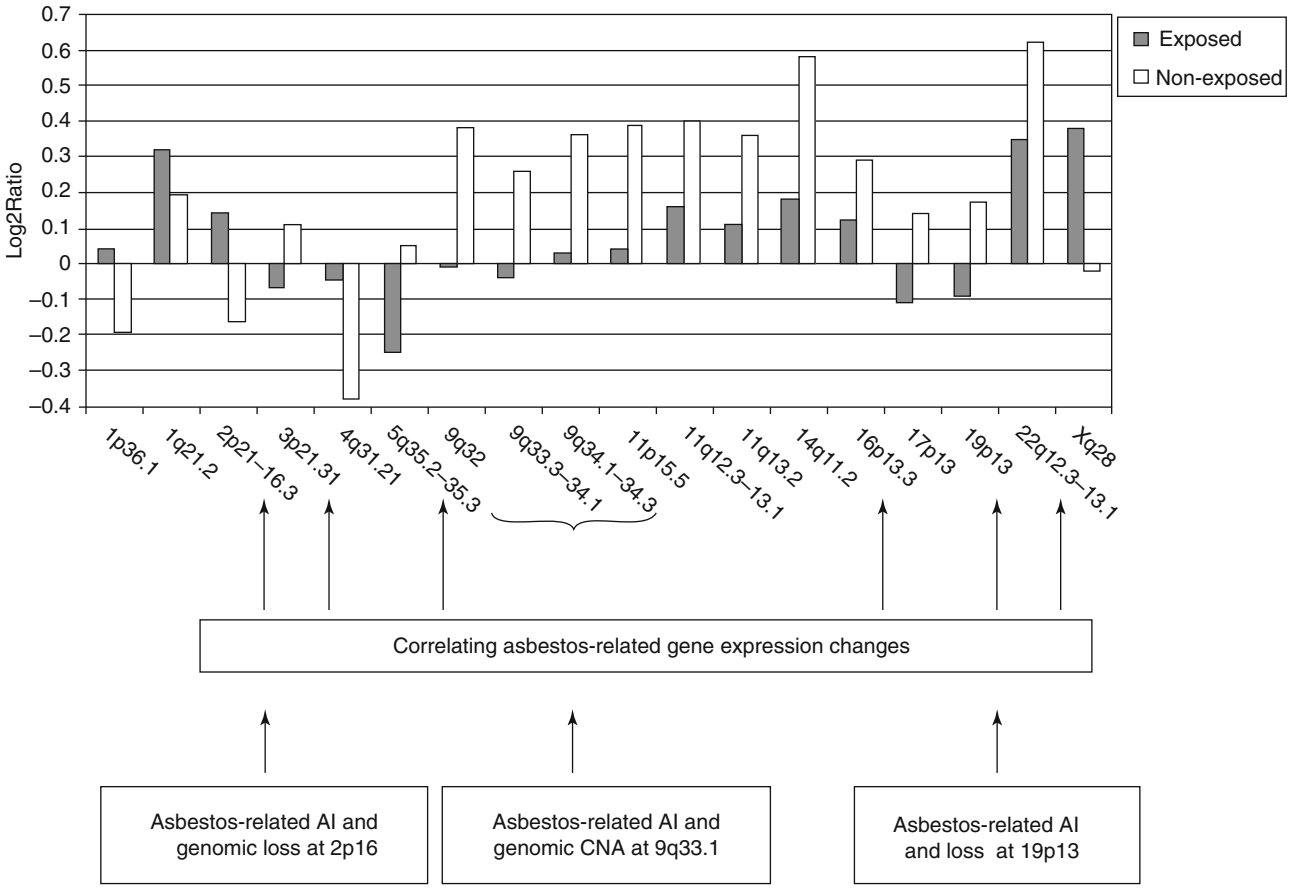


Fig. 12.1 Regions showing different copy numbers between asbestos-related (*gray*) and non-related (*white*) lung cancer using array comparative genomic hybridization (*CGH*). The *Y*-axis represents the average $\log_2$ ratios of all array probes in all samples in each chromosomal region (*X*-axis) (Modified from Nymark et al. [14])

mesothelioma [38, 39]. In addition, loss of another region in the short arm of chromosome 3, namely 3p14 containing the *FHIT* gene, has been associated with asbestos exposure and tobacco smoking [12]. However, Pylkkänen et al. detected reduced *FHIT* expression in both asbestos-exposed and non-exposed patients' lung tumors [11]. The region contains a fragile site, FRA3, and it has been reported that asbestos-related CNA may be associated with fragile sites [14], indicating that asbestos may preferentially cause DNA damage at such sites.

p16/INK4A (9p21.3), a regulator of p53, has been found to be affected by homozygous deletion more frequently among asbestos-exposed patients' lung tumors than among non-exposed patients' lung tumors, which, in contrast, show more frequent methylation of the gene [15] (Fig. 12.2). The frequencies of homozygous deletion (50 %) and methylation (24 %) in asbestos-related lung cancer were similar to those seen in malignant mesothelioma (40–70 and 13–19 %, respectively; see Chap. 19 and [40–42]), while non-asbestos-related lung cancer showed opposite frequencies (24 and 49 %, respectively) [15]. Others have, however, reported that both mechanisms of inactivation correlate with asbestos exposure in non-small cell lung cancer (NSCLC) [43, 44] and, in general, also epigenetic changes, such as methylation, are thought to contribute significantly to the development of asbestos-related lung cancer [45].

The chromosomal region 9q33.1 is affected by both AI and CNA more frequently in asbestos-related than in non-related NSCLC [16] (Fig. 12.3a). Furthermore, CNA in this region increased in frequency with the intensity of exposure, showing a dose-response relationship with the pulmonary asbestos fiber count [16]. The most significant dose dependence was seen among adenocarcinoma (AC) (Fig. 12.3a). Interestingly, losses initiating at 9q33.1 have also been identified in malignant mesothelioma [39]. In vitro, chromosome 9 has been shown to be affected by breaks at the centromere in human amniotic fluid cells exposed to asbestos [17].

Asbestos-related losses and allelic imbalance (AI) in human lung cancer have also been observed in the 19p13.3 region [19, 37]. AI at 19p13.3 appeared to be common in lung AC regardless of the patients' asbestos exposure, whereas in the other major histological types, AI in this region was associated with asbestos exposure [19]. In contrast, loss at 19p13 in AC, detected by FISH, increased in frequency with the intensity of exposure, i.e., showed a dose-dependent response to increasing pulmonary fiber count (Fig. 12.3b). We did not see such a trend with all histological types combined (Fig. 12.3b), although recent results from our laboratory using an increased number of samples indicate a similar dose dependence for 19p13.3 loss among all histological types. Interestingly, monosomy of chromosome 19 has been detected in vitro in asbestos-transformed human bronchial epithelial cell lines [18]. In addition, other in vitro

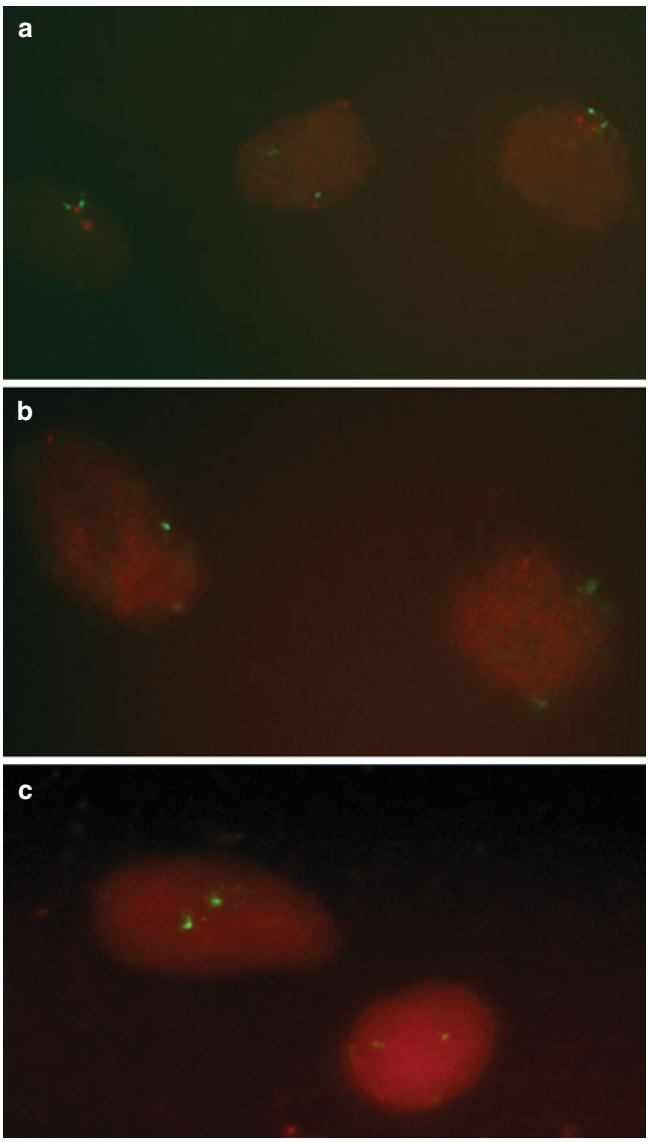


Fig. 12.2 Dual-color FISH with a *P16/CDKN2A*-specific DNA probe (*red signal*) and a chromosome 9 centromere probe (*green signal*). **(a)** Normal lung tissue with two *red signals* and two *green signals*. **(b)** NSCLC case showing two *green signals* and one *red signal* indicating a loss of heterozygosity of the *P16/CDKN2A* gene. **(c)** NSCLC case showing two *green signals* and no *red signal*, indicating a homozygous deletion of the *P16/CDKN2A* gene. *NSCLC* non-small cell lung cancer (Reprinted from Andujar et al.[15], Copyright 2010, with permission from Elsevier)

experiments showed that 19p fragments were lost through micronuclei (MN) induced by exposure to crocidolite asbestos in the immortalized human bronchial epithelial cell line [19]. MN are formed from whole chromosomes or chromosomal fragments that lag behind during cell division, which provides a mechanistic explanation as to how the 19p fragments are lost. Recently, loss of chromosome 19 was also reported as the second most frequent numerical change in malignant mesothelioma [46]. In addition, in the same study,

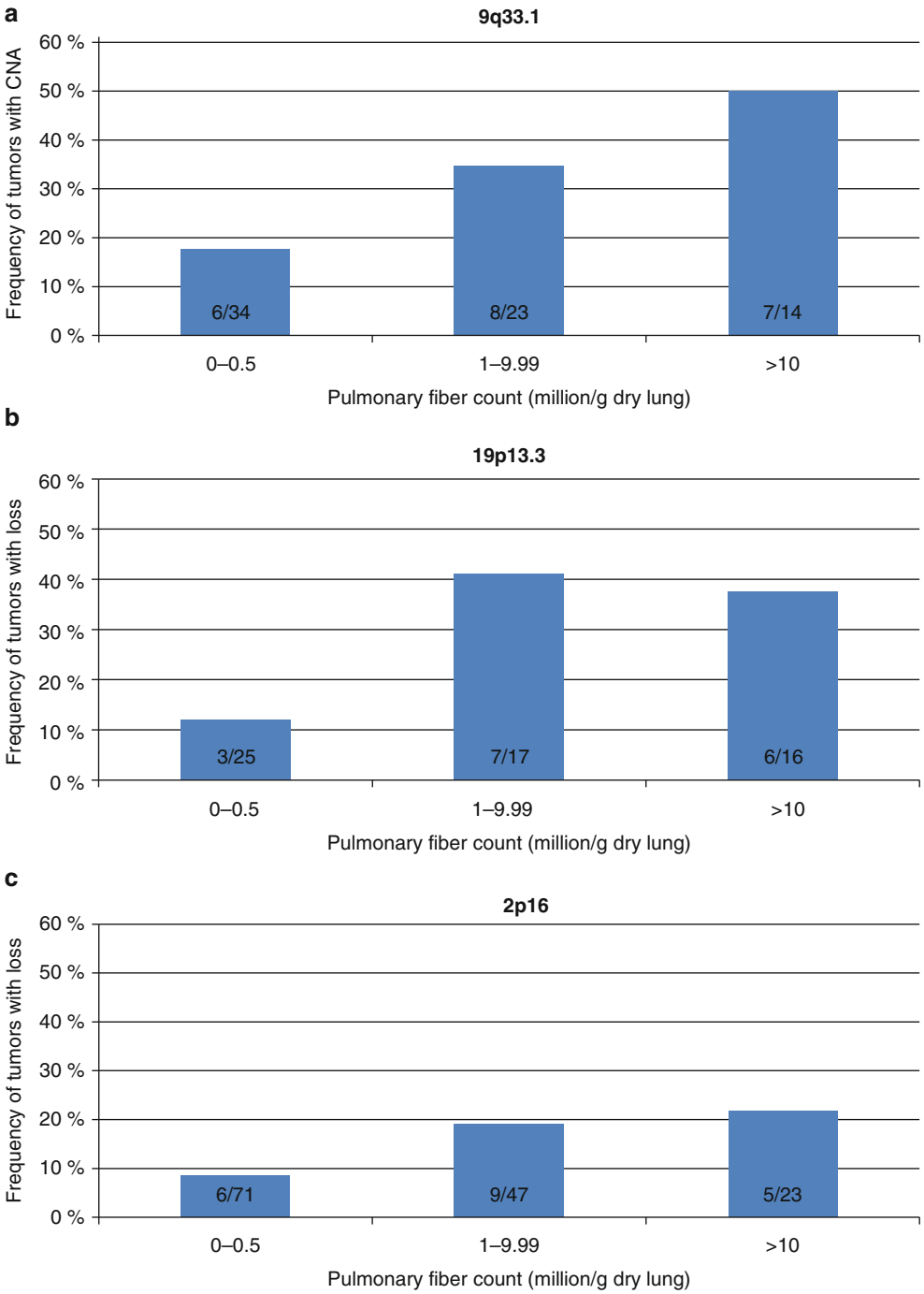


Fig.12.3 Frequency and dose–response of asbestos-related copy number alterations (*CNA*) in lung cancer. (**a**) CNA at 9q33.1 in non-small cell lung cancer, (**b**) loss at 19p13 in all histological tumor types, and (**c**) loss at 2p16 in all histological tumor types in asbestos-exposed (≥10 and 1–9.9 million fibers/g dry lung) and non-exposed (0–0.5 million fibers/g) patients. The number of samples with CNA/number of all samples is shown at the bottom of each column (**a** Reprinted from Nymark et al. [16])

a minimal common area deleted in malignant mesothelioma cases was localized close to region 19p13 [46].

Loss at 2p16, although very rare in lung cancer, has been found to be more frequent in asbestos-related than in non-related lung cancer [10] (Fig. 12.3c), and the losses showed a dose-response relationship with increasing exposure, similarly to 9q33.1 and 19p13 (Fig. 12.3c). Furthermore, an in vitro study found gene expression changes to be enriched at 2p in asbestos-exposed cell lines compared to untreated cells [47]. Interestingly, the region contains a fragile site, similarly to the 3p region, as mentioned above.

Another region worth mentioning is 14q11.2, which we found to be affected by a copy number change in asbestos-related lung cancer different to that of non-related lung cancer in a whole-genome screening study comparing lung cancers of exposed and non-exposed individuals (mentioned

above) [14]. The region lies within an area (14q11.2-q21) that was recently specifically associated with asbestos exposure in mesothelioma ([48]; see Chap. 19).

Finally, polyploidy has been shown to be more frequent in asbestos-related (48 %) compared to non-related lung cancer (29 %; [16]). Indeed, in vitro, asbestos has shown to induce polyploidy by sterically blocking cytokinesis [20] (see Chap. 17 for a more detailed discussion).

Tumor Suppressor Gene and Oncogene Markers

TP53 is probably the most extensively studied gene in relation to asbestos exposure in lung cancer, as to many other cancers, due to its crucial role in DNA damage response. At this point, we must touch on the subject of gene expression, which will, however, be discussed in detail below. *TP53* has been found to be upregulated after asbestos exposure in vitro, and abnormal accumulation of the protein has been detected more frequently in tumors and serum from exposed lung cancer patients compared to those of patients without asbestos exposure [21–24]. *TP53* mutations are known to be associated with abnormal accumulation of p53 protein, and indeed, many [25–27] but not all studies [49] have reported the mutations in the gene as being more frequent in the lung tumors of asbestos-exposed patients than in those of non-exposed patients. *TP53* mutations have also been identified in vitro after crocidolite exposure to mouse fibroblasts [50]. Some studies on human lung tumors have linked specific mutations, i.e., predominantly in exons 9–11, to asbestos exposure [51, 52], but we could speculate that at least a part of these mutations are primarily caused by tobacco-specific carcinogens, such as benzo[*a*]pyrene, which have shown to have an enhanced mutagenic effect following coexposure with amosite asbestos in the rat lung [53].

In conclusion, p53 seems to be a good marker for lung cancer itself but does not differentiate cancers according to etiological factors. Problems arise especially when occupationally exposed patients are also smokers, and although p53 may be a good marker for the early detection of lung cancer, it still does not solve the problem as to whether the cancer is derived from occupational exposure or from tobacco smoke. Therefore, it is not useful in medicolegal issues. However, a statistically significant association between serum anti-p53 antibody and the development of cancer in an asbestosis cohort has been demonstrated, and since the anti-p53 antibody is very rare in healthy controls, these results are considered to have high predictive value even if sensitivity is very low [54]. p53 antibodies have specifically been associated with detectable mutations in *TP53* in lung tumors [55].

Asbestos exposure causes oxidative stress, which induces 8-OHG adducts (see Chap. 10). These adducts are mutagenic and may cause G:C to T:A transversions. Such nucleotide transversions have been found to be more frequent in the tumors of asbestos-exposed individuals than in those with no history of asbestos exposure [56]. High levels of G to T transversions in codon 12 especially but also in codons 13 and 61 of the *KRAS* oncogene have been reported in lung cancer patients exposed to asbestos, especially in asbestos-related lung AC, in some studies [30, 31], but not in all [49]. In contrast, no mutations could be found in the *KRAS* gene in five asbestos-transformed malignant cell lines, which suggests that these mutations may be a result of the synergistic effects of asbestos and tobacco carcinogens [57].

Gene Expression Markers

Several genes are differentially regulated in asbestos-related lung cancer; however, most of them are related to the general response of a cell to foreign material, e.g., oxidative stress, inflammation, DNA damage response, mitochondrial activity, and apoptosis. These types of genes are often also deregulated in lung cancer without occupational association. Changes in expression that can directly be assumed to be related to asbestos exposure and therefore could be used as asbestos-associated molecular markers have rarely been identified. Nevertheless, some have, which we will describe below.

The epidermal growth factor receptor (*EGFR*) is a well-known oncogene. Serum EGFR has been found to be higher in patients with asbestosis (asbestos-induced pulmonary fibrosis) who developed lung cancer than in asbestosis patients without cancer and healthy non-exposed controls [1, 58]. In addition, oncoprotein Ras (p21) has been detected in the serum of asbestosis patients prior to cancer development [1, 29].

Furthermore, some single genes have been found to be differentially regulated in asbestos-related lung cancer compared to non-related. For example, *ADAM28* was identified as a potential oncogene in asbestos-related AC [59], and interestingly the gene has been predicted to be regulated by a microRNA (miR-429), which has shown to be downregulated in mesothelioma [60, 61]. It has also been found that the *AnxA2* gene is overexpressed in the lung cancer and normal tissue of asbestos-exposed patients [59, 62].

Epigenetic Markers

MicroRNAs (miRNAs) have recently become very highly valued for their prognostic signatures in several types of cancer. miRNAs are small noncoding RNA molecules that regulate the translation of protein-coding mRNAs and appear to be more specific in predicting clinical outcome, compared to mRNAs [63]. The deregulated expression of a few miRNAs

has recently been associated with asbestos-related lung cancer [64]. An integrative study using DNA copy number, gene expression (mRNA), and miRNA expression data from the same patients indicated that asbestos-related lung cancers, primarily those with AC histology, could be identified based on the expression of a few specific miRNAs (e.g., miR-148b, miR-202, miR-96, and let-7d/e). Integration of mRNA and miRNA data identified several inversely correlated target genes, such as *GADD45A* and *FOSB*, which have both been proposed to be tumor suppressors. Furthermore, the squamous cell carcinoma (SqCC)-specific miRNA miR-205 has been shown to be overexpressed in the histologically normal lung tissue of patients with asbestos-related lung cancer compared to the normal samples of lung cancer patients without asbestos exposure, indicating that this miRNA may be upregulated at an earlier stage in asbestos-related tumorigenesis of the lung [64]. However, these results call for verification in larger study populations and with techniques targeting specific miRNAs.

Markers of Asbestos Attribution: Specificity and Sensitivity

The use of a molecular assay as a sign of attribution requires that the molecular alteration in question has been shown to be specific to a carcinogen, preferably in humans as well as in experimental settings, and is known to play a role in the carcinogenic process. The determination of the specificity and especially the sensitivity of a marker is difficult even when asbestos exposure has been reliably assessed by the exposure history and pulmonary asbestos body and fiber counts in the study population. The sensitivity is hampered by the fact that in any group of asbestos-exposed lung cancer patients, not all cancers are caused by asbestos, and the proportion of causally associated cancers is dependent on the risk level in that group (e.g., with a twofold risk, 50 % of cancers are caused by asbestos). However, the development of a molecular assay for asbestos attribution would enhance recognition of asbestos-related occupational cancers and could possibly pick up some asbestos-related cancers which cannot be conventionally recognized, for example, lung cancer of a nonsmoker or smoker with low-level exposure, or exclude the occupational factor in lung cancer of a smoker.

We have recently determined the specificity and sensitivity of the previously identified asbestos-associated gene copy number changes in the detection of asbestos exposure, i.e., AI and loss at 2p16 and 19p13 and AI and CNA at 9q33.1, described above. AI and copy number alterations at these regions were studied in 100–over 200 lung tumors from asbestos-exposed and non-exposed patients, depending on the region. In general, asbestos exposure could be detected by FISH probes with a very high specificity and low sensitivity, whereas AI gave lower specificities and higher sensitivities [65]. By combining FISH results from the three regions, the specificity of 100 % was reached, whereas the sensitivity remained low. AI from all regions gave the specificity of 89 % and the sensitivity of 74–76 % [65]. The feasibility of a molecular assay in the determination of asbestos attribution should be evaluated by comparison with the present criteria of attribution preferably in international multicenter studies, taking into account exposures to different asbestos fiber types.

Molecular Markers Identified in Lung Cancer with Occupational Exposures Other than Asbestos

Molecular alterations either specific to or typical of occupational lung cancer derived from exposures to lung carcinogens, other than asbestos, are not well known. These alterations are discussed in Chap. 10, in association with carcinogenic mechanisms. As noted above, studies on sufficiently large series of lung cancer cases with tissue material available, and well-characterized occupational carcinogen exposure, are rare. Moreover, workers are seldom exposed to a single carcinogenic compound but to a mixture of carcinogenic agents, and smoking, either personal or secondhand, complicates the exposures even further.

Molecular changes in lung cancer, for example, *TP53* and *KRAS* mutations related to tobacco carcinogens, and occupational exposures to similar compounds, such as PAH, are not separable (see above). Moreover, many carcinogenic agents, including asbestos, silica, metals, and ionizing radiation, induce oxidative stress, with similar effects regardless of the exposure. Although many of the alterations found in lung cancers related to these exposures may be associated to the common carcinogenic pathways, a few changes may be more specific, consequent to unique carcinogenic mechanisms (discussed in Chap. 10). Examples of these alterations include the typical gene copy number changes in the lung cancer of arsenic-exposed populations [66] and epigenetic alteration profiles in the lung cancer of chromate workers [67, 68].

Conclusion

The search for molecular markers for carcinogen-derived cancers has benefitted from technology, permitting large-scale screening of genetic and epigenetic changes, and the discovery of previously unknown mechanisms and molecular alterations. The best example is asbestos-related lung cancer, with several molecular alterations, found to be associated with patients' occupational asbestos exposure, and the alterations in agreement with the known mechanisms of asbestos carcinogenesis. In studies

on human lung cancer, the difficulty is to find patients and tissue materials with a detailed exposure history available and a sufficiently homogenous study population as regards exposures, patients, and tumor characteristics. Experimental studies using human lung cell lines and animal experiments provide important mechanistic and supporting data for the search of carcinogen-specific molecular markers. The development of clinically useful markers requires validations and the standardization of detection methods as well as an efficient combination of different markers in so-called molecular assays. Furthermore, the sensitivity and specificity of these markers and marker combinations should be evaluated in prospective multicenter studies.

Acknowledgments The writing of this chapter was financially supported by the Jalmari and Rauha Ahokas Foundation, Helsinki (PN), and Helsinki and Uusimaa Health Care District Research Funds (SA).

References

1. Helmig S, Schneider J. Oncogene and tumor-suppressor gene products as serum biomarkers in occupational-derived lung cancer. Expert Rev Mol Diagn. 2007;7:555–68.
2. Talaska G, Roh J, Zhou Q. Molecular biomarkers of occupational lung cancer. Yonsei Med J. 1996;37:1–18.
3. Kamp DW. Asbestos-induced lung diseases: an update. Transl Res. 2009;153:143–52.
4. Gessner C, Rechner B, Hammerschmidt S, et al. Angiogenic markers in breath condensate identify non-small cell lung cancer. Lung Cancer. 2010;68:177–84.
5. Corradi M, Gergelova P, Mutti A. Use of exhaled breath condensate to investigate occupational lung diseases. Curr Opin Allergy Clin Immunol. 2010;10(2):93–8.
6. Mutti A. Molecular diagnosis of lung cancer: an overview of recent developments. Acta Biomedica. 2008;79 Suppl 1:11–23.
7. Carpagnano GE, Foschino-Barbaro MP, Spanevello A, et al. 3p microsatellite signature in exhaled breath condensate and tumor tissue of patients with lung cancer. Am J Resp Crit Care Med. 2008;177:337–41.
8. Nymark P, Wikman H, Hienonen-Kempas T, Anttila S. Molecular and genetic changes in asbestos-related lung cancer. Cancer Lett. 2008;265:1–15.
9. Gube M, Taeger D, Weber D, et al. Performance of biomarkers SMRP, CA125, and CYFRA 21-1 as potential tumor markers for malignant mesothelioma and lung cancer in a cohort of workers formerly exposed to asbestos. Arch Toxicol. 2010;85:185–92.
10. Kettunen E, Aavikko M, Nymark P, et al. DNA copy number loss and allelic imbalance at 2p16 in lung cancer associated with asbestos exposure. Br J Cancer. 2009;100:1336–42.
11. Pylkkänen L, Wolff H, Stjernvall T, et al. Reduced Fhit protein expression and loss of heterozygosity at FHIT gene in tumours from smoking and asbestos-exposed lung cancer patients. Int J Oncol. 2002;20:285–90.
12. Nelson H, Wiencke J, Gunn L, Wain J, Christiani D, Kelsey K. Chromosome 3p14 alterations in lung cancer: evidence that FHIT exon deletion is a target of tobacco carcinogens and asbestos. Cancer Res. 1998;58:1804–7.
13. Marsit CJ, Hasegawa M, Hirao T, et al. Loss of heterozygosity of chromosome 3p21 is associated with mutant TP53 and better patient survival in non-small-cell lung cancer. Cancer Res. 2004;64:8702–7.
14. Nymark P, Wikman H, Ruosaari S, et al. Identification of specific gene copy number changes in asbestos-related lung cancer. Cancer Res. 2006;66:5737–43.
15. Andujar P, Wang J, Descatha A, et al. p16INK4A inactivation mechanisms in non-small-cell lung cancer patients occupationally exposed to asbestos. Lung Cancer. 2010;67:23–30.
16. Nymark P, Kettunen E, Aavikko M, et al. Molecular alterations at 9q33.1 and polyploidy in asbestos-related lung cancer. Clin Cancer Res. 2009;15:468–75.
17. Dopp E, Schuler M, Schiffmann D, Eastmond DA. Induction of micronuclei, hyperdiploidy and chromosomal breakage affecting the centric/pericentric regions of chromosomes 1 and 9 in human amniotic fluid cells after treatment with asbestos and ceramic fibers. Mutat Res/Fundam Mol Mech Mutagen. 1997;377:77–87.
18. Suzuki M, Piao C, Zhao Y, Hei T. Karyotype analysis of tumorigenic human bronchial epithelial cells transformed by chrysolite asbestos using chemically induced premature chromosome condensation technique. Int J Mol Med. 2001;8:43–7.
19. Ruosaari S, Nymark P, Aavikko M, et al. Aberrations of chromosome 19 in asbestos-associated lung cancer and in asbestos-induced micronuclei of bronchial epithelial cells in vitro. Carcinogenesis. 2008;29:913–7.
20. Jensen C, Jensen L, Rieder C, Cole R, Ault J. Long crocidolite asbestos fibers cause polyploidy by sterically blocking cytokinesis. Carcinogenesis. 1996;17:2013–21.
21. Mishra A, Liu J, Brody A, Morris G. Inhaled asbestos fibers induce p53 expression in the rat lung. Am J Respir Cell Mol Biol. 1997; 16:479–85.
22. Nuorva K, Mäkitaro R, Huhti E, et al. p53 protein accumulation in lung carcinomas of patients exposed to asbestos and tobacco smoke. Am J Respir Crit Care Med. 1994;150:528–33.
23. Matsuoka M, Igisu H, Morimoto Y. Phosphorylation of p53 protein in A549 human pulmonary epithelial cells exposed to asbestos fibers. Environ Health Perspect. 2003;111:509–12.
24. Pääkkö P, Rämet M, Vähäkangas K, et al. Crocidolite asbestos causes an induction of p53 and apoptosis in cultured A-549 lung carcinoma cells. Apoptosis. 1998;3:203–12.
25. Panduri V, Surapureddi S, Soberanes S, Weitzman SA, Chandel N, Kamp DW. P53 mediates amosite asbestos-induced alveolar epithelial cell mitochondria-regulated apoptosis. Am J Respir Cell Mol Biol. 2006;34:443–52.
26. Wang X, Christiani D, Wiencke J, et al. Mutations in the p53 gene in lung cancer are associated with cigarette smoking and asbestos exposure. Cancer Epid Biomark Prev. 1995;4:543–8.
27. Liu B, Fu D, Miao Q, Wang H, You B. p53 gene mutations in asbestos associated cancers. Biomed Environ Sci. 1998;11:226–32.
28. Jaurand M. Mechanisms of fiber-induced genotoxicity. Environ Health Perspect. 1997;105:1073–84.
29. Brandt-Rauf P, Smith S, Hemminki K, et al. Serum oncoproteins and growth factors in asbestosis and silicosis patients. Int J Cancer. 1992;50:881–5.
30. Husgafvel-Pursiainen K, Hackman P, Ridanpaa M, et al. K-ras mutations in human adenocarcinoma of the lung: association with smoking and occupational exposure to asbestos. Int J Cancer. 1993; 53:250–6.
31. Nelson HH, Christiani DC, Wiencke JK, Mark EJ, Wain JC, Kelsey KT. k-ras mutation and occupational asbestos exposure in lung adenocarcinoma: asbestos-related cancer without asbestosis. Cancer Res. 1999;59:4570–3.
32. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers – a different disease. Nat Rev Cancer. 2007;7:778–90.
33. Lange JH, Hoskins J, Mastrangelo G. Smoking rates in asbestos workers. Occup Med. 2006;56:581.

34. Lee YJ, Kim J-H, Kim SK, et al. Lung cancer in never smokers: change of a mindset in the molecular era. Lung Cancer. 2011;72: 9–15.
35. Pfeifer G, Denissenko M, Olivier M, Tretyakova N, Hecht S, Hainaut P. Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene. 2002;21:7435–51.
36. Vähäkangas KH, Bennett WP, Castrén K, et al. p53 and K-ras mutations in lung cancers from former and never-smoking women. Cancer Res. 2001;61:4350–6.
37. Wikman H, Ruosaari S, Nymark P, et al. Gene expression and copy number profiling suggests the importance of allelic imbalance in 19p in asbestos-associated lung cancer. Oncogene. 2007;26:4730–7.
38. Taniguchi T, Karnan S, Fukui T, et al. Genomic profiling of malignant pleural mesothelioma with array-based comparative genomic hybridization shows frequent non-random chromosomal alteration regions including JUN amplification on 1p32. Cancer Sci. 2007;98: 438–46.
39. Lindholm P, Salmenkivi K, Vauhkonen H, et al. Gene copy number analysis in malignant pleural mesothelioma using oligonucleotide array CGH. Cytogenet Genome Res. 2007;119:46.
40. Christensen BC, Godleski JJ, Marsit CJ, et al. Asbestos exposure predicts cell cycle control gene promoter methylation in pleural mesothelioma. Carcinogenesis. 2008;29:1555–9.
41. Wong L, Zhou J, Anderson D, Kratzke RA. Inactivation of p16INK4a expression in malignant mesothelioma by methylation. Lung Cancer. 2002;38:131–6.
42. Sekido Y. Genomic abnormalities and signal transduction dysregulation in malignant mesothelioma cells. Cancer Sci. 2010;101:1–6.
43. Dammann R, Strunnikova M, Schagdarsurengin U, et al. CpG island methylation and expression of tumour-associated genes in lung carcinoma. Eur J Cancer. 2005;41:1223–36.
44. Kraunz KS, Nelson HH, Lemos M, Godleski JJ, Wiencke JK, Kelsey KT. Homozygous deletion of p16/INK4a and tobacco carcinogen exposure in nonsmall cell lung cancer. Int J Cancer. 2006;118:1364–9.
45. Mossman BT, Lippmann M, et al. Pulmonary Endpoints (Lung Carcinomas and Asbestosis) Following Inhalation Exposure to Asbestos. Journal of Toxicology and Environmental Health, Part B 2011;14(1–4):76–121.
46. Ivanov SV, Miller J, Lucito R, et al. Genomic events associated with progression of pleural malignant mesothelioma. Int J Cancer. 2009;124:589–99.
47. Nymark P, Lindholm P, Korpela M, et al. Specific gene expression profiles in asbestos-exposed epithelial and mesothelial lung cell lines. BMC Genomics. 2007;8:62.
48. Jean D, Thomas E, Manié, et al. Syntenic relationships between genomic profiles of fiber-induced murine and human malignant mesothelioma. Am J Pathol. 2011;178:881–94.
49. Husgafvel-Pursiainen K, Karjalainen A, Kannio A, et al. Lung cancer and past occupational exposure to asbestos. Role of p53 and K-ras mutations. Am J Respir Cell Mol Biol. 1999;20:667–74.
50. Lin F, Liu Y, Liu Y, Keshava N, Li S. Crocidolite induces cell transformation and p53 gene mutation in BALB/c-3T3 cells. Teratog Carcinog Mutagen. 2000;20:273–81.
51. DeMarini DM, Landi S, Tian D, et al. Lung tumor KRAS and TP53 mutations in nonsmokers reflect exposure to PAH-Rich coal combustion emissions. Cancer Res. 2001;61:6679–81.
52. Moyer V, Cistulli C, Vaslet C, Kane A. Oxygen radicals and asbestos carcinogenesis. Environ Health Perspect. 1994;102:131–6.
53. Loli P, Topinka J, Georgiadis P, et al. Benzo[a]pyrene-enhanced mutagenesis by asbestos in the lung of lambda-lacI transgenic rats. Mutat Res. 2004;553:79–90.
54. Schneider J, Presek P, Braun A, et al. p53 protein, EGF receptor, and anti-p53 antibodies in serum from patients with occupationally derived lung cancer. Br J Cancer. 1999;80:1987–94.
55. Wild C, Ridanpää M, Anttila S, et al. p53 antibodies in the sera of lung cancer patients: comparison with p53 mutation in the tumour tissue. Int J Cancer. 1995;64:176–81.
56. Guinee Jr DG, Travis WD, Trivers GE, et al. Gender comparisons in human lung cancer: analysis of p53 mutations, anti-p53 serum antibodies and C-erbB-2 expression. Carcinogenesis. 1995;16: 993–1002.
57. Hei T, Wu L, Piao C. Malignant transformation of immortalized human bronchial epithelial cells by asbestos fibers. Environ Health Perspect. 1997;105:1085–8.
58. Partanen R, Hemminki K, Koskinen H, Luo J, Carney W, Brandt-Rauf P. The detection of increased amounts of the extracellular domain of the epidermal growth factor receptor in serum during carcinogenesis in asbestosis patients. J Occup Med. 1994;36: 1324–8.
59. Wright CM, Larsen JE, Hayward NK, et al. ADAM28: a potential oncogene involved in asbestos-related lung adenocarcinomas. Genes Chromosomes Cancer. 2010;49:688–98.
60. Guled M, Lahti L, Lindholm PM, et al. CDKN2A, NF2, and JUN are dysregulated among other genes by miRNAs in malignant mesothelioma – a miRNA microarray analysis. Genes Chromosomes Cancer. 2009;48:615–23.
61. Gee GV, Koestler DC, Christensen BC, et al. Downregulated microRNAs in the differential diagnosis of malignant pleural mesothelioma. Int J Cancer. 2010;127:2859–69.
62. Yasuda M, Hanagiri T, Shigematsu Y, et al. Identification of a tumour associated antigen in lung cancer patients with asbestos exposure. Anticancer Res. 2010;30:2631–9.
63. Nair VS, Maeda LS, Ioannidis JPA. Clinical outcome prediction by microRNAs in human cancer: a systematic review. JNCI. 2012; 104:528–40.
64. Nymark P, Guled M, Borze I, et al. Integrative analysis of microRNA, mRNA and aCGH data reveals asbestos- and histology-related changes in lung cancer. Genes Chromosomes Cancer. 2011; 50:585–97.
65. Nymark P, Aavikko M, Mäkilä J, Ruosaari S, Hienonen-Kempas T, Wikman H, Salmenkivi K, Pirinen R, Karjalainen A, Vanhala E, Kuosma E, Anttila S, Kettunen E. Accumulation of genomic alterations in 2p16, 9q33.1 and 19p13 in lung tumours of asbestos-exposed patients. Mol Oncol. 2013;1:29–40.
66. Martinez VD, Buys TPH, Adonis M, et al. Arsenic-related DNA copy-number alterations in lung squamous cell carcinomas. Br J Cancer. 2010;103:1277–83.
67. Kondo K, Takahashi Y, Hirose Y, et al. The reduced expression and aberrant methylation of p16INK4a in chromate workers with lung cancer. Lung Cancer. 2006;53:295–302.
68. Ali AHK, Kondo K, Namura T, et al. Aberrant DNA methylation of some tumor suppressor genes in lung cancers from workers with chromate exposure. Mol Carcinog. 2011;50:89–99.

Malignant Mesothelioma: Epidemiology

13

Paolo Boffetta

Keywords
Mesothelioma • Peritoneal mesothelioma • Pleural cancer • Occupation • Asbestos

Introduction

Primary malignant neoplasms of the pleura and peritoneum originate from the mesothelial cells that line the respective cavities. The majority of these tumors are mesotheliomas; rare forms include lymphomas, synovial sarcomas, solitary fibrous tumors, and calcifying tumors, which are not reviewed here. Mesothelioma is a relatively rare but very severe neoplasm, the pleura being the most commonly affected organ, followed by the peritoneum. Mesothelioma may also very rarely develop from the pericardium, the tunica vaginalis of the testis, and the ovary. Symptoms are unspecific and appear late in the development of the disease. A biopsy is usually necessary to establish the diagnosis, which in many cases represents a pathological and clinical challenge. As a consequence, most tumors are diagnosed at advanced stage. Various treatment modalities, including radical surgery, chemotherapy, and radiation therapy, are used, but survival remains poor.

Since the late 1950s, cases of pleural mesothelioma have been reported in miners from South Africa and American workers exposed to asbestos [122, 61, 101]. As early as 1964, the causal link between exposure to asbestos and development of mesothelioma in humans was recognized by international panels [119]. The strong causal role of asbestos, the rarity of the disease in populations not exposed to asbestos, and the diagnostic complexity of mesothelioma complicate the epidemiology of this neoplasm, since exposure might influence diagnosis. Studies based on autopsy series revealed that a sizable proportion of mesotheliomas may remain undiagnosed (e.g., 45 % in a series of male cases from Trieste, Italy [21].

P. Boffetta, MD, MPH
Institute for Translational Epidemiology
and Tisch Cancer Institute, Icahn School of Medicine
at Mount Sinai, One Gustave L. Levy Place,
New York, NY 10029, USA
e-mail: paolo.boffetta@mssm.edu

Asbestos

An increased risk of mesothelioma has been convincingly shown in many occupational groups exposed to asbestos, such as miners, insulation workers, manufacturers of cement, textiles, and other asbestos-based products and shipyard workers. However, the widespread use of asbestos has caused important exposure in many industries, and cases of asbestos-related pleural mesothelioma have been reported among workers in diverse trades, such as thermoelectric power plants [20], oil refining [118], textile production [80, 81], pulp and paper production [44, 50], petroleum industry [29], cigarette filter manufacture [114], and railroad industry [78]. In many high-income countries, the classic circumstances of high exposure to asbestos are nowadays of relatively little importance, because of the ban of most if not all uses of asbestos and precautions taken when exposure is known, and the greatest exposure is likely to occur among maintenance and construction workers [49]. In many low- and medium-income countries, on the other hand, high levels of exposure are still prevalent in many industries [5, 35].

Industry-Based Studies

Table 13.1 shows the results of selected studies of cohorts of workers exposed to asbestos. Given the large body of evidence available, only studies of occupational groups primarily exposed to asbestos have been included in the table. When interpreting the results of the table, one should consider that the estimate of the magnitude of the risk of pleural mesothelioma following asbestos exposure based on

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_13, © Springer-Verlag London 2014

Table 13.1 Results of selected cohort studies of mesothelioma in workers exposed to asbestos

Reference	Industry	Asbestos type	Country	Period of employment***	Diagnostic evidence	Sex	Number of workers	Total deaths	Lung cancer deaths	SMR of lung cancer **	Pleura mesothelioma deaths	Peritoneal mesothelioma deaths
[45]	Gas mask manufacture	P Cr	UK	1938–1945	MR	F	578	166	12	[1.94*]	13	4
[97]	Shipyard	NA	UK	1947	BE	M	6,292	1,043	84	0.70*	31	NA
[1]	Gas mask manufacture	Ch	UK	1939	DC	F	570	177	6	[1.25]	1	0
		Cr	UK	1939	DC	F	757	219	13	[2.10*]	3	2
[66]	Textile product manufacture	P Ch	USA	1938–1958	DC	M	4,137	1,392	NA	NA	10	4
[115]	Cement workers	P Ch	UK	1936–1977	DC	M	1,592	351	30	0.93	2	0
[25]	Cement workers	Mix	Canada	1955–1959	DC	M	535	108	26	4.90*	11	8
[65]	Friction product manufacture	Ch	USA	1939–1958	DC	M	3,641	1,267	73	1.49*	0	0
[2]	Insulation manufacture	Am	UK	1945–1978	DC	M	4,820	333	57	[1.96*]	4	1
[78]	Railroad repair work	Mix	Sweden	1939–1980	DC	M	3,442	925	37	1.16	5	0
[84]	Textile product manufacture	P Ch	UK	1933–1974	DC	M	3,211	1,113	132	1.31*	10	1
[77]	Cement workers	P Ch	Sweden	1943–1976	DC	M	1,216	220	11	1.23	0	0
[48]	Shipyard	Mix	USA	1950–1969	CR	M	5,191	668	61	[1.09]	8	0
[6]	Cement workers	Mix	France	1940–1977	DC	M	1,506	206	12	2.17*	3	1
[75]	Mixed	Mix	UK	1933–1964	DC	M	4,695	818	158	[2.50*]	31	NA
					DC	F	932	274	37	[7.40*]	14	NA
[112]	Mixed	P Ch	Poland	1945–1985	DC	M	2,403	527	35	1.41	1	0
[125]	Mixed	Mix	Germany	1930–1974	DC	PM	3,070	185	22	1.44	6	0
[100]	Mixed	Am	USA	1941–1945	BE	M	820	593	102	4.97*	8	9
[28]	Cement workers	Ch	UK	1941–1983	DC	MF	2,167	486	41	0.97	1	0
[40]	Mixed	Mix	UK	1969–1981	DC	M	31,565	1,128	186	1.26*	35	NA
[42]	Cement workers	P Ch	USA	1937–1970	BE	M	6,931	2,143	NA	NA	9	1
[7]	Vermiculite miners	Tre, Act	USA	1970–1981	DC	M	569	161	20	2.23*	2	0
[24]	Mixed	Mix	USA	1941–1967	DC	M	1,074	617	77	2.71*	6	2
[8]	Crocidolite miners	Cr	Australia	1943–1966	DC	PM	6,916	843	93	2.64*	33	1
[76]	Friction product manufacture	P Ch	UK	1941–1979	DC	M	8,404	2,055	240	1.08	11	NA
[92]	Cement workers	Mix	Denmark	1928–1984	CR	M	7,996	1,305	162	1.80*	10	NA
[4]	Cement workers	P Ch	Sweden	1907–1977	CR	M	1,465	592	27	NA	12	NA
[74]	Cement workers	P Ch	Austria	1950–1981	DC	NA	2,816	540	50	1.7*	7	3
[86]	Miners	Ch	Italy	1946–1987	DC	M	1,058	427	22	1.1	2	NA
[39]	Electrochemical	NA	Norway	NA	CR	NA	287	186	18	3.16*	6	NA
[102]	Insulation workers	Mix	USA	1967	BE	M	17,800	4,951	1,008	3.75*	173	285

[98]	Shipyard	P Ch	Sweden	1977–1979	DC	M	3,893	NA	22	0.85	11	0
[105]	Miners	Am, Cr	S Africa	1945–1981	BE	M	7,317	1,225	63	1.72*	22	6
[68]	Railroad constr. work	Mix	Italy	1978–1989	DC	M	1,543	194	28	1.45*	3	2
[31]	Cement workers	P Ch	Italy	1952–1987	DC	NA	3,341	274	33	1.24	5	NA
[71]	Miners	Antho	Finland	1953–1967	CR	M	736	NA	76	2.88*	3	1
[57]	Cement workers	P Ch	Italy	1950–1980	DC	M	2,605	1,147	162	2.48*	53	23
[126]	Mixed	Mix	China	1972–1981	DC	M	NA	260	34	NA	1	NA
	Miners	Ch	China	1972–1981	DC	M	NA	240	24	NA	3	NA
[54]	Miners	Ch	Canada	1902–1971	DC	M	10,918	8,009	646	1.37*	38	NA
[79]	Sprayers, asbestosis patients	Mix	Finland	1955–1976	CR	PM	247	NA	43	[11*]	8	NA
[113]	Cement workers	Mix	Poland	1945–1980	CR	M	3,405	473	41	0.97	5	NA
[30]	Asbestosis patients	Mix	Italy	1979	DC	F	631	277	16	4.83*	14	12
[119]	Cement workers	Mix	Israel	1953–1992	BE	M	3,057	NA	28	1.35	20	1
[46]	Asbestosis patients	Mix	Finland	1964–1995	CR	MF	1,376	NA	133	[6.9*]	10	0
[91]	Shipyard	NA	Italy	1960–1981	DC	M	3,984	2,376	298	1.77*	60	NA
[111]	Asbestosis patients	Mix	Poland	1970–1997	DC	M	907	300	39	1.68*	3	0
[120]	Cement workers	P Ch	Norway	1942–1976	CR	M	541	NA	33	3.1*	18	0
[106]	Cement workers	Ch	Lithuania	1956–1985	CR	MF	2,787	473	30	0.9	1	0
[87]	Textile product manufacture	Mix	Italy	1946–1984	DC	M	889	377	62	2.52*	12	5
						F	1,077	168	14	5.96*	11	9
[109]	Miners	Tr	USA	1935–1981	DC	M	1,672	767	89	1.7*	14	1
[37]	Textile product manufacture	Ch	USA	1940–1965	DC	M	1,807	1,252	137	1.84*	3	0
						F	1,265	709	61	2.22*	0	0
[56]	Textile product manufacture	P Ch	USA	1950–1973	DC	PM	5,770	2,583	277	[1.96*]	4	0
[33]	Mixed	Mix	UK	1983–1987[a]	DC	PM	98,117	15,496	1,882	1.87*	137	85
[69]	Cement workers	Mix	Italy	1950–1986	DC	M	1,247	508	84	1.53*	24	9
[117]	Ship insulators	Ch, Am	Japan	1947–1979	DC	M	90	63	7	2.64*	0	0
	Ship boiler repairers	Ch, Am	Japan	1947–1979	DC	M	159	95	8	1.61	1	1
[15]	Asbestosis patients	Mix	Hong Kong	1981–2008	DC	M	124	86	14	7.91*	17	0
[11]	Mixed	Ch	China	1972	DC	M	577	259	53	4.08*	1	1

When multiple reports have been published for the same cohort, only the most recent one is summarized in the table

DC death certificate, *CR* cancer registry, *BE* best evidence, *MR* medical records, *P Ch* predominantly chrysotile, *Ch* chrysotile, *Cr* crocidolite, *Am* amosite, *Mix* mixed exposure, *Tre* tremolite, *Act* actymolite, *Antho* anthophyllite, *M* males, *F* females, *MF* males and females, *PM* predominantly males, *NA* not available

*$p < 0.05$

**SMR are in square brackets if calculated from raw data

***Period of diagnosis for cohort of asbestosis patients

[a]Period of enrolment in the survey

Table 13.2 Possible sources of bias in quantifying asbestos carcinogenicity based on SMR of pleural neoplasms

Source of bias	Consequence	Effect on risk estimate
Rarity of the disease in the absence of asbestos exposure	Lack of truly unexposed (reference) groups, since most mesotheliomas in the reference population occur in individuals exposed to asbestos	Underestimate of the effect
Poor sensitivity of disease assessment	Mesotheliomas classified as lung cancer or other neoplasms	Possible overestimate of the effect (knowledge of exposure may influence diagnosis)
Poor specificity of disease assessment	Inclusion of neoplasms not related to asbestos, e.g., mediastinal tumors, lymphomas	Underestimate of the effect
Poor sensitivity of exposure assessment	Misclassification of exposure (also in internal analyses)	Underestimate of the effect (most likely)

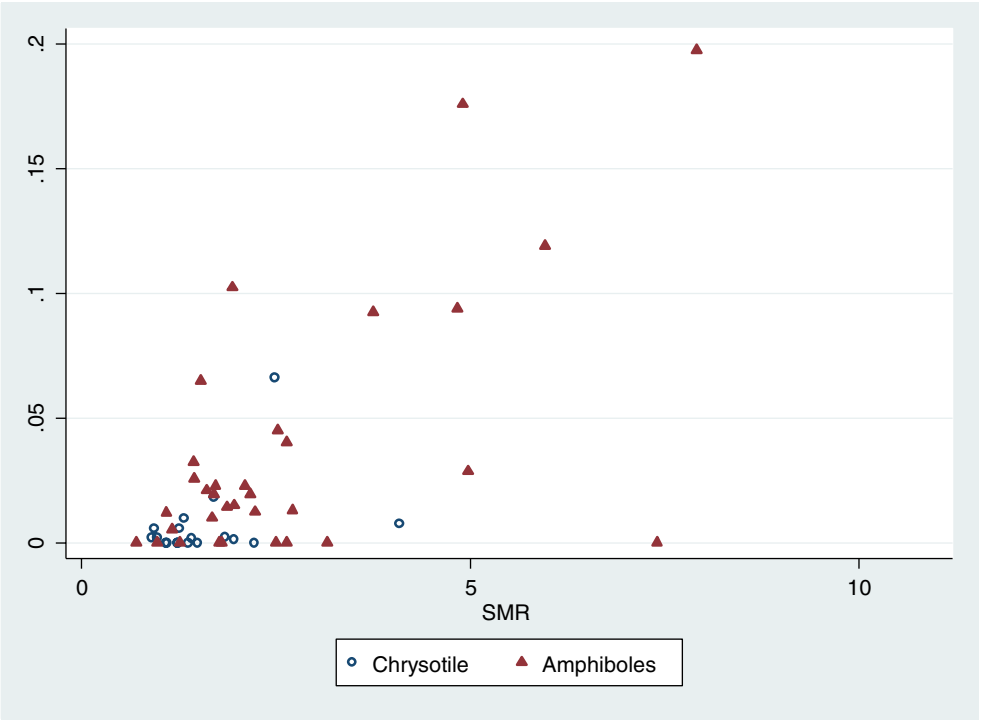


Fig. 13.1 Scatter plot of ratio of mesothelioma over total deaths and lung cancer SMR, by asbestos fiber type. Chrysotile includes pure and predominant chrysotile; amphiboles include pure and predominant amphiboles and mixed/unknown fibers

standardized mortality ratios (SMR) of pleural neoplasms or similar measures can suffer from a number of biases, as discussed in Table 13.2. Although some of these biases are common to studies of other exposures and diseases, the likelihood of bias is particularly important in the case of asbestos and mesothelioma because of the strength of the association and the possibility that diagnostic accuracy depends on knowledge of exposure. Because of the possible biases, the numbers of pleural and peritoneal mesothelioma deaths were reported in the table rather than the SMR, allowing calculating the proportion of mesothelioma deaths over total deaths and the ratio of mesothelioma to excess lung cancer deaths (the latter can be derived from the table as [N·(R−1)], where N is the number of lung cancer deaths and R is the SMR for lung cancer). Furthermore, only populations in with at least 80 total deaths or 20 lung cancer deaths were observed are included in the table, to reduce the random variability of the results. In some of the studies listed in Table 13.1, the study population was defined according to the presence of asbestosis rather than employment in a given industry where these individuals primarily developed their disease as a consequence of occupational exposure to asbestos.

One or more deaths from pleural mesothelioma have been reported in all but four of the 62 populations listed in Table 13.1. The proportion of pleural mesothelioma over total deaths was 1 % or more in 33 out of 56 populations in which this ratio could be measured. In six cohorts [45, 25, 102, 30, 87 [female cohort]; [15], more than 9 % of total deaths were due to pleural or peritoneal mesothelioma. A correlation was present between the percentage of pleura mesothelioma deaths over total deaths and the SMR of lung cancer (correlation coefficient 0.65, *p-value* <0.0001, Fig. 13.1).

Table 13.3 Proportion of mesotheliomas over total death (%) by type of asbestos fibers

Type of asbestos	*N* studies[a]	Mean	Standard deviation
Pure chrysotile	10	0.2	0.3
Predominantly chrysotile	12	1.0	1.9
Amphiboles[b]	10	2.9	2.8
Mixed, unknown	24	3.8	5.7

[a]Studies listed in Table 13.1
[b]Pure/predominant amphiboles or mixed chrysotile and amphiboles

Effect of Different Asbestos Fibers

Workers exposed to amphibole asbestos, including in particular crocidolite and amosite experienced a higher risk of mesothelioma than workers exposed predominantly to the most widely used type of asbestos, chrysotile. The proportion of mesothelioma deaths over the total was lower in the cohorts of workers classified as exposed to pure or predominant chrysotile than in the other cohorts (Table 13.3). The difference in the proportion of total deaths as mesotheliomas was not significant between studies of workers exposed only to chrysotile or predominantly to chrysotile ($p = 0.2$) nor between studies of workers exposed to amphiboles or to mixed and unknown fibers ($p = 0.6$). However, the difference between studies of pure or predominant chrysotile and amphiboles/mixed/unknown exposure was significant ($p = 0.01$). It is a matter of debate whether exposure to pure chrysotile entails a risk of mesothelioma or whether the relatively small risk detected in workers classified as exposed to chrysotile can be attributed to low-level contamination by (or concomitant exposure to) amphiboles [67, 64, 107].

Studies of lung fiber burden have shown that crocidolite and amosite persist for a longer period in the lung than chrysotile [17]. This finding might contribute to explain the lower risk of mesothelioma following inhalation of chrysotile as compared to amphiboles. Given the contamination of most commercially available chrysotile by amphiboles, and notably that of Canadian chrysotile by tremolite fibers [107], data from good quality studies on cancer risk among asbestos workers for whom amphibole exposure can be excluded with certainty are not available.

Shape of the Dose-Response Relationship

A quantitative relationship between mesothelioma risk and asbestos exposure can be derived from the occupational cohorts with good exposure data and sufficient latency. A widely accepted model involves a power function of time since first exposure and time since cessation of exposure of the form:

$$I(t) = k * E * \left[(t - t_1)^n - (t - t_2)^n \right]$$

where I(t) is the incidence of mesothelioma at time t caused by exposure at constant level E (expressed in fb/ml) starting at time t_1 and ending at time t_2 [84, 36]; k is a constant expressing the carcinogenic potency on the pleura, which is specific to industry and type of asbestos fiber; and n is an exponent estimated between 3 and 4. The formula assumes that the excess is equal to the total incidence, that is, no mesothelioma cases or deaths are expected without exposure. Given the third or fourth power of the exponent n, and the fact that $(t–t_1) > (t–t_2)$, the effect of cessation of exposure is relatively modest and the predominant determinant of risk is time since the beginning of exposure. This has also been shown empirically [33, 51]. In the case of multiple exposure periods at different levels, the overall incidence will be

$$I(t) = k * \sum_i E_i \left[(t - t_{1i})^n - (t - t_{2i})^n \right]$$

where each ith period of exposure starts at time t_{1i} and ends at time t_{2i}. However, because of the third or fourth power of time-related variables, the main determinant of risk is $(t–t_{11})$, i.e., time since the beginning of the first exposure, and the contribution of recent periods of exposure is limited from a practical viewpoint. The model can be refined by applying a lag of 10 years.

Risk After Cessation of Exposure

As discussed above, current models of asbestos-related mesothelioma imply that the time since the first exposure (latency) is the key determinant of subsequent risk. In line with this result, a recent review of the risk of mesothelioma according to time since cessation of exposure found little evidence that, for workers exposed in the distant past, the risk of mesothelioma is not appreciably modified by subsequent exposures and that stopping exposure does not materially modify the subsequent risk of mesothelioma [51]. Results of selected studies are summarized in Table 13.4. There are, however,

Table 13.4 Risk of pleural mesothelioma by time since cessation of asbestos exposure

Reference	Study population[a]	Years since cessation	*N* deaths	Measure of association		95 % CI
[89]	1,966; Italy; 1 month; 1946–1984; textile; 1946–2004	<15	12	SMR	19.9	*10.3, 34.8*
		15–24	30		68.4	*46.2, 97.7*
		25+	36		43.8	*28.6, 64.1*
[58]	3,434; Italy; no minimal dur.; 1950–1986; cement; 1965–2003	<3	13	RR[b]	0.67	0.32, 1.40
		3–15	55		1.00	–
		15–30	55		0.90	0.53, 1.43
		>30	16		0.65	0.26, 1.63
[88]	1,056; Italy; 1 year; 1930–1975; miners; 1946–2003	0	1	SMR	6.19	*0.16, 34.5*
		1–9	2		7.22	*0.87, 26.1*
		10+	2		1.75	*0.21, 6.32*
[33, 34]	98,912; UK; no minimal dur.; 1971–2005, mixed; 1971–2005	<10	334	RR[c]	1.00	–
		10–19	225		0.90	0.76, 1.08
		20–29	89		0.99	0.78, 1.26
		30+	1		0.99	0.14, 7.02

Numbers in italics were derived from raw data presented in the original reports.
SMR standardized mortality ratio, *CI* confidence interval
[a]*N* of cohort members; country; minimal duration of exposure; period of employment; industry; period of follow-up
[b]Relative risk adjusted for duration of exposure and latency; reference category: 3–15 years since cessation
[c]Relative risk adjusted for sex and age; reference category: <10 years since cessation

Table 13.5 Proportion of cases of mesothelioma with occupational exposure to asbestos in community-based studies

Reference	Country, years of diagnosis	Design	Exposure assessment	*N* cases	% exposed cases	Comments
[18]	California, USA, 1972–1988	PCC	EE	101	36	Low sensitivity of exposure assessment
[14]	Italy, 1970–1988	CS	JEM	100	72	
[73]	New York, USA, 1981–1990	HCC	JEM	124	79	
[41]	England, 1979–1991	PCC	JEM	185	81	
[43]	France, 1987–1993	HCC	EE	405	71	
[94]	South Africa, 1988–1990	HCC	EE	123	96[a]	Area of crocidolite mining
[3]	Spain, 1993–1996	PCC	EE	132	61	
[95]	Germany, 1988–1991	PCC	EE	125	91	
[83]	California, USA, 1988–1997	PCC	EE	2,354 M	66	
				554 W	45	
[93]	Great Britain, 2001–2006	PCC	JEM	512 M	93	Employment in high-risk jobs
				110 W	34	

Only studies with at least 100 cases of mesothelioma and assessment of occupational exposure to asbestos based on the whole occupational history
HCC hospital-based case-control study, *PCC* population-based case-control study, *CS* case-series, *EE* expert evaluation, *JEM* job-exposure matrix, *M* men, *W* women
[a]Including environmental exposure

surprisingly little data on the shape of the mesothelioma risk function following cessation of asbestos exposure. A more precise understanding of the role of cessation of exposure would help guiding surveillance programs of previously exposed workers.

Community-Based Studies

The strongest evidence on the risk of pleural mesothelioma following occupational exposure to asbestos comes from industry-based studies, as reviewed above. In addition, several studies, mainly of case-control design, have been conducted in populations not selected for specific occupational exposures: while these investigations can suffer from selection and information bias, they are useful to identify the main industries and occupation at risk of mesothelioma in different populations and to estimate the proportion of cases without recognized asbestos exposure. Table 13.5 summarizes these studies: the proportion of mesothelioma cases exposed to asbestos in the workplace varies according to the study population and the sensitivity of the method used to estimate exposure; in most studies, however, this proportion is in the range 60–75 %. In two studies, a detailed assessment of employment circum-

stances has led to a quantitative estimate of the risk following asbestos exposure [43, 95]. In both studies, a linear dose-response relationship has been derived, with a small but detectable increase in mesothelioma risk below a cumulative exposure of 1 fiber/ml-year, which is compatible with exposure limits currently implemented in many countries. However, caution should be used in the interpretation of these results since the level of exposure was estimated retrospectively by industrial hygienists, possibly resulting in quantitative underestimate of past exposure, which in turn would lead to an overestimate of the dose-response relationship [103].

Following the implementation of exposure control measures in most countries, the number of workers with heavy asbestos exposure and high risk of mesothelioma, who were employed in asbestos mining, manufacturing, and application, has dramatically decreased, although their consequences in terms of delayed cancer occurrence are still apparent. If potential occupational exposure to asbestos has generally decreased, it remains prevalent in many occupational settings and in particular in the construction industry. An important characteristic of community-based studies is their ability to evaluate the risk of mesothelioma in a large spectrum of jobs and industries. One of the most informative studies is the Great Britain Asbestos Survey [33, 34]: an analysis of 649 pleural cancer deaths among 98,912 asbestos workers included in the survey revealed the highest risk of mesothelioma among insulation workers (RR 4.03; 95 % CI 3.26–4.99, using workers in manufacturing industry as reference) and among workers involved in stripping and removal (RR 1.92; 95 % CI 1.58–2.34) [34]. In a large case-control conducted in England during 2001–2006, the risk of mesothelioma was higher in construction workers (and specifically carpenters) than in other occupational groups (41 % of all male cases were employed at least 5 years in the construction industry) [93]. In a similar study from France, the risk was elevated among plumbers, sheet-metal workers, welders, metal molders, coremakers, and cabinetmakers, in addition to occupations entailing high asbestos exposure, such as nonmetallic mineral product makers and manufacturers of asbestos products [96]. Elevated risks were also found in several industries: shipbuilding, construction, manufacturing of metal products, chemicals, and railroad and aircraft equipment.

Risk in Carriers of Pleural Plaques

Pleural plaques are characteristic patches of the parietal pleura. They represent the most common lesions found in individuals exposed to asbestos; they are asymptomatic and are detected radiologically. Although pleural plaques have been for long time considered only a marker of past asbestos exposure [124], an increased risk of mesothelioma has been shown in several series of carriers. In an early study of shipyard workers from the UK followed up between 1961 and 1970, the cumulative incidence of mesothelioma was 3/408 carriers of plaques and 0/404 non-carriers ($p=0.08$) [26]. In an autopsy-based study from Italy, Bianchi and colleagues [10] calculated an odds ratio of mesothelioma for the presence of plaques equal to 12.7 (95 % CI 1.71–7.94) in men and 7.59 (95 % CI 1.71–45.6) in women and a relationship between mesothelioma risk and size of the lesion. In a prospective study, the incidence of mesothelioma was compared between 1,569 Swedish pleural plaque carriers and the national population, resulting in a standardized incidence ratio of 11.3 (95 % CI 5.13–21.3).

While pleural plaques should be considered markers of mesothelioma risk, it is unclear whether they simply reflect a particularly high exposure, or they are a marker of individual susceptibility to both pleural reaction and cancer development following exposure to asbestos. An important problem in the interpretation of results of studies of pleural plaques is the poor sensitivity and specificity of their diagnosis based on imaging [110].

Risk of Peritoneal Mesothelioma

Results on peritoneal mesothelioma were reported for 46 of the occupationally exposed populations listed in Table 13.2. In 20 of them, no cases were reported; peritoneal mesotheliomas represented more than 1 % of total deaths in 11 populations. A strong correlation is present between percentage of deaths from pleural and peritoneal mesothelioma (correlation coefficient 0.5, $p=0.003$). Studies of workers exposed only or predominantly to chrysotile resulted in lower mean percentage of total deaths from peritoneal mesothelioma than other studies (means 0.21 % ± 0.51 vs. 1.4 % ± 2.1, $p=0.03$). In all studies with adequate number of cases, a strong association has been found between occupational exposure to asbestos and risk of peritoneal mesothelioma [45, 25, 100, 24, 74, 102, 105, 57, 30]. In a study based on death certificates from 24 of the US states during 1984–1992, 657 deaths from peritoneal neoplasms were identified [19]. An increased risk was found among men employed in the same occupations and industries which entail a risk of pleural mesothelioma, such as insulators and construction workers; results among women were hampered by small numbers. A relationship was found between peritoneal neoplasm risk and probability and intensity of exposure to asbestos as estimated with a job-exposure matrix.

Risk of Mesothelioma in Other Organs

Albeit rare, cases of mesothelioma have been reported in the pericardium and the tunica vaginalis of the testis [116, 70]. Occupational exposure to asbestos has been ascertained in a proportion of cases of these diseases, although a formal assessment of the strength of the association is not possible.

Table 13.6 Mesothelioma deaths in cohorts of synthetic mineral fiber production workers

Study	Country	Total number of deaths	*N* mesothelioma deaths	Comments
Glass wool				
[62]	USA	9,060	0	
[11]	Europe	1,281	1	
[72]	France	N/A	0	
Continuous filament				
[11]	Europe	191	0	
[16]	USA	437	0	
[123]	USA	161	0	
Rock/slag wool				
[62]	USA	1,011	1	Case not confirmed during pathology review
[11]	Europe	1,679	4	Two cases with heavy asbestos exposure
Refractory ceramic fibers				
[53]	USA	87	0	

Other Occupational Exposures

No excess mortality from mesothelioma has been reported among workers employed in the production of man-made vitreous fibers: among almost 14,000 deaths occurring in workers included in the available cohorts, only six were from mesothelioma (Table 13.6). Two of these cases had possible or probable concomitant exposure to asbestos. In two community-based studies, an increased risk of mesothelioma has been reported following estimated exposure to man-made vitreous fibers: after adjustment for asbestos exposure, the ORs were 1.5 (95 % CI 0.6–3.7) in a study from the USA [73] and 3.1 (95 % CI 1.2–8.1) in a study from Germany [95]. The apparent discrepancy of results between cohort and case-control study might be explained by residual confounding by asbestos exposure in the latter type of investigation. An alternative explanation might be the high exposure level of individuals included in the case-control studies (predominantly applicators). No cases have been reported in a small cohort of workers exposed to refractory ceramic fibers (Table 13.5): the strong excess of mesothelioma among hamsters exposed by inhalation to this type of fibers [63], however, suggests prudence before concluding that refractory ceramic fibers do not pose a mesothelioma risk to humans.

An increased risk of mesothelioma has been reported in sugar refinery workers from Sweden and Italy, which was attributed to exposure to organic fibers [59, 60]. These findings however have not been confirmed studies conducted in Hawaii [104] and Florida [13] and might be due to concomitant exposure to asbestos. No clear excess of mesothelioma has been detected among workers exposed to talc [90].

Conclusion

Occupational exposure to asbestos has shaped the epidemiology of mesothelioma. High-level exposure circumstances in jobs directly entailing exposure to asbestos were responsible for the rapid increase in the number of cases diagnosed in industrialized countries since the mid-twentieth century. Strong control measures have been implemented in industrialized countries since the early 1970s, although in some countries they were delayed until the 1990s. Their result has been to slow down the epidemic of mesothelioma: in most industrialized countries, a decrease in mesothelioma mortality is already apparent in the young birth cohorts. Models have predicted a decrease in the overall mortality rate after 2015–2025, depending on the country [38, 9, 99]. A fraction of mesotheliomas, however, originates in patients without apparent occupational exposure to asbestos (Table 13.5). This is probably explained by lack of sensitivity in the assessment of occupational exposures; the effect of environmental asbestos, including natural sources as well as environmental contamination from industrial uses; and the existence of a small number of cases arising independently from asbestos. The only other established cause of mesothelioma (in addition to asbestiform fibers such as erionite, whose occurrence is primarily environmental [23] is ionizing radiation, which however is responsible for a very small number of cases [12]. The fact that no other important causes of the disease have been identified leaves open the possibility that cases without a recognized source of exposure to asbestos (or other carcinogenic fibers) result from low-level occupational or environmental exposure circumstances that escape epidemiologic surveillance.

Mesothelioma remains a very rare disease in most low- and medium-income countries [22]: it is unclear to which extent this reflects underdiagnosis of the disease. Use of asbestos has greatly increased in many of these countries [47], although the latency might not yet be adequate to show its epidemiologic effect, and it is reasonable to expect an increase in the number of cases in the coming years. However, the fact that the only type of asbestos used in

countries in economic transition is chrysotile suggests that the epidemics might be less severe than that experienced by high-income countries, and cases of mesothelioma in asbestos-exposed workers are increasingly reported from countries in economic transition such as Thailand, China, Korea, Brazil, and Egypt [108, 52, 82, 27].

Specific surveillance programs on mesothelioma have been implemented in several countries such as France [32]. In addition to providing data useful for compensation of occupational disease and information on changing patterns of exposure, these programs have represented a precious support for epidemiologic research. Similar programs should also be established in low- and medium-income countries, and epidemiologic research on the asbestos-mesothelioma association should be encouraged in these countries.

References

1. Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br J Ind Med. 1982;39:344–8.
2. Acheson ED, Gardner MJ, Winter PD, Bennett C. Cancer in a factory using amosite asbestos. Int J Epidemiol. 1984;13:3–10.
3. Agudo A, Gonzalez CA, Bleda MJ, Ramirez J, Hernandez S, Lopez F, et al. Occupation and risk of malignant pleural mesothelioma: a case-control study in Spain. Am J Ind Med. 2000;37:159–68.
4. Albin M, Jakobsson K, Attewell R, Johansson L, Welinder H. Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. Br J Ind Med. 1990;47:602–10.
5. Algranti E. Asbestos: current issues related to cancer and to uses in developing countries. Cad Saude Publica. 1998;14 Suppl 3:173–6.
6. Alies-Patin AM, Valleron AJ. Mortality of workers in a French asbestos cement factory 1940–82. Br J Ind Med. 1985;42:219–25.
7. Amandus HE, Wheeler R. The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. Am J Ind Med. 1987;11:15–26.
8. Armstrong BK, de Klerk NH, Musk AW, Hobbs MS. Mortality in miners and millers of crocidolite in Western Australia. Br J Ind Med. 1988;45:5–13.
9. Banaei A, Auvert B, Goldberg M, Gueguen A, Luce D, Goldberg S. Future trends in mortality of French men from mesothelioma. Occup Environ Med. 2000;57:488–94.
10. Bianchi C, Brollo A, Ramani L, Zuch C. Pleural plaques as risk indicators for malignant pleural mesothelioma: a necropsy-based study. Am J Ind Med. 1997;32:445–9.
11. Boffetta P, Saracci R, Andersen A, Bertazzi PA, Chang-Claude J, Cherrie J, et al. Cancer mortality among man-made vitreous fiber production workers. Epidemiology. 1997;8:259–68.
12. Boffetta P, Stayner LT. Pleural and peritoneal neoplasms. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006. p. 659–73.
13. Brooks SM, Stockwell HG, Pinkham PA, Armstrong AW, Witter DA. Sugarcane exposure and the risk of lung cancer and mesothelioma. Environ Res. 1992;58:195–203.
14. Chellini E, Fornaciai G, Merler E, Paci E, Costantini AS, Silvestri S, et al. Pleural malignant mesothelioma in Tuscany, Italy (1970–1988): II. Identification of occupational exposure to asbestos. Am J Ind Med. 1992;21:577–85.
15. Chen M, Tse LA, Au RK, Yu IT, Wang XR, Lao XQ, et al. Mesothelioma and lung cancer mortality: a historical cohort study among asbestosis workers in Hong Kong. Lung Cancer. 2012;76:165–70.
16. Chiazze Jr L, Watkins DK, Fryar C. Historical cohort mortality study of a continuous filament fiberglass manufacturing plant. I. White men. J Occup Environ Med. 1997;39:432–41.
17. Churg A, Wright JL. Persistence of natural mineral fibers in human lungs: an overview. Environ Health Perspect. 1994;102 Suppl 5:229–33.
18. Cicioni C, London SJ, Garabrant DH, Bernstein L, Phillips K, Peters JM. Occupational asbestos exposure and mesothelioma risk in Los Angeles County: application of an occupational hazard survey job-exposure matrix. Am J Ind Med. 1991;20:371–9.
19. Cocco P, Dosemeci M. Peritoneal cancer and occupational exposure to asbestos: results from the application of a job-exposure matrix. Am J Ind Med. 1999;35:9–14.
20. Crosignani P, Forastiere F, Petrelli G, Merler E, Chellini E, Pupp N, et al. Malignant mesothelioma in thermoelectric power plant workers in Italy. Am J Ind Med. 1995;27:573–6.
21. Delendi M, Riboli E, Peruzzo P, Stanta G, Cocchi A, Gardiman D, et al. Comparison of diagnoses of cancers of the respiratory system on death certificates and at autopsy. IARC Sci Publ. 1991;112:55–62.
22. Delgermaa V, Takahashi K, Park EK, Le GV, Hara T, Sorahan T. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. Bull World Health Organ. 2011;89(716–24):724A–C.
23. Dikensoy O. Mesothelioma due to environmental exposure to erionite in Turkey. Curr Opin Pulm Med. 2008;14:322–5.
24. Enterline PE, Hartley J, Henderson V. Asbestos and cancer: a cohort followed up to death. Br J Ind Med. 1987;44:396–401.
25. Finkelstein MM. Mortality among employees of an Ontario asbestos-cement factory. Am Rev Respir Dis. 1984;129:754–61.
26. Fletcher DE. A mortality study of shipyard workers with pleural plaques. Br J Ind Med. 1972;29:142–5.
27. Gaafar RM, Eldin NH. Epidemic of mesothelioma in Egypt. Lung Cancer. 2005;49 Suppl 1:S17–20.
28. Gardner MJ, Winter PD, Pannett B, Powell CA. Follow up study of workers manufacturing chrysotile asbestos cement products. Br J Ind Med. 1986;43:726–32.
29. Gennaro V, Finkelstein MM, Ceppi M, Fontana V, Montanaro F, Perrotta A, et al. Mesothelioma and lung tumors attributable to asbestos among petroleum workers. Am J Ind Med. 2000;37:275–82.
30. Germani D, Belli S, Bruno C, Grignoli M, Nesti M, Pirastu R, et al. Cohort mortality study of women compensated for asbestosis in Italy. Am J Ind Med. 1999;36:129–34.
31. Giaroli C, Belli S, Bruno C, Candela S, Grignoli M, Minisci S, et al. Mortality study of asbestos cement workers. Int Arch Occup Environ Health. 1994;66:7–11.
32. Goldberg M, Imbernon E, Rolland P, Gilg Soit Ilg A, Savès M, de Quillacq A, et al. The French National Mesothelioma Surveillance Program. Occup Environ Med. 2006;63:390–5.
33. Harding AH, Darnton A, Wegerdt J, McElvenny D. Mortality among British asbestos workers undergoing regular medical examinations (1971–2005). Occup Environ Med. 2009;66:487–95.
34. Harding AH, Darnton AJ. Asbestosis and mesothelioma among British asbestos workers (1971–2005). Am J Ind Med. 2010;53:1070–80.
35. Harris LV, Kahwa IA. Asbestos: old foe in 21st century developing countries. Sci Total Environ. 2003;307:1–9.
36. Health Effects Institute. Asbestos in public and commercial buildings. Cambridge, MA: Health Effects Institute; 1991.
37. Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. Occup Environ Med. 2007;64:616–25.
38. Hemminki K, Li X. Time trends and occupational risk factors for pleural mesothelioma in Sweden. J Occup Environ Med. 2003;45:456–61.

39. Hilt B, Andersen A, Rosenberg J, Langard S. Cancer incidence among asbestos-exposed chemical industry workers: an extended observation period. Am J Ind Med. 1991;20:261–4.
40. Hodgson JT, Jones RD. Mortality of asbestos workers in England and Wales 1971–81. Br J Ind Med. 1986;43:158–64.
41. Howel D, Arblaster L, Swinburne L, Schweiger M, Renvoize E, Hatton P. Routes of asbestos exposure and the development of mesothelioma in an English region. Occup Environ Med. 1997;54:403–9.
42. Hughes JM, Weill H, Hammad YY. Mortality of workers employed in two asbestos cement manufacturing plants. Br J Ind Med. 1987;44:161–74.
43. Iwatsubo Y, Pairon JC, Boutin C, Menard O, Massin N, Caillaud D, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. Am J Epidemiol. 1998;148:133–42.
44. Jarvholm B, Malker H, Malker B, Ericsson J, Sallsten G. Pleural mesotheliomas and asbestos exposure in the pulp and paper industries: a new risk group identified by linkage of official registers. Am J Ind Med. 1988;13:561–7.
45. Jones JS, Smith PG, Pooley FD, Berry G, Sawle GW, Madeley RJ, et al. The consequences of exposure to asbestos dust in a wartime gas-mask factory. IARC Sci Publ. 1980;30:637–53.
46. Karjalainen A, Pukkala E, Kauppinen T, Partanen T. Incidence of cancer among Finnish patients with asbestos-related pulmonary or pleural fibrosis. Cancer Causes Control. 1999;10:51–7.
47. Kazan-Allen L. Asbestos and mesothelioma: worldwide trends. Lung Cancer. 2005;49 Suppl 1:S3–8.
48. Kolonel LN, Yoshizawa CN, Hirohata T, Myers BC. Cancer occurrence in shipyard workers exposed to asbestos in Hawaii. Cancer Res. 1985;45:3924–8.
49. Koskinen K, Pukkala E, Reijula K, Karjalainen A. Incidence of cancer among the participants of the Finnish Asbestos Screening Campaign. Scand J Work Environ Health. 2003;29:64–70.
50. Langseth H, Andersen A. Cancer incidence among male pulp and paper workers in Norway. Scand J Work Environ Health. 2000;26:99–105.
51. La Vecchia C, Boffetta P. Role of stopping exposure and recent exposure to asbestos in the risk of mesothelioma. Eur J Cancer Prev. 2012;21:227–30.
52. Lee KH, Yoon HS, Choi SJ, Kang D. Asbestos exposure and malignant mesothelioma in Korea. Asian Pac J Cancer Prev. 2009;10:707–10.
53. LeMasters GK, Lockey JE, Yiin JH, Hilbert TJ, Levin LS, Rice CH. Mortality of workers occupationally exposed to refractory ceramic fibers. J Occup Environ Med. 2003;45:440–50.
54. Liddell FD, McDonald AD, McDonald JC. The 1891–1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. Ann Occup Hyg. 1997;41:13–36.
55. Lin S, Wang X, Yu IT, Yano E, Courtice M, Qiu H, et al. Cause-specific mortality in relation to chrysotile-asbestos exposure in a Chinese cohort. J Thorac Oncol. 2012;7:1109–14.
56. Loomis D, Dement JM, Wolf SH, Richardson DB. Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers. Occup Environ Med. 2009;66:535–42.
57. Magnani C, Terracini B, Ivaldi C, Mancini A, Botta M. Tumor mortality and from other causes in asbestos cement workers at the Casale Montferrato plant. Med Lav. 1996;87:133–46.
58. Magnani C, Ferrante D, Barone-Adesi F, Bertolotti M, Todesco A, Mirabelli D, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. Occup Environ Med. 2008;65:164–70.
59. Malker HR, Malker BK, Blot WJ. Mesothelioma among sugar refinery workers. Lancet. 1983;2:858.
60. Maltoni C, Pinto C, Valenti D, Carnuccio R, Amaducci E, Minardi F. Mesotheliomas following exposure to asbestos used in sugar refineries: report of 12 Italian cases. Med Lav. 1995;86:478–83.
61. Mancuso TF, Coulter EJ. Methodology in industrial health studies. Arch Environ Health. 1963;6:210–26.
62. Marsh GM, Gula MJ, Youk AO, Buchanich JM, Churg A, Colby TV. Historical cohort study of US man-made vitreous fiber production workers: II. Mortality from mesothelioma. J Occup Environ Med. 2001;43:757–66.
63. Mast RW, Hesterberg TW, Glass LR, McConnell EE, Anderson R, Bernstein DM. Chronic inhalation and biopersistence of refractory ceramic fiber in rats and hamsters. Environ Health Perspect. 1994;102 Suppl 5:207–9.
64. McDonald AD, Case BW, Churg A, Dufresne A, Gibbs GW, Sebastien P, et al. Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. Ann Occup Hyg. 1997;41:707–19.
65. McDonald AD, Fry JS, Woolley AJ, McDonald JC. Dust exposure and mortality in an American chrysotile asbestos friction products plant. Br J Ind Med. 1984;41:151–7.
66. McDonald AD, McDonald JC, Pooley FD. Mineral fibre content of lung in mesothelial tumours in North America. Ann Occup Hyg. 1982;26:417–22.
67. McDonald JC, Armstrong B, Case B, Doell D, McCaughey WT, McDonald AD, et al. Mesothelioma and asbestos fiber type. Evidence from lung tissue analyses. Cancer. 1989;63:1544–7.
68. Menegozzo M, Belli S, Bruno C, Canfora V, Costigliola A, Di Cintio P, et al. Mortality due to causes correlatable to asbestos in a cohort of workers in railway car construction. Med Lav. 1993;84:193–200.
69. Menegozzo S, Comba P, Ferrante D, De Santis M, Gorini G, Izzo F, et al. Mortality study in an asbestos cement factory in Naples, Italy. Ann Ist Super Sanita. 2011;47:296–304.
70. Mensi C, Pellegatta M, Sieno C, Consonni D, Riboldi L, Bertazzi PA. Mesothelioma of tunica vaginalis testis and asbestos exposure. BJU Int. 2012;110:533–7.
71. Meurman LO, Pukkala E, Hakama M. Incidence of cancer among anthophyllite asbestos miners in Finland. Occup Environ Med. 1994;51:421–5.
72. Moulin JJ, Mur JM, Wild P, Perreaux JP, Pham QT. Oral cavity and laryngeal cancers among man-made mineral fiber production workers. Scand J Work Environ Health. 1986;12:27–31.
73. Muscat JE, Wynder EL. Cigarette smoking, asbestos exposure, and malignant mesothelioma. Cancer Res. 1991;51:2263–7.
74. Neuberger M, Kundi M. Individual asbestos exposure: smoking and mortality – a cohort study in the asbestos cement industry. Br J Ind Med. 1990;47:615–20.
75. Newhouse ML, Berry G, Wagner JC. Mortality of factory workers in east London 1933–80. Br J Ind Med. 1985;42:4–11.
76. Newhouse ML, Sullivan KR. A mortality study of workers manufacturing friction materials: 1941–86. Br J Ind Med. 1989;46:176–9.
77. Ohlson CG, Hogstedt C. Lung cancer among asbestos cement workers. A Swedish cohort study and a review. Br J Ind Med. 1985;42:397–402.
78. Ohlson CG, Klaesson B, Hogstedt C. Mortality among asbestos-exposed workers in a railroad workshop. Scand J Work Environ Health. 1984;10:283–91.
79. Oksa P, Pukkala E, Karjalainen A, Ojajarvi A, Huuskonen MS. Cancer incidence and mortality among Finnish asbestos sprayers and in asbestosis and silicosis patients. Am J Ind Med. 1997;31:693–8.
80. Paci E, Dini S, Buiatti E, Seniori CA, Lenzi S, Zappa M. Malignant mesothelioma in non-asbestos textile workers in Florence. Am J Ind Med. 1987;11:249–54.

81. Paci E, Zappa M, Paoletti L, Buiatti E, Chellini E, Merler E, et al. Further evidence of an excess of risk of pleural malignant mesothelioma in textile workers in Prato (Italy). Br J Cancer. 1991;64:377–8.
82. Pedra F, Tambellini AT, Pereira Bde B, da Costa AC, de Castro HA. Mesothelioma mortality in Brazil, 1980–2003. Int J Occup Environ Health. 2008;14:170–5.
83. Pan XL, Day HW, Wang W, Beckett LA, Schenker MB. Residential proximity to naturally occurring asbestos and mesothelioma risk in California. Am J Respir Crit Care Med. 2005;172:1019–25.
84. Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann Occup Hyg. 1985;29:305–55.
85. Peto J, Hodgson JT, Matthews FE, Jones JR. Continuing increase in mesothelioma mortality in Britain. Lancet. 1995;345:535–9.
86. Piolatto G, Negri E, La Vecchia C, Pira E, Decarli A, Peto J. An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. Br J Ind Med. 1990;47:810–4.
87. Pira E, Pelucchi C, Buffoni L, Palmas A, Turbiglio M, Negri E, et al. Cancer mortality in a cohort of asbestos textile workers. Br J Cancer. 2005;92:580–6.
88. Pira E, Pelucchi C, Piolatto PG, Negri E, Bilei T, La Vecchia C. Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners. Occup Environ Med. 2009;66:805–9.
89. Pira E, Pelucchi C, Piolatto PG, Negri E, Discalzi G, La Vecchia C. First and subsequent asbestos exposures in relation to mesothelioma and lung cancer mortality. Br J Cancer. 2007;97:1300–4.
90. Price B. Industrial-grade talc exposure and the risk of mesothelioma. Crit Rev Toxicol. 2010;40:513–30.
91. Puntoni R, Merlo F, Borsa L, Reggiardo G, Garrone E, Ceppi M. A historical cohort mortality study among shipyard workers in Genoa, Italy. Am J Ind Med. 2001;40:363–70.
92. Raffn E, Lynge E, Juel K, Korsgaard B. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. Br J Ind Med. 1989;46:90–6.
93. Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. Br J Cancer. 2009;100:1175–83.
94. Rees D, Myers JE, Goodman K, Fourie E, Blignaut C, Chapman R, et al. Case-control study of mesothelioma in South Africa. Am J Ind Med. 1999;35:213–22.
95. Rodelsperger K, Jockel KH, Pohlabeln H, Romer W, Woitowitz HJ. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study. Am J Ind Med. 2001;39:262–75.
96. Rolland P, Gramond C, Lacourt A, Astoul P, Chamming's S, Ducamp S, et al. Occupations and industries in France at high risk for pleural mesothelioma: A population-based case-control study (1998–2002). Am J Ind Med. 2010;53:1207–19.
97. Rossiter CE, Coles RM. HM Dockyard, Devonport: 1947 mortality study. IARC Sci Publ. 1980;30:713–21.
98. Sanden A, Jarvholm B, Larsson S, Thiringer G. The risk of lung cancer and mesothelioma after cessation of asbestos exposure: a prospective cohort study of shipyard workers. Eur Respir J. 1992;5:281–5.
99. Segura O, Burdorf A, Looman C. Update of predictions of mortality from pleural mesothelioma in the Netherlands. Occup Environ Med. 2003;60:50–5.
100. Seidman H, Selikoff IJ, Gelb SK. Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. Am J Ind Med. 1986;10:479–514.
101. Selikoff IJ, Churg J, Hammond EC. Asbestos exposure and neoplasia. JAMA. 1964;188:22–6.
102. Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987. Ann N Y Acad Sci. 1991;643:1–14.
103. Siemiatycki J, Boffetta P. Invited commentary: Is it possible to investigate the quantitative relation between asbestos and mesothelioma in a community-based study? Am J Epidemiol. 1998;148:143–7.
104. Sinks T, Goodman M, Kolonel L, Anderson B. A case-control study of mesothelioma and exposure to biogenic silica fibers. Am J Epidemiol. 1992;136:1015.
105. Sluis-Cremer GK, Liddell FD, Logan WP, Bezuidenhout BN. The mortality of amphibole miners in South Africa, 1946–80. Br J Ind Med. 1992;49:566–75.
106. Smailyte G, Kurtinaitis J, Andersen A. Cancer mortality and morbidity among Lithuanian asbestos-cement producing workers. Scand J Work Environ Health. 2004;30:64–70.
107. Stayner LT, Dankovic DA, Lemen RA. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. Am J Public Health. 1996;86:179–86.
108. Subhannachart P, Dumavibhat N, Siriruttanapruk S. Asbestos-related diseases in Thailand and review literature. J Med Assoc Thai. 2012;95 Suppl 8:S71–6.
109. Sullivan PA. Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. Environ Health Perspect. 2007;115:579–85.
110. Svenes KB, Borgersen A, Haaversen O, Holten K. Parietal pleural plaques: a comparison between autopsy and X-ray findings. Eur J Respir Dis. 1986;69:10–5.
111. Szeszenia-Dabrowska N, Urszula W, Szymczak W, Strzelecka A. Mortality study of workers compensated for asbestosis in Poland, 1970–1997. Int J Occup Med Environ Health. 2002;15:267–78.
112. Szeszenia-Dabrowska N, Wilczynska U, Szymczak W. Risk of cancer in women occupationally exposed to asbestos dust. Med Pr. 1986;37:243–9.
113. Szeszenia-Dabrowska N, Wilczynska U, Szymczak W. Cancer risk in asbestos-cement industry workers in Poland. Med Pr. 1997;48:473–83.
114. Talcott JA, Thurber WA, Kantor AF, Gaensler EA, Danahy JF, Antman KH, et al. Asbestos-associated diseases in a cohort of cigarette-filter workers. N Engl J Med. 1989;321:1220–3.
115. Thomas HF, Benjamin IT, Elwood PC, Sweetnam PM. Further follow-up study of workers from an asbestos cement factory. Br J Ind Med. 1982;39:273–6.
116. Thomason R, Schlegel W, Lucca M, Cummings S, Lee S. Primary malignant mesothelioma of the pericardium. Case report and literature review. Tex Heart Inst J. 1994;21:170–4.
117. Tomioka K, Natori Y, Kumagai S, Kurumatani N. An updated historical cohort mortality study of workers exposed to asbestos in a refitting shipyard, 1947–2007. Int Arch Occup Environ Health. 2011;84:959–67.
118. Tsai SP, Waddell LC, Gilstrap EL, Ransdell JD, Ross CE. Mortality among maintenance employees potentially exposed to asbestos in a refinery and petrochemical plant. Am J Ind Med. 1996;29:89–98.
119. Tulchinsky TH, Ginsberg GM, Iscovich J, Shihab S, Fischbein A, Richter ED. Cancer in ex-asbestos cement workers in Israel, 1953–1992. Am J Ind Med. 1999;35:1–8.
120. UICC. Report and recommendations of the working group on asbestos and cancer: convened under the auspices of the geographical pathology committee of the International Union against Cancer (U.I.C.C.). Br J Ind Med. 1965;22:165–71.

121. Ulvestad B, Kjaerheim K, Martinsen JI, Damberg G, Wannag A, Mowe G, et al. Cancer incidence among workers in the asbestos-cement producing industry in Norway. Scand J Work Environ Health. 2002;28:411–7.
122. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med. 1960;17:260–71.
123. Watkins DK, Chiazze Jr L, Fryar C. Historical cohort mortality study of a continuous filament fiberglass manufacturing plant. II. Women and minorities. J Occup Environ Med. 1997;39:548–55.
124. Weiss W. Asbestos-related pleural plaques and lung cancer. Chest. 1993;103:1854–9.
125. Woitowitz HJ, Lange HJ, Beierl L, Rathgeb M, Schmidt K, Ulm K, et al. Mortality rates in the Federal Republic of Germany following previous occupational exposure to asbestos dust. Int Arch Occup Environ Health. 1986;57:161–71.
126. Zhu H, Wang Z. Cancer epidemiology investigation for workers exposed to asbestos. In: The Ministry of Public Health of China, editor. National epidemiological study on 8 occupational cancers. Beijing: The Ministry of Public Health of China; 1996. p. 1–121.

Malignant Mesothelioma: Clinical and Imaging Findings

14

Naveed Z. Alam and Raja M. Flores

Keywords
Malignant mesothelioma • Mesothelioma surgical treatment • Mesothelioma imaging • Mesothelioma symptoms • Mesothelioma clinical findings

Primary pleural tumors had been reported since the eighteenth century; however, the epidemiology of mesothelioma first came to light in 1960 with the report by Wagner and colleagues of 33 asbestos mine workers from South Africa who developed mesothelioma [1]. Malignant mesothelioma (MM) is a rare tumor. Although the geographical distribution of the disease is diverse due to varying asbestos use, taken as a whole, the United States has an incidence just under 1 per 100,000 [2]. The incidence has been rising since the 1970s with a male to female ratio of 5:1 which is likely due to the increased frequency of occupational exposure to asbestos in men.

Clinical Presentation

The clinical presentation of MM is usually insidious and nonspecific. A careful occupational history is required, to ascertain asbestos exposure. 80–90 % of patients have known asbestos exposure, although they may not initially recollect or be aware of their exposure [3]. The most common presenting complaint is dyspnea, usually due to an associated pleural effusion, which is unilateral in the majority of cases. Drainage of the effusion may alleviate these symptoms. As the disease progresses, patients experience ill-defined, mild, but continuous chest discomfort. At this juncture, patients' dyspnea occasionally resolves as the tumor causes fusing of the visceral and parietal pleural surfaces resulting in resolution of the associated effusions.

As the disease becomes more locally advanced, chest pain becomes a more predominant feature due to local invasion of the chest wall and intercostals nerves. This is accompanied by the sensation of progressive chest tightness and dyspnea related to the restrictive effects on ventilation associated with lung entrapment by the tumor. These symptoms are related to the near-total encasement of the lung, mediastinal pleura, and chest wall by the tumor and may be associated with mediastinal shift and subsequent compression of the contralateral lung and associated vascular compromise. Direct extension of the tumor through the pericardium can result in pericardial metastases, pericardial effusion and cardiac tamponade, or pericardial constriction. Similarly, direct extension through the diaphragm can result in peritoneal seeding and ascites. The symptoms may further be exacerbated by contralateral metastases with accompanying contralateral pleural effusions. Other symptoms that may be present include a persistent dry cough, fever, night sweats, and weight loss. Uncommon symptoms include hemoptysis, dysphagia (due to restriction or shift of the esophagus), hoarseness (due to local invasion of the recurrent laryngeal nerve), and Horner's syndrome. A few cases have presented with spontaneous pneumothorax [4]. Mesotheliomas can also metastasize to distant sites with liver, bone, brain, and contralateral pleura and lung all being reported [5]; the metastases are not always clinically prominent and are often diagnosed only in the autopsy.

The presence of paraneoplastic symptoms is uncommon. Autoimmune hemolytic anemia, hypercalcemia, hypoglycemia,

N.Z. Alam, MD, FRCSC, FRACS
Division of Cardiothoracic Surgery,
St. Vincent's Hospital, Melbourne, Melbourne, VIC, Australia

R.M. Flores, MD (✉)
Department of Thoracic Surgery, Mount Sinai Medical Center,
1190 Fifth Avenue, New York, NY 10029, USA
e-mail: raja.flores@mountsinai.org

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_14, © Springer-Verlag London 2014

the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and hypercoagulability have been reported [6]. There have also been reports of thrombocytosis, defined as a platelet count greater than 400,000/ml, although this has not been associated with an increased frequency of thromboembolic events [7].

The results of physical examination are also dependent on the stage of disease and are often nonspecific. Findings associated with a pleural effusion, i.e., dullness to percussion and decreased breath sounds, may predominate. As the disease progresses to later stages and the tumor burden increases, the hemithorax becomes encased in tumor. This results in markedly decreased breath sounds as well as diffuse dullness to percussion. The affected side of the chest becomes contracted and there is a noticeable decrease in chest wall excursion. Scoliosis may develop as a result of the contraction of the chest wall [8]. A subtle fullness in the intercostal spaces can often be appreciated as well. There may also be palpable chest wall masses, particularly if the tumor has grown through the intercostal spaces. Previous sites of biopsies, thoracentesis, or VATS incisions can also present with tumor masses or subcutaneous nodules. The presence of palpable supraclavicular or axillary lymphadenopathy suggests metastases to these regions [5]. Other late local effects include signs of superior vena cava syndrome, with collateralization of neck and chest wall veins.

Peritoneal malignant mesothelioma presents in a similarly insidious fashion. Due to the even lower index of clinical suspicion than that of pleural MM, the disease often presents quite late. The majority of patients present with serous ascites due to peritoneal tumor nodules. The combination of ascites and tumor nodules results in a buildup of intraperitoneal pressure that is the most significant cause of morbidity. Increasing abdominal girth, abdominal pain, and abdominal and pelvic masses are the most common presenting complaints in decreasing order of frequency. Occasionally patients present with a new abdominal wall hernia, related to the increasing intra-abdominal pressure secondary to the ascites and tumor burden. Constitutional symptoms of weight loss and fever may also be present in some patients. One quarter of women present with gynecologic symptoms such as a pelvic mass or infertility. Associated pleural effusions may coexist [9].

Imaging

The initial chest X-ray (CXR) in early MM will most likely show unilateral pleural effusion (Fig. 14.1) and possibly some pleural plaques indicative of asbestos exposure [10]. In more advanced cases, the CXR may also demonstrate pleural thickening and nodularity.

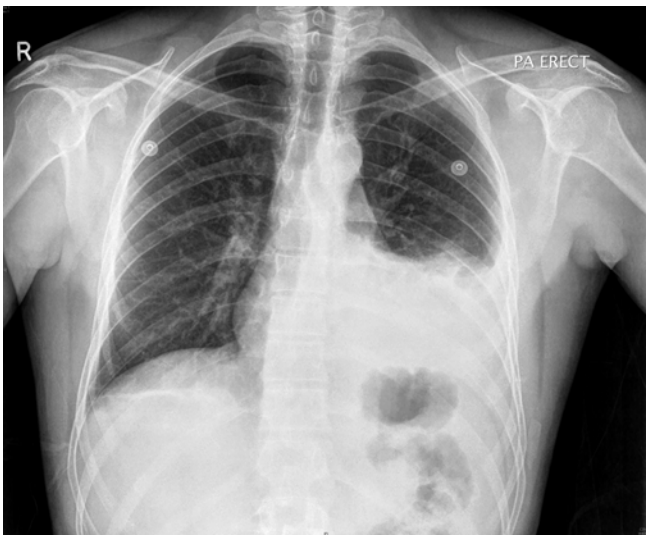


Fig. 14.1 CXR PA erect – early simple pleural effusion

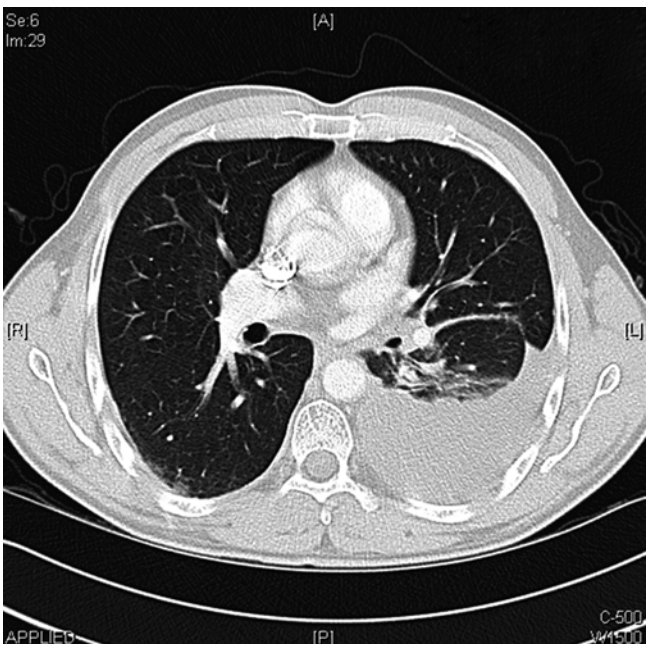


Fig. 14.2 CT – early disease – simple pleural effusion

Computed Tomography (CT)

Contrast-enhanced CT is the foundation of imaging for MM. Information about extent of disease, staging, and progression over time can all be gleaned from CT [11]. There is, once again, a great deal of variability in the appearance of MM on CT depending on the stage of presentation. In early stages, the abnormality may consist solely of a simple pleural effusion with or without changes associated with asbestos exposure, similar to those seen on CXR (Figs. 14.2 and 14.3). Alternatively, the first presen-

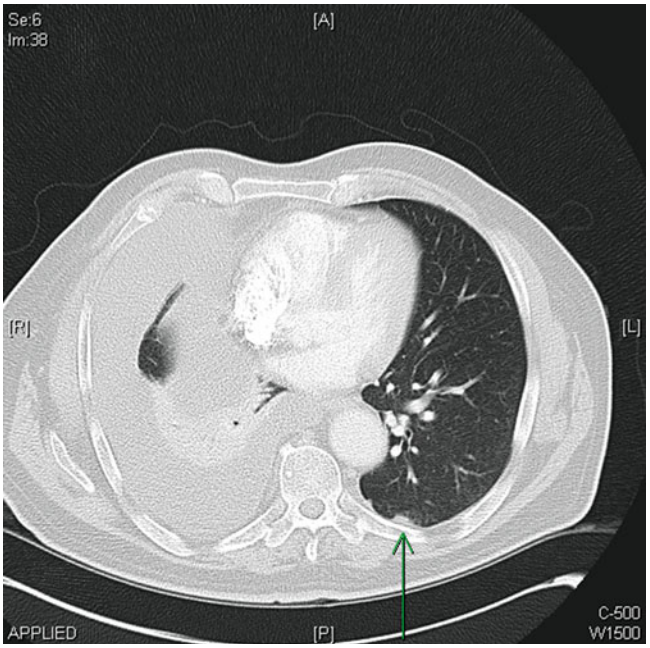


Fig. 14.3 CT – early disease. Simple pleural effusion with contralateral asbestos plaque (*green arrow*)

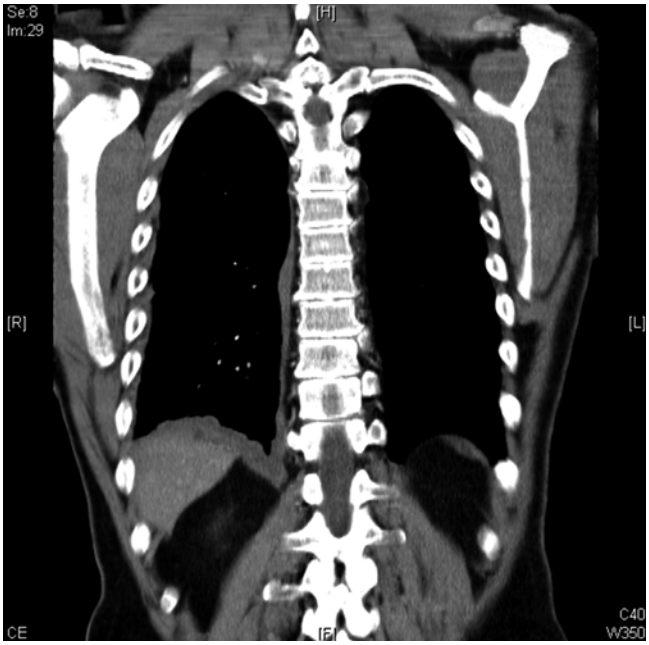


Fig. 14.5 Thickening of diaphragmatic and mediastinal pleural surfaces

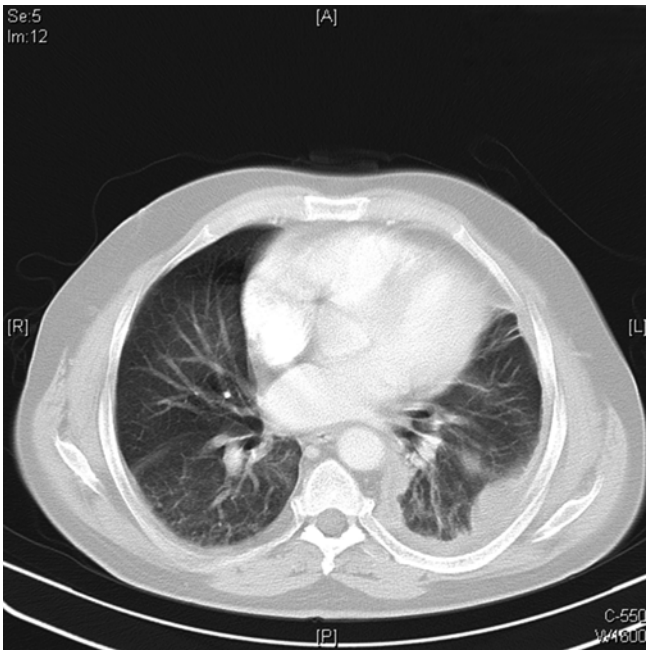


Fig. 14.4 Pleural mass with effusion

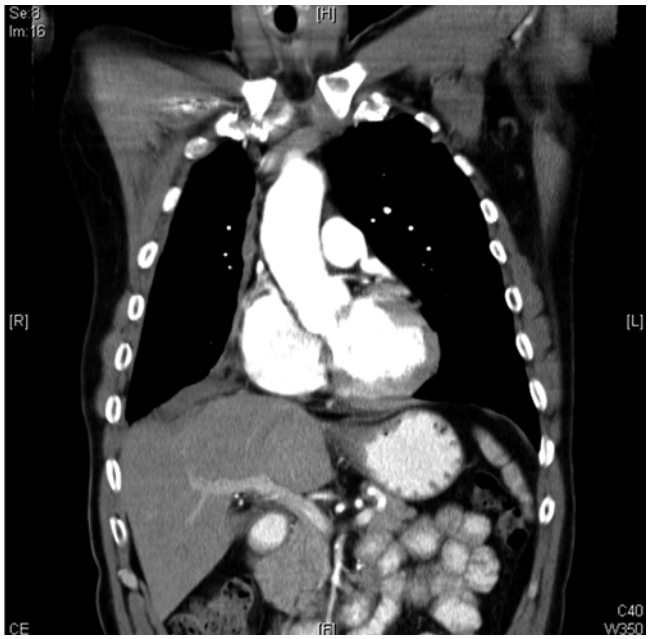


Fig. 14.6 Thickening of pericardium and mediastinal pleura. Note contraction of right hemithorax

tation on CT may consist of subtle pleural thickening or one or more discrete pleural-based masses (Fig. 14.4). These masses may be on any of the pleural surfaces, including the visceral pleural reflections within the fissures (Figs. 14.5, 14.6, 14.7, and 14.8). As the disease progresses, larger masses are evident and may become confluent (Fig. 14.9). There may be associated multiloculated pleural effusions. Although a solitary dominant pleural mass may occasionally be present initially (Fig. 14.10a), the disease almost always progresses to a diffuse, thick, confluent pleural rind which encases the lung and obliterates the pleural space [12].

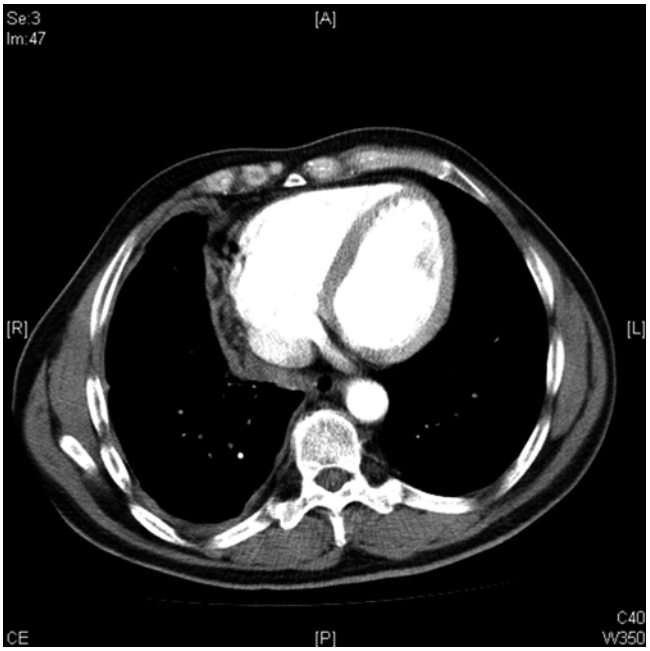


Fig. 14.7 Pericardial thickening

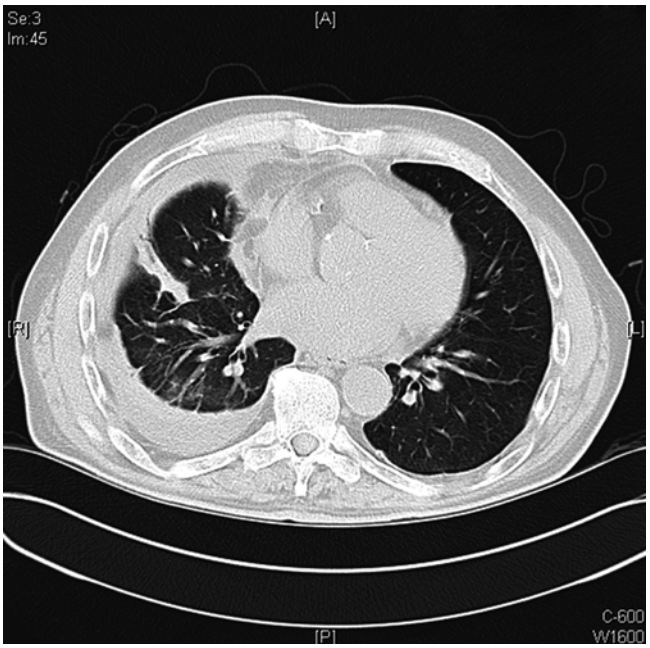


Fig. 14.8 Tumor in oblique fissure

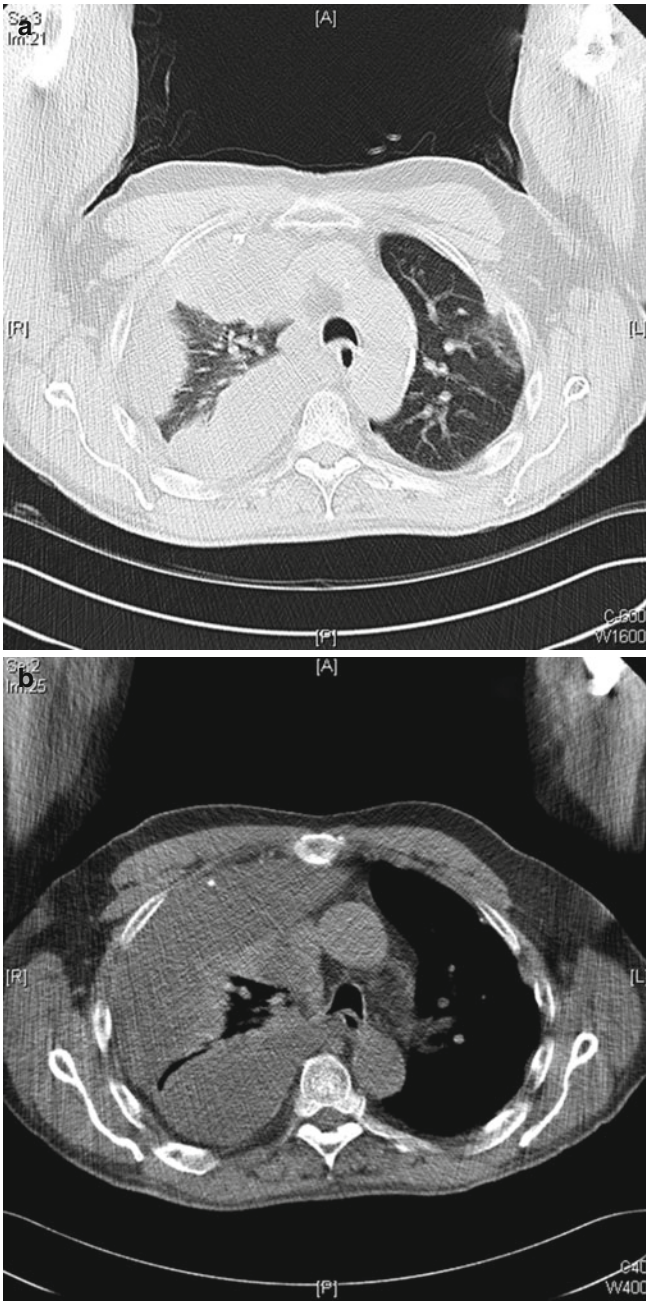


Fig. 14.9 (**a**) Multiple large, confluent masses. (**b**) Note mediastinal shift

In advanced cases the presence of mediastinal lymphadenopathy may be evident (Fig. 14.11). In addition to lymph node metastases in the usual lung cancer locations, e.g., paratracheal, para-aortic, and subcarinal, lymph node enlargement in the internal mammary chain may be evident as this is the site of lymphatic drainage for the anterior chest wall and pleura (Fig. 14.12). Direct extension of tumor through the chest wall, extension through and into the pericardium, and invasion of the mediastinum or diaphragm may all be present in late disease and are readily evident on CT. Chest wall invasion is characterized by bone destruction, intercostal muscle invasion, and loss of extrapleural fat planes (Fig. 14.10a) [13].

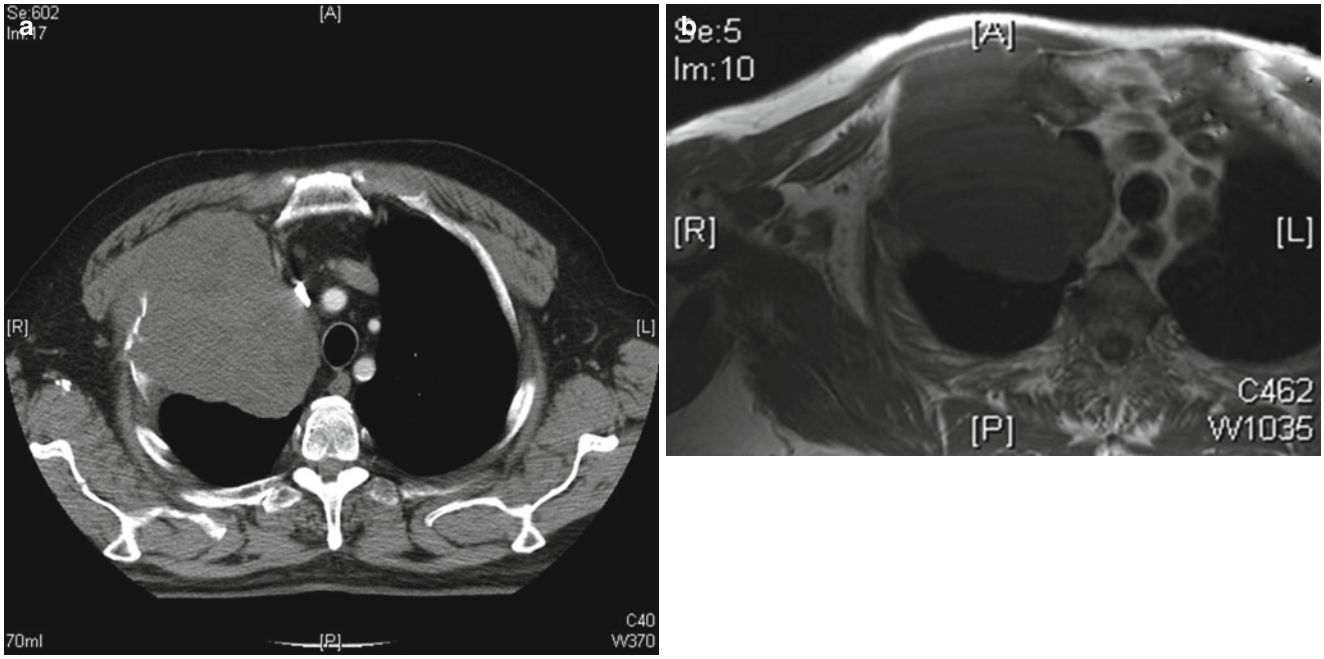


Fig. 14.10 (**a**) Unusual solitary dominant mass. Note chest wall invasion through intercostal muscles. (**b**) MRI showing chest wall invasion

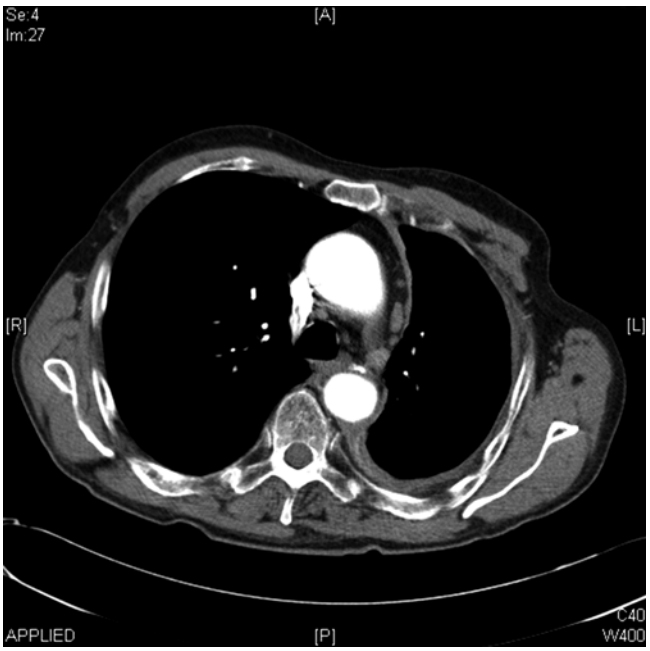


Fig. 14.11 Para-aortic lymphadenopathy

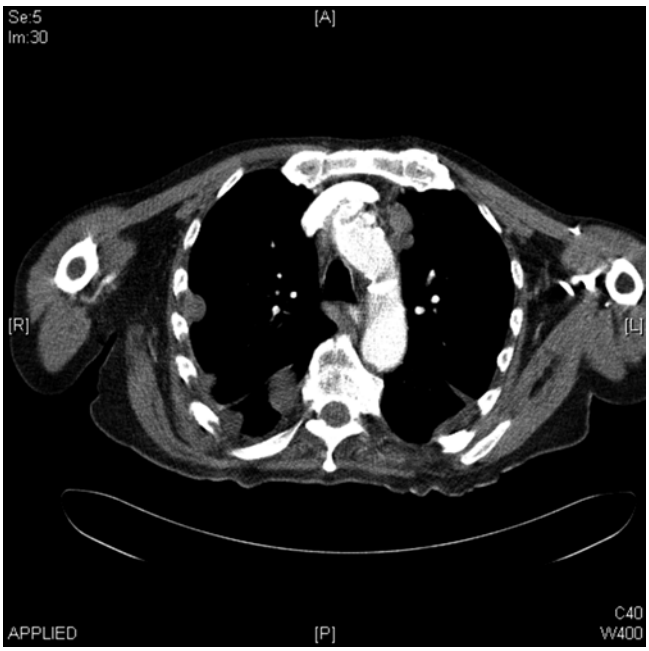


Fig. 14.12 Left internal mammary chain lymphadenopathy

Magnetic Resonance Imaging (MRI)

The main limitation of CT in evaluation of MM is related to assessing the presence of chest wall invasion (Fig. 14.10b) or extension through the diaphragm. In this setting, MRI may function as a useful adjunct to CT. The accurate imaging of the tumor extension is needed if the patient is considered for surgical treatment with radical intention, be it extrapleural pneumonectomy or pleurectomy/decortication. MM enhances with the use of gadolinium-based contrast, which aides in the discrimination of tumor from surrounding normal tissue. MM is typically slightly hyperintense on T_1-weighted images and moderately

hyperintense on T_2-weighted images [14]. MRI may be superior to CT in identifying endothoracic fascia invasion which may render patients unresectable [15]. MRI may also be useful in patients unable to tolerate intravenous CT contrast.

Positron Emission Tomography

Fluorodeoxyglucose positron emission tomography (FDG-PET) has been widely accepted as an imaging method in a multitude of malignant disease sites. In MM it has a role in staging. PET has been shown to distinguish between benign and malignant disease of the pleura using mean standardized uptake values (SUV-PET). SUV-PET also has increased accuracy over CT in the detection of mediastinal nodal metastases but infectious/inflammatory processes can result in false positive findings [16]. It has also been shown to aid in the identification of otherwise occult extrathoracic metastases in up to 10 % of patients being considered for surgery by coauthor (RMF) and colleagues [17].

PET has also been shown to have prognostic value. Coauthor (RMF) and colleagues also demonstrated that high SUV tumors were associated with a 1.9 times greater risk of death than low SUV tumors ($P<0.01$) and median survivals of 9 and 21 months, respectively, ($P=0.02$) [18]. Taken along with stage and histology, PET can stratify patients into better and worse prognoses groups for study purposes and therapeutic decision-making.

Diagnosis

Diagnosis of MM is based on the histological samples from the tumor and obtaining a diagnosis can be difficult. As previously mentioned, the most common finding at presentation is the presence of a pleural effusion and the cytological sample of the pleural fluid is usually the first attempt to reach the diagnosis. However, the diagnosis via cytology is challenging and is only successful in about 30 % even with experienced cytopathologists [19]. This is due to the fact that it is extremely difficult to distinguish between the cells of MM, metastatic adenocarcinoma, and severe atypia. If there is a tumor lesion that can be targeted, then CT-guided percutaneous biopsy can yield a diagnosis in around 80 % of patients [20].

However, for many patients the diagnosis remains elusive and an invasive surgical procedure to obtain adequate amount of tumor tissue to histologically confirm the diagnosis is required. Thoracoscopy is the preferred approach with diagnostic yield approaching 94 % [21]. It is a minimally invasive procedure and allows large amounts of tissue to be biopsied safely. In addition, therapeutic maneuvers such as drainage of associated pleural effusions and pleurodesis of advanced cases can be performed. To facilitate the histological diagnosis, deep biopsies including parietal pleura, endothoracic fascia, and chest wall muscles are the most useful. These biopsies can be performed through a single port with an up-biting rigid bronchoscopy biopsy forcep placed parallel to the 30° thoracoscope. The advantage of the single port is that it minimizes the risk of seeding with tumor. The incision should be placed along the site of a future thoracotomy so that it may be excised if further surgery is considered.

If the pleural space is completely fused, an open pleural biopsy may need to be performed. This need not be a morbid procedure, as placing the incision above a radiologically identified site of bulky tumor enables a biopsy to be performed with no rib spreading. Occasionally a small piece of rib can be excised to facilitate exposure. A great deal of tissue can be obtained in this fashion. Regardless of how the biopsy is performed, specimens should be delivered fresh to the laboratory to enable electron microscopy. Various serum markers have been investigated in the assessment and diagnosis of MM. The most promising to date is serum mesothelin or soluble mesothelin-related peptide (SMRP). It can be useful in detecting recurrence and assessing response to treatment. Mesothelin is a differentiation antigen of mesothelial cells which is highly expressed in mesothelioma [22]. One study showed that SMRP was elevated in 84 % of patients with MM versus 2 % of patients with other cancers or pulmonary diseases [23]. Mesothelin is highly specific for MM (specificity 98 %) but not that sensitive (49 % at diagnosis). At this point in time, there is little evidence to guide how to use this marker, but some clinicians use it to monitor treatment effects (following chemotherapy) or to look for disease progression.

Staging

Staging in MPM, as is the case in other aspects of the disease, lacks consensus. Some argue that it is not required in patients unless they are enrolled in clinical trials [24]. Various staging systems exist. The classic system described by Butchart and colleagues in 1976 is relatively simple and descriptive but was based on only 29 patients [25] (Table 14.1). It has been superseded by a number of other systems. However, the TNM staging published in the AJCC Cancer Staging Manual is the most comprehensive [26] (Table 14.2).

Table 14.1 Butchart staging

Stage 1	Tumor confined to ipsilateral pleura, lung, and pericardium
Stage 2	Tumor invading chest wall or mediastinal structures, e.g., esophagus, heart, opposite pleura
Stage 3	Tumor penetrating diaphragm to involve peritoneum directly
Stage 4	Distant blood-borne metastases

Reproduced from Butchar et al. [25], copyright 1976, with permission from BMJ Publishing Group Ltd

Table 14.2 IMIG staging system for diffuse malignant pleural mesothelioma

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor limited to the ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement		
T1a	No involvement of the visceral pleura		
T1b	Tumor also involving the visceral pleura		
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:		
	Involvement of the diaphragmatic muscle		
	Extension of tumor from visceral pleura into the underlying		
	Pulmonary parenchyma		
T3	Locally advanced but potentially resectable tumor		
	Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:		
	Involvement of the endothoracic fascia		
	Extension into the mediastinal fat		
	Solitary, completely resectable focus of tumor extending into the soft tissue of the chest wall		
	Nontransmural involvement of the pericardium		
T4	Locally advanced technically unresectable tumor		
	Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:		
	Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction		
	Direct transdiaphragmatic extension of tumor to the peritoneum		
	Direct extension of tumor to the contralateral pleura		
	Direct extension of tumor to mediastinal organs		
	Direct extension of tumor into the spine		
	Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes		
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes		
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis present		
Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1,T2	N1	M0
	T1, T2	N2	M0
	T3	N0,N1,N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

Conclusion

The clinical and imaging features of malignant mesothelioma vary widely depending on the stage of presentation. A significantly high index of suspicion is required to make a diagnosis due to the nonspecific nature of the symptoms, signs, and early radiology. Invasive surgical procedures are often required to obtain adequate tumor tissue samples to secure the diagnosis.

References

1. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med. 1960;17:260–71.
2. Verschraegen C. Mesothelioma: incidence and survival rates in the United States. Proc Am Soc Clin Oncol. 2003;22:869.
3. Bégin R. Asbestos related diseases. In: Harber P, Schenker MB, Balmes JR, editors. Occupational and environmental respiratory disease. St. Louis: Mosby-Year Book; 1996. p. 293–321.
4. Sheard JDH, et al. Pneumothorax and malignant mesothelioma in patients over the age of 40. Thorax. 1991;46:584.
5. Law MR, Hodson ME, Heard BE. Malignant mesothelioma of the pleura: relation between histological type and clinical behaviour. Thorax. 1982;37:810.
6. Ruffie P, et al. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. J Clin Oncol. 1981;7:1157.
7. Olesen LL, Thorshauge H. Thrombocytosis in patients with malignant pleural mesothelioma. Cancer. 1988;62:1194.
8. Rudd RM. Malignant mesothelioma. Br Med Bull. 2010;93:105–23.
9. Munkholm-Larsen S, Cao CQ, Yan TD. Malignant peritoneal mesothelioma. World J Gastrointest Surg. 2009;1(1):38–48.
10. Antman KH. Current concepts: malignant mesothelioma. N Engl J Med. 1980;303:200–2.
11. Qureshi NR, Gleeson FV. Imaging of pleural disease. Clin Chest Med. 2006;27:193–213.
12. Gotfried MH, Quan SF, Sobonya RE. Diffuse epithelial pleural mesothelioma presenting as a solitary lung mass. Chest. 1983;84:99.
13. Ng CS, Munden RF, Libshitz HI. Malignant pleural mesothelioma: the spectrum of manifestations on CT in 70 cases. Clin Radiol. 1999;54:415–21.
14. Mujoomdar AA, Sugarbaker DJ. Diffuse pleural malignancies. In: Sugarbaker DJ, Bueno R, Krasna MJ, Mentzer SJ, Zellos L, editors. Adult chest surgery. New York: McGraw Hill Medical; 2009. p. 838–48.
15. Heelan RT, Rusch VW, Begg CB, et al. Staging of malignant pleural mesothelioma: comparison of CT and MR imaging. AJR Am J Roentgenol. 1999;172:1039–47.
16. Bernard F, Sterman D, Smith RJ, et al. Metabolic Imaging of malignant pleural mesothelioma with fluorodeoxyglucose positron emission tomography. Chest. 1998;9:713–72.
17. Flores RM, Akhurst T, Gonen M, et al. Positron emission tomography defines metastatic disease but not locoregional disease in patients with malignant pleural mesothelioma. J Thorac Cardiovasc Surg. 2003;126:11–6.
18. Flores RM, Akhurst T, Gonen M, et al. Positron emission tomography predicts survival in malignant pleural mesothelioma. J Thorac Cardiovasc Surg. 2006;132:763–8.
19. Ismail-Khan R, Robinson LA, Williams CC, et al. Malignant pleural mesothelioma: a comprehensive review. Cancer Control. 2006; 13:255–63.
20. Metintas M, Ozdemir N, Isiksoy S, et al. CT-guided pleural needle biopsy in the diagnosis of malignant mesothelioma. J Comput Assist Tomogr. 1995;19:370–4.
21. Agarwal PP, Seely JM, Matzinger FR, et al. Pleural mesothelioma: sensitivity and incidence of needle track seeding after image-guided biopsy versus surgical biopsy. Radiology. 2006;241:589–94.
22. Rai AJ, Flores RM, Mathew A, et al. Soluble mesothelin related peptides (SMRP) and osteopontin as protein biomarkers for malignant mesothelioma: analytical validation of ELISA based assays and characterization at mRNA and protein levels. Clin Chem Lab Med. 2010;48(2):271–8.
23. Robinson BW, Creaney J, Lake R, et al. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet. 2003;362:1612–6.
24. West SD, Lee GYC. Management of malignant pleural mesothelioma. Clin Chest Med. 2006;27:335–54.
25. Butchart EG, Ashcroft T, Barnsley WC, et al. Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura: experience with 29 patients. Thorax. 1976;31:15–24.
26. Edge SB, Byrd DR, Compton CC, editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.

Malignant Mesothelioma: Asbestos Exposure

15

Richard L. Attanoos

Keywords
Asbestos exposure • Asbestos mineralogy • Malignant mesothelioma • Asbestos type • Asbestos fiber counting • Pulmonary asbestos analysis

Introduction

Asbestos is a recognized high-profile health hazard with an estimated total cancer burden from malignant mesothelioma and lung cancer in industrialized countries to be in the order of 30,000 cancers per year [1] with further deaths related to lung fibrosis (asbestosis) and complications of asbestos-related diffuse pleural thickening. Projections for the 1995–2029 period suggest that male mesothelioma deaths will double over the next 20 years to a peak of 9,000 in 2018 and then decline, with an estimated 250,000 deaths up to 2025 in Europe [2].

The association of asbestos with malignant mesothelioma is discussed in this chapter and has a primacy among occupational cancers for a number of reasons. First, malignant mesothelioma is an unusual diffuse tumor arising from the serosal surfaces (of the pleura, peritoneum, pericardium, and gonads) and whose very existence was controversial at the time of its reported association with asbestos in 1960 [3]. For this reason and others, medical opinion was slow to accept the disease and its relation to asbestos. To this day the pathological diagnosis of malignant mesothelioma is problematic [4]. Second, diffuse malignant mesothelioma is clinically important because it is generally associated with a poor prognosis (median 12–18 months survival from clinical manifestation) regardless of treatment [5]. Third, while most diffuse malignant mesotheliomas are now recognized as associated with prior asbestos exposure, the strength of the association varies with the anatomical tumor site and asbestos fiber type. These factors generate much medicolegal debate. Fourth, despite dust suppression measures in industry, asbestos-related mesothelioma deaths continue to increase in many countries generating continued media concern. In part this relates to the known latent period from initial asbestos exposure to the subsequent clinical development of the tumor. Asbestos-related mesotheliomas show a long latent period where the minimum latent period is in the region of 10 years, there is no upper limit, and the vast majority of bona fide asbestos-related tumors arise after 30 years [6]. In addition the pleura is highly sensitive to the injurious effects of asbestos, and it is now recognized that even very brief, low-dose exposures to amphibole asbestos may significantly increase mesothelioma risk and cause disease in susceptible individuals. Moreover, there is emerging epidemiological evidence that for individuals exposed to asbestos in the distant past, the risk of mesothelioma is not modified by subsequent exposures or exposure cessation [7]. Because the pathogenesis of malignant mesothelioma is incompletely understood, there remains continued debate as to whether malignant mesotheliomas emerge as a cumulative dose-response disease or non-dose-related tumor emerging after initial necessary minimal "trigger dose" exposures in susceptible individuals. The latter would explain why despite stringent efforts to eradicate asbestos exposure there exists an expanding mesothelioma epidemic.

With respect to asbestos-related health hazards, government legislation, scientific expertise, industry, workforce and unions, and the media have a collective responsibility to protect exposed individuals. There is major public concern in particular with malignant mesothelioma because until the 1990s (even among the most progressive authorities)

R.L. Attanoos, BSc, MBBS
Department of Cellular Pathology,
University Hospital of Wales,
Heath Park, Cardiff CF14 4XW, UK
e-mail: richard.attanoos@wales.nhs.uk

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_15,

"controlled" industrial asbestos use was regarded as having *acceptable* risks. It is now appreciated that trivial amphibole asbestos exposures may cause mesothelioma in susceptible individuals and that the risk cannot be adequately controlled by the workplace technology and control regulations. Airborne fibrous dust measurements advanced to monitor asbestos fiber levels in the workplace were established at a time when there was limited knowledge of the effects, detectability, and biological activity of fibers in inducing disease. The effectiveness of hygiene monitoring equipment (membrane filter method – phase contrast light microscopy) in detecting the biologically active respirable fraction of asbestos capable of preventing malignant mesothelioma, in particular, is highly questionable. It appears biologically plausible that even complete compliance with regulatory standards set out in threshold limit values, permissible exposure limits, and other dose regulations and safety measures in the workplace could have limited effect in preventing exposure to the submicroscopic toxic asbestos fibers that, in particular, induce malignant mesothelioma after low-level exposure. For these reasons, the Collegium Ramazzini, whose mission statement is to translate occupational scientific data into public policy, has called for an immediate international ban on asbestos mining and use [8].

In this chapter there is discussion of the mineralogical aspects of asbestos, relation of malignant mesothelioma with asbestos, assessment of asbestos exposure in exposed subjects, and consideration of the historical evolution in the understanding of the fiber and the disease.

Asbestos: Mineralogy

The term *asbestos* refers to a group of mineral fibers that share the properties of thermal and chemical resistance, flexibility, and high tensile strength. Asbestos is a commercial rather than a mineralogical term.

Asbestos is a naturally occurring mineral which is conventionally divided into two mineralogical groups. The amphiboles comprise crocidolite (blue asbestos), amosite (brown asbestos), tremolite, anthophyllite, and actinolite. The other group of asbestos minerals is the serpentine group of which chrysotile (white asbestos) is the sole variety (see Table 15.1 and Figs. 15.1, 15.2, 15.3, 15.4, 15.5, and 15.6 inclusive). Chrysotile accounts for over 95 % of the asbestos used commercially worldwide [9]

Amphiboles and chrysotile are distinct in their chemical, physical, and biological properties, and these factors transfer

Table 15.1 Asbestos minerals

Mineral group	Asbestos	Poly type	Composition
Serpentine	*Chrysotile*[a]	Lizardite, antigorite	$Mg_3\ (Si_2\ O_5)\ (OH_4)$
Amphibole	Actinolite	Actinolite	$CA_2\ (Mg.Fe^{2+}{}_5)\ (Si_8\ O_{22})\ (OH_2)$
	Amosite[a]	Cummingtonite-grunerite	$(Fe^{2+}Mg)_7\ (Si_8\ O_{22})\ (OH_2)$
	Anthophyllite[a]	Anthophyllite	$(Mg.Fe^{2+})_7\ (Si_8\ O_{22})\ (OH_2)$
	Crocidolite[a]	Riebeckite	$Na_2\ Fe^{2+}{}_3Fe_2{}^{3+}\ (Si^8)\ (O_{22})\ (OH)_2$
	Tremolite	Tremolite	$CA_2\ Mg_5\ (Si_8\ O_{22})\ (OH)_2$

[a]Commercial asbestos forms, anthophyllite in Finland

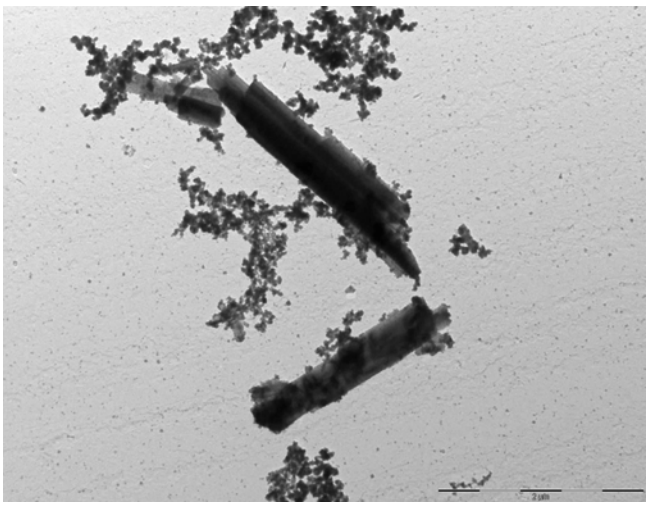


Fig. 15.1 Transmission electron microscopic image of actinolite

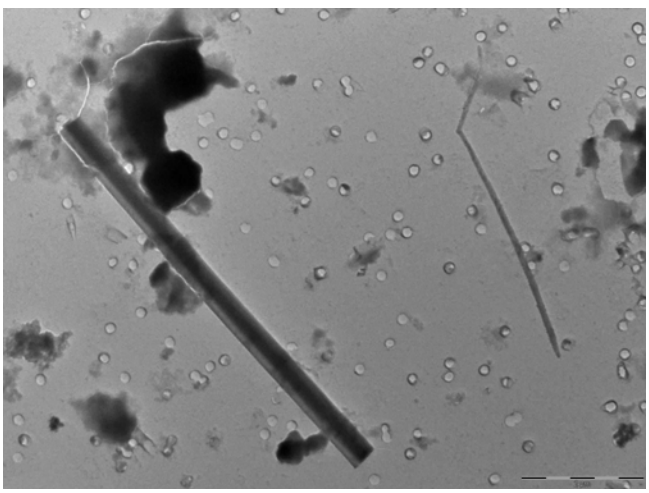


Fig. 15.2 Transmission electron microscopic image of amosite and glass fiber

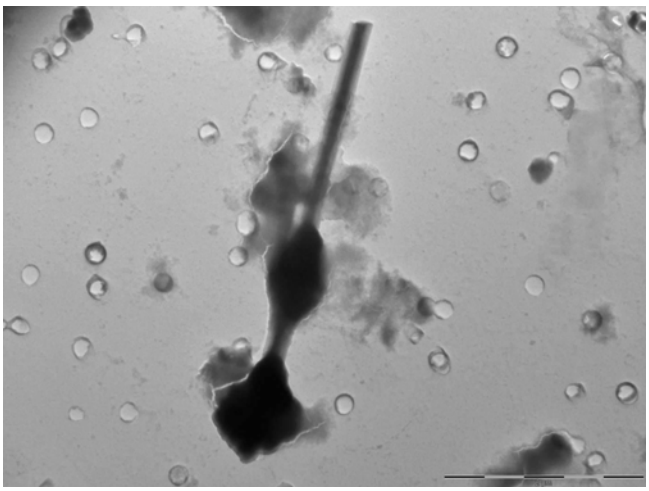


Fig. 15.3 Transmission electron microscopic image of amosite asbestos body

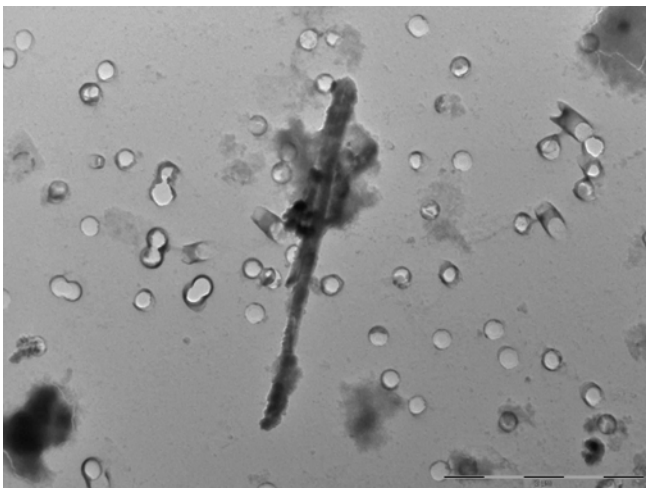


Fig. 15.6 Transmission electron microscopic image of crocidolite

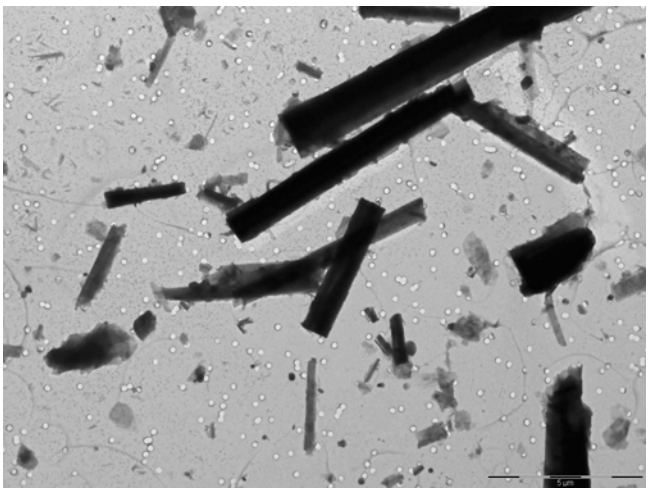


Fig. 15.4 Transmission electron microscopic image of anthophyllite

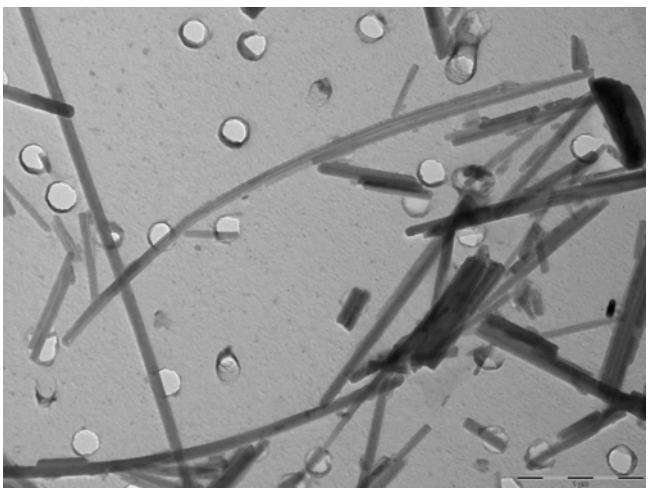


Fig. 15.5 Transmission electron microscopic image of chrysotile, note short fiber size

into significant differences in fiber toxicity and potency to induce diffuse malignant mesothelioma.

The amphibole and serpentine minerals occur both as asbestiform (fibrous) varieties and as non-asbestiform (massive) varieties of identical chemical composition. The non-asbestiform counterpart of crocidolite is known as riebeckite and the non-asbestiform counterpart of amosite is cummingtonite-grunerite. For tremolite, anthophyllite and actinolite non-asbestos counterparts retain the same name as the fibrous asbestiform varieties.

General Considerations

The scientific evolution in asbestos-related disease identified first, lung fibrosis (asbestosis) then later the asbestos-related cancers, lung cancer and later malignant mesothelioma [10]. Initial scientific considerations suggested that all asbestos-related cancers (lung cancer and mesothelioma) arose in subjects with asbestosis. However, further investigations soon identified that malignant mesothelioma may arise *ex asbestosis* and in subjects with environmental and domestic exposures.

Public health concern regarding the adverse effects of asbestos created worldwide attention and governmental regulatory policy to regulate and reduce and/or ban asbestos imports. However, most authorities considered that controlled use of asbestos could continue with compliance with regulatory standards, in particular with chrysotile. By the early 1980s, the threshold dose necessary for clinical degrees of asbestosis was estimated to be 25 fiber/ml-years cumulative exposure (mixed amphibole – chrysotile exposure). By 1989, the World Health Organization recommended an occupational safety limit based on health grounds; they considered that controls to reduce the risk of asbestos-related

cancer to "acceptable" limits would effectively eradicate asbestosis. By 1991 expert scientific opinion considered that the minimum dose necessary to induce malignant mesothelioma (mesothelioma "threshold") was around 5 fiber/ml-years [11] or a dose of 0.1fiber/ml over a lifetime working (50 years). The 0.1fiber/ml was the lowest technologically feasible at the time and adopted in 1993 by the Occupational Health and Safety Administration as its permissible exposure limit (8 h time-weighted average for 40 h week) (OSHA PEL limit). It is now known that there is a substantive increased risk of mesothelioma after very-low-dose amphibole exposure [12] and some authorities argue there is no threshold dose below which there is no increase risk of subsequent mesothelioma. Medical opinion is considerably divided in this regard particularly with respect to chrysotile exposure [13].

The substantive link between malignant mesothelioma and asbestos was reported in 1960 by Wagner and others [14] and since then several publications have documented mesothelioma in various occupational communities. From North American registries about 90 % of male mesothelioma patients have a history of prior asbestos exposure [15]. Among female mesothelioma patients it is estimated that between 60 and 75 % have a history of asbestos exposure, but the exposures are occupational in only about 20 % [16]. Because of the consistency in specificity of the asbestos-mesothelioma relationship, the incidence of mesothelioma in society is usually considered to be an index of past use of asbestos. Malignant mesothelioma incidence rates in different countries are generally in the range of 14–30 cases per million persons per year (over 15 years of age). Several epidemiological studies have examined the broad relationship between asbestos production, use, or imports and the subsequent incidence of mesothelioma, on a countrywide basis [17, 18]. All have shown rises in the incidence of malignant mesothelioma parallel rises in the amount of asbestos in use after about 30 years. This reflects the long latent interval that occurs in human malignant mesothelioma from asbestos exposure to the death of the individual and significance of early "dustier" exposures in susceptible individuals.

Medical opinion is united in accepting that most malignant mesotheliomas are related to prior asbestos exposure; however, there exists considerable dispute as to the percentage of malignant mesotheliomas which should be considered asbestos related. Some authorities believe that virtually all malignant mesotheliomas are asbestos related [19] whereas most experts accept that spontaneous or idiopathic mesotheliomas occur and highlight non-asbestos-related risk factors for the disease [20]. Peritoneal mesotheliomas in women have an inconstant relationship with asbestos. Pericardial mesotheliomas and gonadal mesotheliomas are very rare, and consequently the role of asbestos in their etiology is not yet defined.

Asbestos Fiber Type and Mesothelioma

There exists substantial evidence that the type of asbestos fiber to which exposure occurs is critical in determining the subsequent risk of mesothelioma. Epidemiological and mineralogical studies show amphiboles cause the vast majority of diffuse malignant mesothelioma in males. The role of chrysotile in pleural mesothelioma causation is however controversial. Governmental public policy advocates a conservative approach and does not distinguish between the different forms of asbestos. However the scientific literature in humans consistently illustrates that fiber potency differences for mesothelioma do exist. Not surprisingly medical opinion is divided. On the one hand there exist epidemiological and mineralogical studies in humans which would support the view that chrysotile, uncontaminated by amphiboles, is not a cause for diffuse malignant mesothelioma. However, there also exists epidemiological evidence which shows a small excess risk of mesothelioma in workers exposed to chrysotile, but because in essentially all studies some level of amphibole contamination was present, the results on workers exposed to uncontaminated chrysotile are too limited to allow a clear-cut conclusion. On the other hand some authors have suggested that chrysotile is the main cause for pleural mesothelioma. This reasoning is based on the premise that as asbestos is the major cause of mesothelioma and chrysotile constitutes 95 % of all asbestos use worldwide, it can be concluded that chrysotile asbestos is the main cause of pleural mesothelioma in humans [21].

The influences of asbestos fiber type appear much more marked for malignant mesothelioma than for lung cancer. In a meta-analysis of the risk of mesothelioma from exposure to various fiber types [22], the authors concluded that, at exposure levels seen in occupational cohorts, the comparative risk of mesothelioma from these fiber types was 1:100:500 for chrysotile, amosite, and crocidolite, respectively, i.e., crocidolite was 500-fold and amosite 100-fold more potent than chrysotile in the induction of mesothelioma. The authors did not address in their analysis the distinction between the health effects of chrysotile that may have been contaminated with the amphibole asbestos and chrysotile that is amphibole-free. On a fiber:fiber basis combined commercial amphiboles were 10–50, 1 more potent in inducing lung cancer than chrysotile. In a subsequent publication [23] the same authors from the United Kingdom Health and Safety Executive modelled their calculation by affording chrysotile a zero weight or potency in best predicting mesothelioma mortality in Great Britain from 2002 to 2050.

The proposed technical support document for a protocol to assess asbestos-related risk [24] conducted a similar meta-analysis which demonstrated a substantial difference in the relative potency of amphiboles and chrysotile toward the induction of mesothelioma, with combined amphiboles

estimated as over 800-fold more potent than chrysotile on a fiber:fiber basis.

In an extensive meta-analysis of 71 asbestos-exposed cohorts to evaluate the role of asbestos fiber type relevant to industry and malignant mesothelioma [25], the author concluded that the epidemiological studies show amphiboles cause mesothelioma in humans and epidemiology does not support the view that chrysotile, uncontaminated by amphiboles, cause mesothelioma. In 8 large chrysotile-only cohorts (23,794 workers), no recorded mesotheliomas were found. In a further 14 cohorts exposed to chrysotile without identified amphiboles, 7 mesothelioma cases were found. Careful review identified that either the exposures were likely mixed (with amphibole), diagnosis was questionable or latency inadequate or unstated. Conversely authors have concluded that chrysotile is the main cause of pleural mesothelioma citing that the highest rates of mesothelioma arise in predominant chrysotile-exposed cohorts [21]. However, in most commercial chrysotile ore deposits, there exist minute quantities of contaminant amphibole asbestos, tremolite. The presence of this contaminant amphibole is considered to play a role in the induction of mesothelioma after heavy cumulative doses (in the order necessary to induce asbestosis). Indeed the presence of minute quantities of amphibole in chrysotile exposures appears to exert a disproportionate effect [22].

The differences in toxicity of amphiboles and chrysotile relate in part to differences in the individual fiber types' biodurability in human tissues. The presence of biodurable asbestos fibers at the site of tissue injury is considered an essential early step in fiber-induced pathogenicity and tumorigenesis. Amphibole asbestos fibers persist in tissue over time whereas chrysotile is rapidly cleared from the body. Accordingly, amphiboles are far more potent in inducing malignant mesothelioma.

Asbestos Fiber Dimensions and Malignant Mesothelioma

Mainstream scientific opinion accepts that long (amphibole) fibers are unequivocally more potent in the induction of mesothelioma than short fibers.

The importance of fiber length in relation to asbestos-induced neoplasia in vivo was demonstrated in the United States [26, 27] and in West Germany [28]. These workers independently showed that following the intrapleural or intraperitoneal implantation of asbestos and other mineral fibers, the development of mesotheliomas was most closely related to the number of fibers >8 μm in length and <0.25 μm in diameter. The investigators found that fiber potency was directly correlated with fiber length and inversely related to fiber diameter. Other investigators have confirmed the significance of fiber length in UICC asbestos samples [29, 30] emphasizing the rapid clearance of short fiber chrysotile and lack of lung tissue injury. The results were later corroborated by Bernstein and coworkers [31, 32].

Human studies are limited in addressing the role of short versus long asbestos fibers in the development of malignant mesothelioma because occupational exposures are complex and poorly characterized and respirable dust clouds contain a variety of lengths of mixed dust particulates. With respect to asbestos, no studies have specifically evaluated cancer outcomes associated with fibers shorter than 5 μm in length because no occupational cohort is exposed exclusively to such fibers.

Circumstantial evidence that short fibers have low carcinogenicity in humans emerges from a number of publications:

1. Minnesota mine workers [33]. The workers were exposed to amorphous amosite, and the vast majority of fibers were reported less than 10 μm in length. The study found no increase in overall mortality or mortality from respiratory cancer.
2. South Dakota gold mine workers exposed to amorphous amosite (cummingtonite-grunerite). On long-term follow-up they had no increased risk of respiratory cancer. In this study 94 % of airborne fibers were less than 5 μm in length [34].

The Agency for Toxic Substances and Disease Registry considered the influence of fiber length on malignant disease and concluded that fibers shorter than 5 μm were unlikely to cause cancer in humans [35].

In contrast, a number of case control studies have shown that mesothelioma risk is considerably higher for individuals with larger amounts of long fibers retained in their lungs. In a case control study of 78 Canadian mesotheliomas and age-matched referents, McDonald and coworkers [36] noted that the concentrations of amosite, crocidolite, and tremolite differed between Canadian mesothelioma cases and control referents. Relative risk was related to the risk of long amphibole fibers (≥8 μm) with no additional information provided by shorter fibers.

In an Australian study of mesothelioma subjects, Rogers and coworkers [37] found the best fit relative risk for mesothelioma was greatest for amphibole asbestos fibers longer than 10 μm.

The most recent estimate is that the best fiber metric predicting mesothelioma risk are those fibers >20 μm length and <1.5 μm diameter [38].

The identification of short chrysotile fibers in human tissues and pleura has been reported [39] and has been postulated to be associated with mesothelioma induction [40, 41], but this is of questionable relevance. There exists no convincing scientific evidence base that short chrysotile fibers are pathogenic.

Long commercial amphibole fibers have been identified in the peritoneum and mesentery [42]. In 1996 Boutin and

coworkers [43] showed that the majority of asbestos fibers in parietal pleural anthracotic foci (termed "black spots") contained significant numbers of long amphibole fibers.

Fiber diameter is an important determinant in fiber respirability and penetration (deposition) into the lungs. Correlations exist between fiber length and diameter.

Fibers with high aspect ratio (long length: width ratio) are those long fibers with low fiber width and this fraction of the airborne dust is highly relevant for multiple reasons:

1. The bioactive fraction of long thin (submicroscopic) amphibole fibers represents only a very small fraction of the entire dust cloud; most fibers are short (<3 μm) and these are nontoxic [44].
2. The "bioactive mesothelioma fraction" represents an unregulated fiber component because hygiene control regulatory monitoring equipment (membrane filter method with phase contrast light microscopy) is inadequate in identifying fibers ≤0.25 μm fiber width (irrespective of fiber length).
3. It is this small unregulated fraction of thin submicroscopic fibers that likely have the greatest propensity to penetrate the lung periphery, visceral pleura, and via the mesothelial stomata reach the parietal pleura, site of induction of malignant mesothelioma [45].
4. The delivery of long thin (submicroscopic) biodurable amphibole fibers to the parietal fibers represents a key first step in the pathogenesis of malignant mesothelioma.
5. The delivery of the initial long biodurable amphibole fibers to the parietal pleura (where fiber clearance is very limited) via mesothelial stomata which undergo secondary inflammatory changes, fibrous scarring, and blockage may explain the emerging epidemiological evidence that initial early dose exposures to amphibole asbestos are highly significant and that subsequent exposures or cessation of asbestos exposure plays little role on the subsequent mesothelioma risk.

A threshold dose of asbestos for mesothelioma refers to the upper cumulative dose of the carcinogen to which the organism may be exposed without observing subsequent tumor formation within the lifetime following that exposure. Scientific opinion is divided as to whether a threshold for asbestos-related malignant mesothelioma exists in humans.

Assessment of Asbestos Exposure

Persons with malignant mesothelioma are subject to considerable medicolegal attention with respect to personal injury claims. The determination of an individuals' cumulative asbestos exposure is recognized to be highly problematic, but the assessment of the exposure is important.

Asbestos exposure may be assessed by the clinician, industrial hygienist, and/or pathologist. Each method of asbestos exposure has its advantages and disadvantages; none is perfect. The strengths and limitations of each method are discussed below.

The role of the clinician – The employment history is the most straightforward means of assessing asbestos exposure in a subject with malignant mesothelioma. All individuals with mesothelioma should be subject to a full and careful enquiry of the occupational history commencing with the individuals' first employment and working chronologically through to the final employment. The duration of asbestos exposure and precise job duties are important (see an example of questionnaires in Appendix). The reliability of the history of asbestos exposure varies considerably across exposed populations. Brief, light, and intermittent exposures to asbestos are more subject to significant recall bias particularly given the inherent latency associated with asbestos-related disease. Exposure details decades prior to the clinical manifestation of disease are difficult notwithstanding the fact that in most cases not all visible dust is asbestos and not all of the non-asbestos dust is inert.

In young subjects with malignant mesothelioma, it is important to consider the occupational activities of other household members and the geographic locale and proximity to known heavy industry. Exposure to asbestos in females is also more commonly through the para-occupational (domestic) route. Time trend changes indicate that most females with malignant peritoneal mesotheliomas have no known exposure to asbestos [46]. This does not necessarily infer that these are sporadic mesotheliomas but should be subject to further investigation.

The clinical determination of asbestos exposure is most useful for persons with only chrysotile exposure. This is because chrysotile has low biopersistence in tissues and mineral analysis is limited in determining prior chrysotile exposure.

The clinician has an important additional role in assessing prior asbestos exposure by clinical examination and imaging to determine the presence of other known asbestos-related conditions.

Clinical markers of asbestos exposure – These include pleural plaques, diffuse pleural thickening, asbestosis, and lung cancer. Asbestos-induced lung parenchymal changes (asbestosis and lung cancer) require higher cumulative asbestos doses than is necessary to induce asbestos-related pleural disease (plaques, diffuse pleural thickening, and malignant mesothelioma). Peritoneal mesothelioma in men is typically associated with heavy prior amphibole exposures.

The conventional X-ray is the standard method for recognition of asbestos-related lung and pleural abnormalities [47]. The most common manifestation of asbestos exposure is pleural plaques. These are benign areas of fibrosis which usually arise on the parietal pleura. The vast majority of individuals with plaques alone have no symptoms. Pleural

plaques may occur after brief, intermittent low-level exposures. Pleural plaques tend to occur 20–30 years after exposure. They are classically distributed in the posterolateral chest wall between the 7th and 10th ribs, lateral chest wall between the 6th and 9th ribs, and over the diaphragmatic domes and mediastinal pleura. The number and size of plaques is highly variable. Calcification is reported in 10–15 % of cases. CT scan is more sensitive than conventional X-rays and is particularly useful in distinguishing pleural plaque disease from extra pleural fat. Pleural plaques are a marker of asbestos exposure and do not indicate an increased risk of malignancy. When observed with mesothelioma they favor an asbestos attribution in the said tumor, but the same is not true with lung carcinoma.

Diffuse pleural thickening predominantly affects the visceral pleura and is less specific for asbestos exposure because there are other known causes for the condition (including tuberculosis, collagen vascular disease, drugs, and idiopathic forms). It is typically preceded by recurrent benign pleural effusion. Imaging shows a continuous sheet often involving the costophrenic angles and apices with infrequent calcification. Diffuse pleural thickening may be unilateral or bilateral, cover at least 25 % of the total chest wall (50 % if unilateral), and extend to a thickness of at least 5 mm on one site on the chest radiograph although diagnostic criteria are not well defined and universally applied. The differentiation of pleural thickening from pleural plaques and malignant mesothelioma may be difficult. Diffuse pleural thickening involves the interlobar fissures whereas plaques do not. CT scan is more sensitive and specific than chest radiography in the detection and monitoring of progression of diffuse pleural thickening and mesothelioma.

Clinical degrees of asbestosis are relatively uncommon; most cases are asymptomatic detected by pathological examination in a resected lung cancer specimen. There exist no specific clinical or radiologic features which allow a clinician to distinguish asbestosis from other forms of diffuse interstitial lung fibrosis. There is a usually a history of heavy asbestos exposure, occupational based and protracted over many years. Asbestosis is a dose-response disease with advanced disease following heavy cumulative asbestos exposures. The absence of asbestosis or other asbestos-related changes cannot overrule the occupational history of asbestos exposure in a subject with mesothelioma [48].

The role of the industrial hygienist – Occupational hygiene monitoring may be necessary for a number of reasons: inspectorate compliance testing with the exposure standard, health surveillance in an exposed workforce, and at an individual level for personal injury claims.

Determining an individual's cumulative asbestos exposure (in fiber/ml-years) requires reconstructing a case-specific occupational, domestic, and environmental asbestos exposure history. This requires knowledge of likely industry and professional duties. In some asbestos-exposed industries, there have been detailed workplace airborne asbestos measurements based on either static (area) monitoring, personal monitoring, short-term (collected over 30–60 min) assessment, long-term (full shift) assessment, or peak levels. The most accurate assessment of cumulative exposure is made by obtaining mean weighted average exposures (usually collected over 8 h period). The average airborne asbestos fiber levels for a person working 8 h, 5 days per week, 50 weeks per year (original based on 2,000 working hours/year) are calculated. Exposures in one industry do not apply to another industry, and exposure profiles are different between manufacturing and end product user industries.

It was not until about 1965 that the modern membrane filter method was established [49]. A standardized approach was advocated counting only structures with a length:width ratio of 3 or more and this was an arbitrary figure accepted by the Asbestosis Research Council. Pathogenic fibers were deemed those greater than 5 μm in length and respirable fibers less than 3 μm fiber diameter. Fibers with these coordinates became known as regulated or WHO fibers.

By the mid-1970s the membrane filter method was in widespread use throughout the world for the measurement of workplace asbestos dust concentrations. However, significant differences in sample assessment levels existed and the visibility limit of thin fibers, interpretation of complex particles, personal factors, and interlaboratory variation confounded comparative assessments of compliance with threshold limit values in the workplace. In an attempt to minimize such differences, the Asbestos International Association published in 1979 the "Reference Method for Determination of Airborne Asbestos Concentration at Workplaces by Light Microscopy (Membrane Filter Method)." This established materials and procedures. It served the basis for the European Reference Method adopted by the Council of the European Communities in 1983 [50].

It is emphasized that the fiber count is only an index of the numerical concentration of regulated fibers and not an absolute measure of the number of fibers present in the air sample. Fibers with diameters less than 0.25 μm are not visible using this method. Consequently phase contrast light microscopy represents only a proportion of the total numbers of fibers present. The method does not permit the determination of chemical composition of fibers and cannot be used on its own to distinguish unambiguously between different fiber types. For this purpose electron microscopic mineral analysis with energy dispersive X-ray spectrometry is required. The light microscopic method merely identifies all fibers meeting certain size criteria. Fiber discrimination is dependent on a range of analytical techniques and the skills of the microscopist [51]. It is not possible to discriminate between asbestos and non-asbestos fibers by the light microscopic method.

Airborne asbestos dust measurements advanced to monitor dust levels in the workplace were established in the 1950s at a time when there was limited knowledge of the effects and biological activity of fibers in inducing disease. The same technical counting methodology exists to this day, although electron microscopic detection methods are also available which are superior. The effectiveness of phase contrast light microscopy in detecting the biologically active respirable fraction of asbestos capable of preventing malignant mesothelioma, in particular, is highly questionable.

All clinical and hygiene-based assessments are indirect and subjective, and their accuracy is wholly reliant on the precision of the recollection of exposure history. All clinical and hygiene assessments of an individuals' asbestos exposure seek to determine what exposures and individual was potentially exposed to in the workplace. Both clinical and hygiene assessments do not determine the inhaled, deposited, and retained fibers at the site of tissue injury. Mineral analysis on lung digests is the only objective method by which this assessment can be made.

Role of the Pathologist

At postmortem the role of the pathologist is to accurately diagnose all diseases present and to comment on their likely causation [52, 53]. In persons with malignant mesothelioma, it is important to accurately describe the macroscopic findings and adequately sample the tumor because in about 10 % of cases there is no antemortem diagnosis [54]. This is important because from a clinical perspective malignant pleural mesothelioma is a "default" diagnosis in an asbestos-exposed subject with a diffuse pleural thickening. It is well recognized that pseudomesotheliomatous neoplasms exist and only the pathologist may confirm or refute disease [55]. Multiple tissue blocks are required because good practice necessitates the use of immunohistochemical panels which facilitate the morphological diagnosis.

The College of American Pathologists and Pulmonary Pathology Society asbestosis guidelines committee report [56] represents the state of the art diagnostic criteria for asbestosis. For asbestosis there must be diffuse interstitial fibrosis of appropriate pattern (collagenous and acellular not fibroblastic and inflammatory) plus necessary numbers of asbestos bodies (an average rate of ≥2/1 cm^2 lung section area examined) or an elevated fiber count (total retained amphiboles) within the asbestosis range for the laboratory. The chrysotile count is not included as this does not correlate with the degree of fibrosis. Asbestosis may be present in persons with mesothelioma who have been heavily exposed to asbestos but the absence of asbestosis cannot rule out an association with asbestos in mesothelioma subjects.

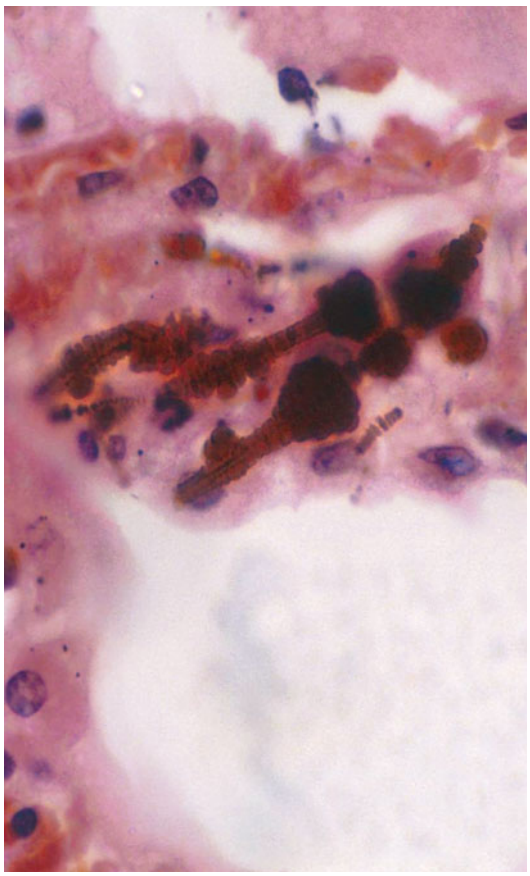


Fig. 15.7 Light microscopic image of asbestos bodies (H&E)

In asbestos-exposed persons with malignant mesothelioma there may also be pleural plaque formation. Less often diffuse pleural thickening may be observed and this is problematic to distinguish macroscopically from malignant mesothelioma. The pathologist may suspect lung interstitial fibrosis when the lungs are firm, shrunken with a bosselated visceral pleural surface and cut sectioning shows lower zone subpleural honeycombing. However this is not a specific feature and is no replacement for careful microscopic and/or mineral analytic investigation [56].

Routine light microscopy allows for a basic assessment of the retained type of dust. By light microscopy multiple lung sections of background nontumor-containing lung should be examined to identify the presence of asbestos bodies. These are histological hallmarks of prior asbestos exposure. Asbestos bodies form on inhaled and retained asbestos fibers coated with a layer of iron protein mucopolysaccharide material after failed ("frustrated") macrophage phagocytosis (Fig. 15.7). The vast majority of asbestos bodies form on long >20 μm amphibole fibers. An analysis of asbestos bodies found in lung noted that 96 % are commercial amphiboles, 2 % noncommercial amphiboles and 2 % chrysotile [57]. Asbestos bodies represent only a small proportion of the total retained asbestos fiber content within the lung and this is

Table 15.2 Types of ferruginous bodies

Mineral fiber	Ferruginous body
Asbestos	Transparent core, straight (often)
Sheet silicates	Broad yellow/brown core, platyform
Carbon, aluminum	Black cores, broad
Iron	Black cores, coarse
Elastin	Brown, wavy (in lung congestion)

dependent on the asbestos fiber type present (amosite > crocidolite > chrysotile) and to host factors. It is rare to identify asbestos bodies in persons with no known occupational asbestos exposure. Consequently if a subject with malignant mesothelioma has asbestos bodies identified by routine light microscopy, then on a balance of probabilities amphibole asbestos is the likely cause of the neoplasm. The detection of asbestos bodies may be facilitated either by Perl's stain for iron or by use of thick unstained (20 μm) sections [57].

The pathologist should be able to distinguish those ferruginous bodies forming on transparent fibrous cores typical of asbestos bodies from those seen in the presence of other minerals. Ferruginous bodies can be formed on non-asbestos minerals such as carbon, iron oxide, rutile, aluminum oxide, chromium oxide, mullite, kaolin, mica, talc, and glass. Types of ferruginous bodies are shown in Table 15.2.

In a significant number of persons with malignant mesothelioma, asbestos bodies are not seen. This does not necessarily infer a sporadic tumor. It is important to consider a full occupational asbestos exposure history particularly if persons are exposed to chrysotile asbestos. Chrysotile has low biopersistence and does not readily form asbestos bodies or is detectable in lung digests.

Mineral Analysis of Lung Digests

The application of microscopic analytical techniques to demonstrate retained elemental or mineral particulates in lung tissues has provided useful information in the understanding of occupational and environmental-related lung disease [48].

The main application of mineral/elemental analysis in pulmonary disease is:

1. To verify types of exposure in subjects utilized in epidemiological studies.
2. To provide quantitative information with respect to cumulative exposure.
3. To assist in the attribution of mesothelioma to mineral fiber exposure.
4. To assist in the attribution of fibrosis or lung cancer to mineral fiber exposure.
5. To assist in the determination of which out of several industrial exposures may be most pertinent to mesothelioma causation.

A mineralogical analysis contributes to the assessment of the intensity of past exposure, especially when data from other sources are unavailable, unreliable, or difficult to interpret quantitatively. Positive results can confirm past exposures but negative ones cannot overrule a clear exposure history, especially where exposure to white (chrysotile) asbestos is concerned. Persons with heavy exposures to commercial chrysotile may have detectable tremolite in their lungs after many years following cessation of exposure.

Phase contrast light microscopy – This is a simple method for detecting a limited number of retained fibers in the lung sample. It is the method used by hygienists to detect fibers in air. Airborne measurements and lung fiber studies performed by light microscopy (phase contrast light microscopy) are insensitive at identifying fibers as asbestos fibers and cannot resolve fibers less than 0.25 μm diameter (irrespective of fiber length). The cumulated fiber diameter distribution obtained by electron microscopy indicated that phase contrast light microscopy was able to visualize only 5 % crocidolite, 26.5 % amosite, and 0.14 % chrysotile present in lung tissue [58].

In 2009, Cardiff researchers reviewed lung fiber dimensions from 402 lungs by transmission electron microscopic analysis analyzing over 4,000 fibers in their UK reference laboratory [59]. Fibers >0.75 μm diameter were rarely detected in alveolated lung digests and presumed non respirable. By correlation with light microscopic fiber diameters measured (measuring fibers >5 μm in length and <3 μm diameter down to the optical microscopy limit of 0.25 μm diameter), it was apparent that phase contrast light microscopy miss a substantial fraction of respirable fibers, mostly crocidolite and chrysotile. The results are shown in the Table 15.3. The majority of fibers were <5 μm length (non regulated).

Phase contrast light microscopy detected would have detected <5 % crocidolite fibers that are respirable into the lung, and 35 % of crocidolite fibers detected were >5 μm long (thereby being potentially toxic) albeit with high aspect ratio (rendering their fiber diameter <0.25 μm – the lowest resolution limit for detection by phase contrast light microscopy). Importantly 40 % crocidolite fibers counted were >5 μm lung with <5 % of the same potentially detectable by phase contrast light microscopy, i.e., the pathogenic undetected fibers were 35 %.

Phase contrast light microscopy would have detected no chrysotile fibers (on the basis of fiber dimension alone) although almost 20 % chrysotile fibers counted were >5 μm long.

There were higher levels of fiber detection with amosite and tremolite, and these fibers better correlate between phase contrast light microscopy and electron microscopy because a higher proportion of both fiber types had wider and therefore detectable) fiber diameters.

Table 15.3 Fiber size dimensions in lung

	Number of fibers	Bioactive fibers >5 μm length (%)	WHO fibers (%)	EM detected fibers >5 μm length and <0.25 μm diameter (%)
Amosite	1,874	42.5	16	26.7
Crocidolite	1,403	40	4.2	35
Chrysotile	1,177	19.3	0	19.3
Tremolite	46	56.5	32.6	17.4

The authors concluded that risk estimates based on airborne fiber measurements set phase contrast light microscopy are limited. Phase contrast light microscopic assessment of airborne asbestos exposures was deemed relatively insensitive, failing to detect a significant proportion of respirable biodurable amphibole fibers. The study shows that significant numbers of bioactive fibers are not optically visible. This implies that there exist considerable difficulties in making risk estimates from anecdotal exposure assessments of historical occupational cohorts.

It is evident that electron microscopic analytic techniques are more sensitive and may be performed in either scanning or transmission mode [53]. Most scanning electron microscopy and transmission electron microscopy instruments are equipped with the capabilities to record selected area electron diffraction spectra and perform energy dispersive X-ray analysis which are necessary to distinguish the mineralogy of structures observed. Analytical counting techniques employed for asbestos analysis identify that scanning electron microscopy has limits of counting fibers no finer than approximately 0.1 μm. Transmission electron microscopy is capable of resolving asbestos fibers over their entire size range (below 0.01 μm diameter). Fiber counts undertaken by TEM are generally threefold higher than the same SEM count [60]. This will vary with fiber and industry.

Mineral fibers may be detected in almost all populations. Therefore, laboratories have to define control (nonoccupationally exposed) populations and establish reference values for certain diseases, for example, asbestosis.

These procedures can be performed on lavage samples or more commonly lung tissue digests. Tissue blocks or preferably wet lung may be used. . In general, the more tissue available the more representative the results obtained – tissue from the apical areas of upper and lower lobes and lung bases are suitable, ideally with pieces being around 2 cm^3 in volume. Care should be taken not to include tissue containing tumor and preferably not severely infected or severely fibrotic.

A high fiber burden indicates exposure but is not proof of disease. A negative result is not proof of the absence of significant exposure, especially when, for example, white (chrysotile) asbestos is concerned, and the exposure history should be correlated carefully with the results of the analysis. Interpretation of the results also has to be considered in relation to the pathological process; causal attribution of lung cancer and interstitial fibrosis (asbestosis) requires higher levels of fiber counts (within the asbestosis range) than is necessary to causally attribute a mesothelioma to prior asbestos exposure.

Conclusion

In summary, there is now considerable evidence to suggest that the risk of developing malignant mesothelioma is related to fiber type, industry, and date of first asbestos exposure. The assessment of asbestos in a subject with malignant mesothelioma is facilitated by a multidisciplinary approach incorporating clinical, radiologic, and pathological information; some may be by incorporating mineral analytic data.

As heavy asbestos exposures in industrial settings diminish, the proportion of malignant mesotheliomas arising following lower dose or with no known exposure will increase, as will the observed sporadic cases. This will result in even more technical challenges with causal attribution given difficulties in substantiating exposure histories, longer latency, no coexistent asbestos pathology, and nonelevated fiber counts.

References

1. Tossavainen A. Asbestos, asbestosis and cancer: exposure criteria for clinical diagnosis. People Work Res Rep. 1997;14:8–27. Helsinki: Finnish Institute of Occupational Health.
2. Peto J, Decarli A, La Vecchia C, et al. The European mesothelioma epidemic. Br J Cancer. 1999;79:666–72.
3. Willis RA. Pathology of tumors. Washington, DC: Butterworth; 1960. 185.
4. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma. A consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2009;133:1317–31.
5. Antman K, Shemin R, Ryan L, et al. Malignant mesothelioma. Prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over two decades, 1965–1985. J Clin Oncol. 1988;6:147–53.
6. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. J Occup Med. 1992;34:718–21.
7. La Vecchia C, Boffetta P. Role of stopping exposure and recent exposure to asbestos in the risk of mesothelioma. Eur J Cancer Prev. 2012;21(3):227–30.
8. La Dou J. The asbestos cancer epidemic. Environ Health Perspect. 2004;112:285–90.

9. Craighead JE, Gibbs AR, Pooley FD. Mineralogy of asbestos. In: Craighead JE, Gibbs AR, editors. Asbestos and its disease. New York: Oxford University Press; 2008. p. 23–38. Chapter 2.
10. Bartrip PW. History of asbestos-related disease. Postgrad Med J. 2004;80:72–6.
11. Browne K. Thresholds of risk. In: Gibbs GW, Dunnigan J, Kido M, Higashi T, editors. Health risks from exposure to mineral fibres. An international perspective. North York: Captus University Publications; 1991. p. 355.
12. Iwatsubo Y, Pairon JC, Boutin C, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case control study. Am J Epidemiol. 1998;148: 133–42.
13. Gibbs AR, Pooley FD. Role of asbestos and other fibres in the development of diffuse malignant mesothelioma. Thorax. 1990;45: 649–54.
14. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med. 1960;17:260–71.
15. Spirtas R, Heineman EF, Bernstein L, et al. Malignant mesothelioma; attributable risk of asbestos exposure. Occup Environ Med. 1994;51:804–11.
16. Roggli VL, Oury TD, Moffatt EJ. Malignant mesothelioma in women. Anat Pathol. 1997;2:147–63.
17. Xu Z, Armstrong BK, Blunsdon BJ, et al. Trends in mortality for malignant mesothelioma of the pleura, and production and use of asbestos in Australia. Med J Aust. 1985;143:185–7.
18. Andersson M, Olsen JH. Trend and distribution of mesothelioma in Denmark. Br J Cancer. 1985;51:699–705.
19. Mark EJ, Yokoi T. Absence of evidence for a significant background incidence of diffuse malignant mesothelioma from asbestos exposure. Ann N Y Acad Sci. 1991;643:196–204.
20. Peterson JT, et al. Non asbestos-related malignant mesothelioma: a review. Cancer. 1984;54:951.
21. Smith AH, Wright CC. Chrysotile asbestos is the main cause of pleural mesothelioma. Am J Ind Med. 1996;30(3):252–66.
22. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg. 2000;44(8):565–601.
23. Hodgson JT, et al. The expected burden of mesothelioma mortality in Great Britain from 2002–2050. Br J Cancer. 2005;92(3):587–93.
24. Berman DW, Crump KS. Final draft: technical support document for a protocol to assess asbestos related risk. US Environmental Protection Agency;2003.
25. Yarborough CM. Chrysotile as a cause of mesothelioma: an assessment based on epidemiology. Crit Rev Toxicol. 2006;36:165–87.
26. Stanton MF, Wrench C. Mechanisms of mesothelioma induction with asbestos and fibreglass. J Natl Cancer Inst. 1972;48:797.
27. Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst. 1981;67:965–75.
28. Pott F, Huth F, Fredericks K. Tumorogenic effect of fibrous dust in experimental animals. Environ Health Perspect. 1974;9:313–5.
29. Davis JMG, Jones AD. Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. Br J Exp Pathol. 1988;69:717–37.
30. Platek F, et al. Chronic inhalation of short asbestos fibres. Fundam Appl Toxicol. 1985;5:327–40.
31. Bernstein DM, et al. Comparison of Calidria chrysotile asbestos to pure tremolite: final results of the inhalation biopersistence and histopathology examination following short-term exposure. Inhal Toxicol. 2005;17(9):427–49.
32. Bernstein DM, Rogers RA, Sepulveda R, et al. Quantification of the pathological response and fate in the lung and pleura of chrysotile in combination with fine particles compared to amosite-asbestos following short-term inhalation exposure. Inhal Toxicol. 2011; 23(7):372–91.
33. Higgins ITT, Glassman JH, Oh MS, et al. Mortality of reserve mining company employees in relation to taconite dust exposure. Am J Epidemiol. 1983;118(5):710–9.
34. McDonald JC, Gibbs GW, Liddell DK, et al. Mortality after long exposure to cummintonite-grunerite. Am Rev Respir Dis. 1978;118.
35. Report of Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibres: the influence of fibre length. Agency for toxic substances and disease registry. Atlanta; 2003.
36. McDonald JC, et al. Mesothelioma and asbestos fibre type. Evidence from lung tissue analyses. Cancer. 1989;63(8):1544–7.
37. Rogers A, Leigh J, Berry G, Ferguson DA, Mulder HB, Ackad M. Relationship between lung asbestos fibre type and concentration and relative risk of mesothelioma. Cancer. 1991;67:1912–20.
38. Berman DW. Apples to apples: the origin and magnitude of differences in asbestos cancer risk estimates derived using varying protocols. Risk Anal. 2010;31:1539–6924.
39. Suzuki Y, Yuen SR. Asbestos tissue burden study on human malignant mesothelioma. Ind Health. 2001;39:150–60.
40. Suzuki Y, Yuen SR. Asbestos fibres continuing to the induction of human malignant mesothelioma. Ann N Y Acad Sci. 2002;982: 160–76.
41. Chiappino G. Mesotelioma: Ruyolo Delle Fibre Ultrafini Aire Conseguenti Riflessi In: Campo Preventivo Aire Medico-Legale. Med Lab. 2005;96:3–23.
42. Dodson RF, O'Sullivan MF, Huang J, et al. Asbestos in extrapulmonary sites – omentum and mesentery. Chest. 2000;117: 486–93.
43. Boutin C, Dumortier P, Rey F, et al. Black spots concentration oncogenic asbestos fibres in the parietal pleura. Thoracoscopic and mineralogic study. Am J Respir Crit Care Med. 1996;153:444–9.
44. Ontario Royal Commission. The Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario. J. Stefan Dupre, J. Fraser Mustard, Robert J. Uffen. Ontario Ministry of the Attorney General. 1983 Three Volumes.
45. Craighead JE, Gibbs AR, Pooley FD. Mineralogy of asbestos. In: Craighead JC, Gibbs AR, editors. Asbestos and its diseases. Oxford: Oxford University Press; 2008. p. 23–38. Chapter 2.
46. Moolgavkar SH, Meza R, Turim J. Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973–2005. Cancer Causes Control. 2009;20:935–44.
47. Roach HD, Davies GJ, Attanoos R, et al. Asbestos: when the dust settles – an imaging review of asbestos related disease. Radiographics. 2002;22:S167–84.
48. De Vuyst P, Karjalainen A, Dumortier P, et al. Guidelines for mineral fibre analysis in biological samples: report of the ERS Working Group. Eur Respir J. 1998;11:1416–26.
49. Holmes S. Developments in dust sampling and counting techniques in the asbestos industry. Ann N Y Acad Sci. 1965;132:288–97.
50. The Asbestos International Association. Reference method for the determination of airborne asbestos fibre concentrations at workplaces by light microscopy (membrane filter method). London: Asbestos International Association; 1979.
51. Walton WH. The natures hazards and assessment of occupational exposure to airborne asbestos dust: a review. Ann Occup Hyg. 1982;25:117–247.
52. Gibbs AR, Attanoos RL. Examination of lung specimens. J Clin Pathol. 2000;53:507–12.
53. Attanoos RL, Gibbs AR. An approach to industrial post mortems. Histopathology. 2009;54(1):134–42.
54. Attanoos RL, Gibbs AR. The comparative accuracy of different pleural biopsy techniques in the diagnosis of malignant mesothelioma. Histopathology. 2008;53(3):340–4.
55. Attanoos RL, Gibbs AR. Pseudomesotheliomatous' carcinomas of the pleura – a 10 year analysis of cases from the Environmental

Lung Disease Research Group, Cardiff. Histopathology. 2003; 43(5):444–52.
56. Roggli VL, Gibbs AR, Attanoos RL, Churg A, Popper H, Cagle P, Corrin B, Franks T, Galateau-Salle F, Galvin J, Hasleton P, Henderson D, Honma K. Pathology of asbestosis – an update of the diagnostic criteria. Report of the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society. Arch Pathol Lab Med. 2010;134:462–80.
57. Roggli VL. Chapter 3. In: Roggli VL, Oury TD, Sporn TA, editors. Asbestos bodies and nonasbestos ferruginous bodies pathology of asbestos associated diseases. 2nd ed. Verlag: Springer; 2004; p. 34–70.
58. Pooley FD, Ranson DL. Comparison of the results of asbestos fibre dust counts in lung tissue obtained by analytical electron microscopy and light microscopy. J Clin Pathol. 1986;39:313–7.
59. Christian A, Pooley FD, Attanoos RL, Gibbs AR. Lung mineral fibre analysis from a National Referral Centre of 402 cases and >4000 fibres – the Cardiff experience in 2006. J Pathol. 2009;221(S1):S8.
60. Tuomi T. Fibrous minerals in the lungs of mesothelioma patients; comparison between data on SEM, TEM and personal interview information. Am J Ind Med. 1992;21:155–62.

Malignant Mesothelioma: Pathology

16

Sisko Anttila

Keywords
Malignant mesothelioma • Pathology • Cytology • Immunohistochemistry • Mesothelioma subtypes • Mesothelioma diagnosis

Introduction

The majority of malignant mesotheliomas (MMs) occur in the pleura, but they may also arise in the peritoneum, the pericardium, or the tunica vaginalis testis. MM is a great mimic and its morphology is so variable that a vast number of different primary and secondary tumors of the body cavities must be considered in differential diagnosis. Another diagnostic challenge is distinguishing MM from reactive lesions, i.e., epithelioid MM from benign mesothelial hyperplasia and sarcomatoid or desmoplastic MM from fibrous pleuritis. Diffuse MM arising in any site and exhibiting any subtype or morphological pattern may have asbestos etiology. Localized MM is an uncommon circumscribed tumor of the serosal membranes, with microscopic characteristics of MM. It is so rare that a possible causal association with asbestos is not known [1].

Diffuse MM usually manifests by unilateral, recurrent bloody effusion in the pleura or by ascites in the peritoneal cavity. It is normally not possible to make a definite diagnosis of MM based on cytological specimens of serous fluids, due to the fact that MM diagnosis requires detection of invasion in the histological specimen [2, 3]. However, a cytological MM diagnosis may be made when appropriate cytological features are present together with typical clinical and imaging findings of MM [4]. Typical gross findings of MM include tumor nodules and diffuse thickening of the serosal surface, and at a late stage, the tumor tissue may encase the visceral organs (Fig. 16.1). Imaging and clinical findings are necessary information for the pathologist, as unusual presentation of the disease, e.g., a tumor mass in the body cavity, strongly favors a diagnosis other than diffuse MM. The differential diagnosis of MM is discussed in this chapter.

Morphological Subtypes of Malignant Mesothelioma

MM is divided into epithelioid, biphasic, and sarcomatoid main morphological subtypes. Desmoplastic MM, a variant of sarcomatoid MM, is classified as a separate subtype in the present WHO classification of lung tumors [5]. Although the prognosis of all diffuse MM is poor, it is worse for sarcomatoid and desmoplastic MM than for epithelioid MM [6, 7], which makes it important to include the subtype in the pathologist's report. Furthermore, patients with a diagnosis of sarcomatoid or desmoplastic MM do not benefit from extrapleural pneumonectomy [8–10]. Biphasic MM contains an epithelioid subtype together with either a sarcomatoid or desmoplastic component, and each component should cover at least 10 % of the tumor tissue [11]. Smaller areas other than the principal subtype are commonly seen in MM if several tissue blocks are available for examination. In these cases, the other type has no influence on subtyping the tumor, but recognition of even a very small epithelioid component in otherwise sarcomatoid tumor tissue may aid the correct diagnosis of MM.

S. Anttila, MD, PhD
Jorvi Hospital Laboratory of Pathology,
Helsinki University Central Hospital,
Hospital District of Helsinki and Uusimaa,
Laboratory Services, HUSLAB, Helsinki, Finland

Health and Work Ability,
Finnish Institute of Occupational Health, Helsinki, Finland
e-mail: sisko.l.anttila@hus.fi

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_16, © Springer-Verlag London 2014

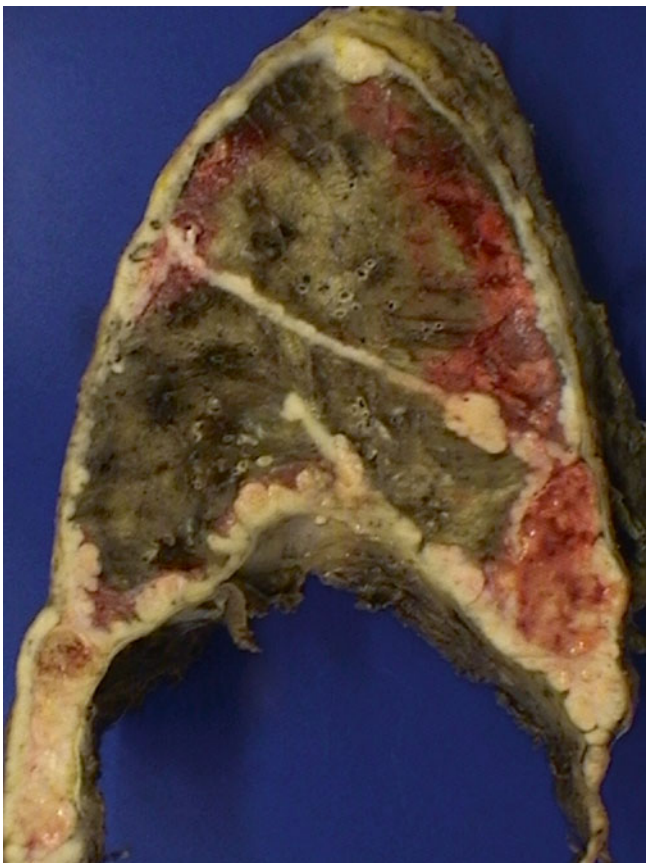


Fig. 16.1 Extrapleural pneumonectomy specimen. Malignant mesothelioma tumor tissue encases the lung and fills interlobar spaces (Photo courtesy of Dr. Mikko Rönty)

In addition to the main subtypes, a few rare growth patterns of epithelioid and sarcomatoid MM are known, such as clear cell, deciduoid, adenoid cystic, signet ring, and small cell patterns of epithelioid MM and lymphohistiocytoid and heterologous MM patterns of sarcomatoid MM [12, 13]. These rare histopathologic growth patterns have no known prognostic significance independent of the epithelioid or sarcomatoid subtype, but it may be important to recognize them as belonging to the morphological spectrum of MM, especially in small biopsies. In larger biopsies and autopsy samples, more common morphological patterns can also usually be observed. The different morphological MM subtypes may arise in any location.

Epithelioid Malignant Mesothelioma

Epithelioid and biphasic are the most common subtypes of MM, together constituting approximately 70–90 % of all MM, the proportions of each type depending on the study [14–17]. Epithelioid MM may take several different growth patterns. Epithelioid cells may form solid sheets, tubular or papillary structures, and acinar (glandular) structures or have a microcystic or micropapillary configuration [3, 12] (Fig. 16.2). Solid epithelioid MM may be either well or poorly differentiated [12]. Two patterns do not clearly belong to any main subtype, namely, pleomorphic, consisting of anaplastic cells and tumor giant cells, and transitional, where epithelioid and sarcomatoid features bend in the same cells (Fig. 16.2d). Pleomorphic MMs have been classified under both epithelioid and sarcomatoid types [12]. Kadota et al. analyzed 232 epithelioid MMs by their predominant growth pattern and observed that the best prognosis was associated with the trabecular pattern followed by tubulopapillary, micropapillary, solid, and pleomorphic patterns [18]. The survival of patients with pleomorphic growth pattern was as poor as that of the patients with biphasic and sarcomatoid MM, leading the authors to propose that pleomorphic MM should be classified into sarcomatoid subtype [18].

Typical well-differentiated epithelioid MMs consist of round, polygonal, or cuboidal cells with moderate or abundant eosinophilic cytoplasm and central nuclei with a single nucleolus (Fig. 16.2). The nuclear to cytoplasmic ratio appears to remain constant regardless of the differentiation [19]. Cells in sheets and structures can often be seen by light microscopy to be loosely adhered to each other, probably due to long surface microvilli which are an ultrastructural hallmark of epithelioid MM [20, 21]. Other ultrastructural features include abundant intermediate filaments in a perinuclear disposition, limited cytoplasmic organelles, an absence of secretory granules, and an accumulation of intracytoplasmic glycogen [20, 21]. Similarly to the light microscopical and immunohistochemical features, these characteristics are expressed to varying degrees in individual cases, and the lack of any of them does not rule out the diagnosis of MM [20]. The amount of stroma in epithelioid MM varies from scanty to abundant myxoid stroma, in which islands of epithelioid cells appear to be floating. Cytoplasmic Alcian blue-positive vacuoles are hyaluronic acid, whereas diastase-resistant PAS-positive mucin is exceptional in MM, and numerous PAS-positive intracytoplasmic vacuoles favor the diagnosis of metastatic adenocarcinoma [3, 19, 22]. PAS-positive glycogen granules occur commonly in epithelioid MM. Psammoma bodies may be observed in epithelioid MM with a papillary growth pattern [3].

Effusion Cytology in Epithelioid and Biphasic MM

An injury of the serosal surface, caused by a large number of different conditions, results in the vascular events of inflammation with an increased permeability of capillaries, followed by the exfoliation of mesothelial cells, the accumulation of fibrin and inflammatory cells, and the formation of effusion [23]. A chronic persistent injury of the serosal surface leads to mesothelial cell hyperplasia and the proliferation of

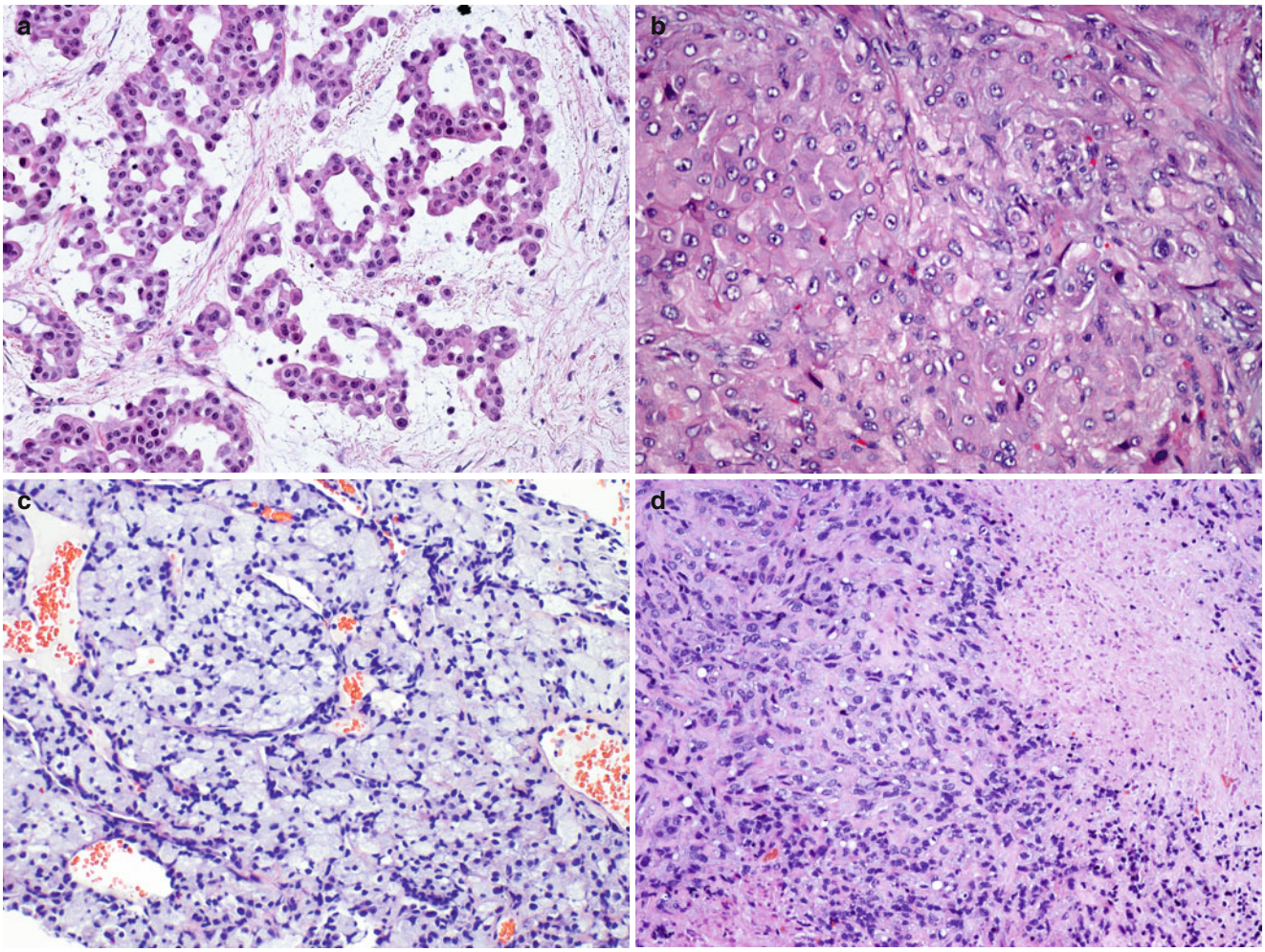


Fig. 16.2 Epithelioid malignant mesothelioma. Papillary structures in loose myxoid stroma (**a**). Solid pattern with deciduoid features (**b**), clear cell pattern (**c**), and transitional pattern between epithelioid and sarcomatoid type and necrosis (**d**) (H&E; medium magnification)

myofibroblastic cells [23]. Malignant neoplasms of the body cavities, including MM, cause hemorrhagic effusions with the characteristics of exudates, i.e., a high protein concentration, specific gravity, and cellularity [24].

A definite diagnosis of metastatic carcinoma can often be made by means of the recognition of a foreign cell population in cytological preparations of effusions, and the diagnosis is confirmed by using cell block preparations and immunocytochemistry with appropriate antibodies [25]. In contrast, the sensitivity of effusion cytology in the diagnosis of MM is poor. The diagnosis of MM has been rendered or suspected on the basis of effusion cytology with sensitivity ranging from 38 to 64 % for epithelioid and biphasic MM and 20 % or less for sarcomatoid MM [2, 26, 27]. In the study of Renshaw et al., the negative fluids either lacked mesothelial cells or contained them in insufficient numbers for a diagnosis of malignancy [2].

The challenges of effusion cytology in the diagnosis of MM include recognition of malignant cells with mesothelial origin (as compared to carcinoma cells) and differentiation between benign hyperplastic and malignant mesothelial cells. The features of MM include an excessive number of cells in the effusion and cell clusters of varying size with scalloped borders (Fig. 16.3). Sometimes a population of cells that are considerably larger than their normal and hyperplastic counterparts can be observed [23, 28]. Other characteristics described are observation of a monotonous single-cell population, cells with a relatively low nuclear to cytoplasmic ratio, cells with eosinophilic cytoplasm that is denser around the nucleus than in the periphery, cell-in-cell arrangements, vacuolated cytoplasm, multinucleation, irregularity of nuclear contours, rounded nuclei, single prominent nucleoli, and cellular windows (distinct clearing between two cells), among other features [23, 29]. However, features such as cluster formation, psammoma bodies, multinucleation, hyperchromatic nuclei, high nuclear to cytoplasmic ratio, prominent nucleoli, and a high mitotic rate may occur in reactive mesothelial hyperplasia [23, 28].

In the study of Renshaw et al., the delay from initial symptoms to the diagnosis of MM was considerably longer

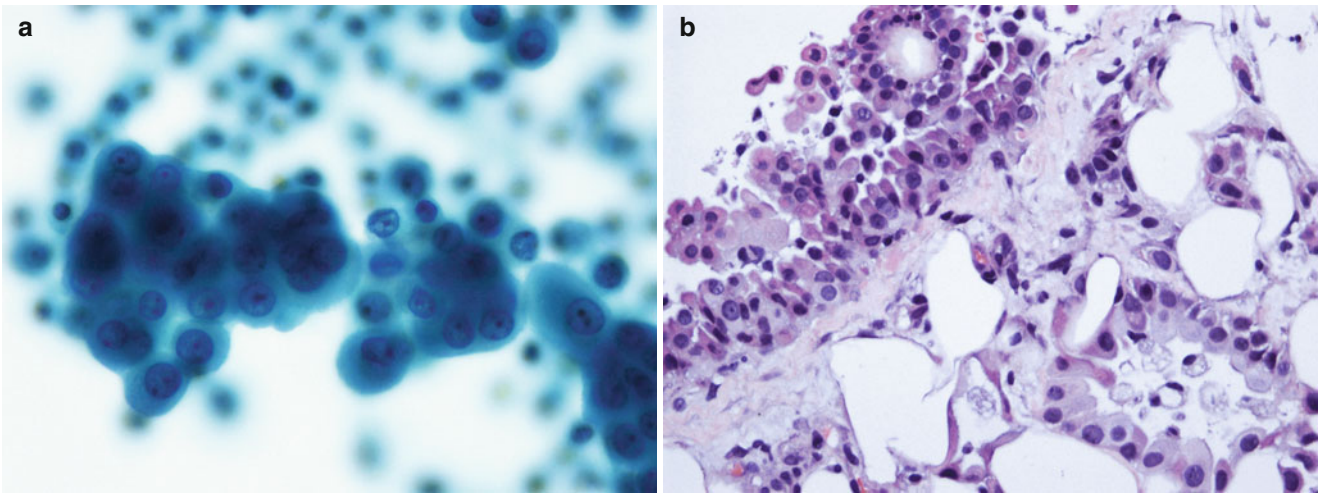


Fig. 16.3 Effusion cytology of epithelioid malignant mesothelioma. A cluster of tumor cells in a cytological specimen (**a**, Papanicolaou's stain, high magnification). Histology of the same mesothelioma case (**b**, H&E; medium magnification)

in patients with negative than in those with positive effusion cytology [2]. The diagnosis of MM without delay requires the integration of clinical and imaging findings and confirmation of the diagnosis with a biopsy as soon as the suspicion of MM has risen, regardless of a positive or negative result of effusion cytology [2].

Differential Diagnosis of Epithelioid Malignant Mesothelioma

Metastatic carcinomas are the most common malignancies of the body cavities. For the diagnosis of epithelioid MM, immunohistochemistry with a panel of antibodies is always required. It has been recommended that the panel includes a pancytokeratin antibody and a minimum of two mesothelial and two carcinoma-associated markers [3, 30, 31]. This rule cannot be followed strictly, because the selection of antibodies depends on the location of the tumor in the pleural or peritoneal cavity, morphological features, possible previous malignant diseases, and clinical and imaging findings. Furthermore, the availability of antibodies and the experience of the laboratory influence the antibody panel. Each laboratory should optimize the immunostaining protocol for the antibodies used by immunostaining a series of typical epithelioid MM and using markers with a sensitivity and specificity of 80 % or more in the detection of MM [31–33]. Positive and negative markers for the differential diagnosis of epithelioid MM and metastatic carcinomas of pleural and peritoneal cavity are suggested in Tables 16.1, 16.2, and 16.3. The proportions of tumors given in Tables 16.1, 16.2, and 16.3 with positive staining are allusive, as the staining results vary between different studies, due to a number of factors related to tissue fixation and processing, the antibodies and pretreatments used in immunostaining, and the different criteria for positive staining.

Well-differentiated epithelioid MM is always positive with several mesothelial markers and cytokeratins, in particular cytokeratins 5/6, 7, 8, 18, and 19 [34, 35], whereas poorly differentiated, pleomorphic, or sarcomatoid MM may be negative or only partially positive with some or all mesothelial markers [36, 37]. Pancytokeratins are recommended for the antibody panel in order to separate epithelioid MM from nonepithelial tumors including malignant melanoma, lymphomas, and sarcomas (e.g., epithelioid sarcoma, epithelioid hemangioendothelioma, epithelioid angiosarcoma, and desmoplastic small round cell tumor), which may be primary or secondary tumors of body cavities. The so-called mesothelial markers are not specific to epithelioid MM, as some other tumors of mesothelial and non-mesothelial origin are positive with calretinin, CK5/6, thrombomodulin, WT-1, or podoplanin. For example, thymomas and thymic carcinomas express cytokeratin 5/6 and may be positive with calretinin and thrombomodulin, epithelioid angiosarcoma and epithelioid hemangioendothelioma express thrombomodulin and podoplanin, and synovial sarcoma and desmoplastic small round cell tumor may be focally positive for calretinin [35, 38–43].

Mesothelial lesions, such as a benign adenomatoid tumor, multicystic mesothelioma, and well-differentiated papillary mesothelioma, all of which are entities separate from diffuse MM, are naturally positive with mesothelial markers [44]. All of them are most common in the peritoneal cavity but may also occur in other body cavities [44]. Some authors consider multicystic mesothelioma a reactive lesion, and it is possible that this entity encloses a spectrum of reactive and neoplastic lesions [44]. Well-differentiated papillary mesothelioma was originally known as a rare peritoneal tumor

Table 16.1 Positive markers of epithelioid malignant mesothelioma. Comparison of immunostaining in epithelioid malignant mesothelioma and relevant other tumor types

	Marker positivity, %					
Tumor type	Calretinin[a]	CK5/6[b]	WT-1	Mesothelin	Thrombomodulin	Podoplanin[c]
Epithelioid MM	73–100	53–100	72–93	75–100	68–78	75–100
Lung adenocarcinoma	12–23	5–39	0–10	39–52	13	0–7
Squamous cell lung carcinoma	23–40	87–100	0	16–31	87–100	0–50
Large cell lung carcinoma	37–38	47	ND	14	13	
Small cell lung carcinoma	40–49	27–49	ND	0	27	
Breast cancer, various types	4–44	31	0	0	ND	0–19
Renal cell carcinoma	0–17	0–37	0–13	0	2	0–39
Ovarian/peritoneal serous carcinoma	0–46	22–50	75–83	89–100	3–30	13–65
Endometrial carcinoma	3	50	ND	67	ND	0
Colon, adenocarcinoma	6	0	0	31	ND	0
Hepatocellular carcinoma	2	4	ND	ND	ND	ND
Cholangiocarcinoma	ND	14	ND	ND	ND	ND
Pancreas, adenocarcinoma	5	38	ND	91	ND	0
Stomach, adenocarcinoma	6	0	ND	50	ND	0

Modified from Anttila [110] with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2012. College of American Pathologists

Range of positive immunostaining, if more than one study (Data from Refs. [32, 66, 92–109])

Abbreviations: *MM* malignant mesothelioma, *CK5/6* cytokeratin 5/6, *WT-1* Wilms tumor protein-1

[a]Nuclear and cytoplasmic staining is required in epithelioid MM. Weak or focal cytoplasmic staining is common in many tumor types

[b]Focal staining common in lung adenocarcinoma

[c]D2-40 is an antibody clone for podoplanin

Table 16.2 Examples of negative markers for differential diagnosis of epithelioid MM and metastatic pleural tumors

Tumor type	Marker	Positivity in metastatic tumors, %	Positivity in epithelioid MM, %	References
Lung adenocarcinoma	TTF-1	58–76	0	[32, 92, 93, 103, 107–108]
	CEA	83	2–5	[32]
	CD15 (LeuM1)	72	0–7	[32]
	Ber-EP4	80–100	5–26	[32, 93, 107]
	BG-8 (Lewis^y)	93–100	2–7	[32, 93, 103]
	MOC-31	93–100	5–13	[32, 92, 93]
Squamous cell lung carcinoma	p63	100	7	[96]
	MOC-31	97	5–13	[96]
	Ber-EP4	87	5–26	[96]
	BG-8 (Lewis^y)	80	2–7	[96]
Renal cell carcinoma	CD15 (LeuM1)[a]	25–100	0–3	[97]
	MOC-31[b]	38–75	5–13	[97]
	RCC Ma[c]	50–75	8–26	[91, 97]
	Ber-EP4	42	5–26	[97]
Breast carcinoma	BG-8 (Lewis^y)	96–100	2–7	[93, 103]

Modified from Anttila [110] with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2012. College of American Pathologists

Abbreviations: *MM* malignant mesothelioma, *TTF-1* thyroid transcription factor-1, *CEA* carcinoembryonic antigen, *RCC Ma* renal cell carcinoma marker

[a]Chromophobe type 25 %

[b]Papillary type 38 %

[c]Chromophobe type negative

among young women but has also been described among men and in pleural, pericardial, and tunica vaginalis testis locations [45–49]. Histologically it is characterized by fungating papillary structures with a fibrovascular core and a single layer of mesothelial cells with benign appearance (Fig. 16.4). Although some reported patients have been

Table 16.3 Examples of negative markers for differential diagnosis of epithelioid MM and ovarian/peritoneal serous carcinoma

Marker	Positivity in ovarian/peritoneal carcinoma, %	Positivity in epithelioid MM, %	References
Ber-EP4	87–100	5–26	[98, 99, 100, 101, 111]
MOC-31	93–100	3–15	[98, 99, 100]
Estrogen receptor	60–100	0	[100, 111, 112]
B72.3	73–87	0	[98, 99, 111]
BG-8 (Lewisγ)	73	2–3	[98]
CA19-9	60–73	0	[98, 99, 111]
CD15 (LeuM1)	30–63	0–6	[98, 99, 100, 101, 111]

Modified from Anttila [110] with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2012. College of American Pathologists
Abbreviation: *MM* malignant mesothelioma

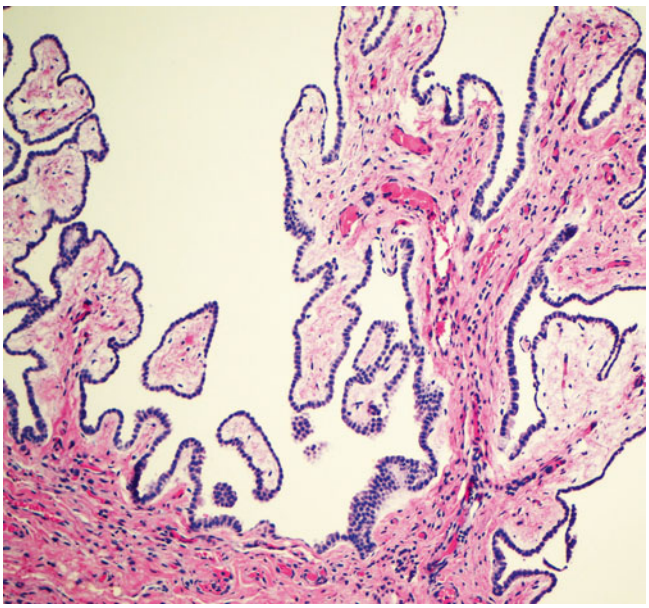


Fig. 16.4 Well-differentiated papillary mesothelioma. Fungating papillary structures on the serosal surface (H&E; low magnification)

exposed to asbestos, no epidemiological correlation between well-differentiated papillary mesothelioma and asbestos exposure has been established [49]. The recognition of this entity as separate from diffuse MM is important because of its different etiology and remarkably better prognosis.

Localized Malignant Mesothelioma

Localized MM is a very rare tumor with all the morphological and immunohistochemical characteristics of MM but a gross presentation as a localized mass. All different subtypes of MM have been described as localized MM [1]. Intrapulmonary and mediastinal locations are most common, but peritoneal, intrahepatic, and intrapancreatic tumors with a serosal origin have been described [1, 50–53]. Allen et al. reported 23 cases of localized MM. Some of the tumors had pedunculated or sessile attachment to the serosal membrane, and none had gross invasion of the lung or chest wall [1]. All the patients underwent surgical resection of the tumor, and according to follow-up data, 10 out of 21 were alive without evidence of disease from 18 months to 11 years after diagnosis [1]. Several patients died of metastatic disease, but none of the patients had developed a diffuse MM at the time of death [1]. It is not known whether asbestos exposure is an etiological factor of localized MM, because of the rarity of the disease and the lack of information regarding exposure in many reported cases.

Reactive Mesothelial Hyperplasia

The differential diagnosis between a reactive mesothelial hyperplasia and epithelioid or biphasic MM is one of the most difficult differential diagnoses in the pathology of serosal membranes. The most reliable criterion of malignancy is invasion – in the thoracic cavity invasion of the lung or the parietal pleural fat layer. Immunostaining for mesothelial markers and pancytokeratins may aid the detection of invasion. The recognition of invasion is not always straightforward, as tissue cut *en face* or the organization of fibrinous exudate and the subsequent formation of new mesothelial layers may simulate invasion [19, 54, 55]. Several features of mesothelial proliferations have been suggested to favor either a benign or a malignant mesothelial proliferation. Large cellular nodules on the serosal surface and the so-called full-thickness cellularity, i.e., a mesothelial cell proliferation extending from the surface to the fat layer, are features that often associate with malignancy. Branching tubular and complex papillary structures in the thickened serosal surface are linked with malignancy, whereas short and simple structures are more common in benign proliferations. Cellular atypia and mitotic figures are not reliable criteria of malignancy in the serosa, because these features may be observed in reactive hyperplasia, whereas malignant mesothelioma often consists of monotonous cell population with minimal nuclear atypia and rare mitoses [19, 54, 55]. However, the presence on the serosal surface of nodules or masses of obviously neoplastic cells with severe pleomorphism, aberrant mitoses, or bland necrosis should be considered malignant [55]. The features of benign and malignant mesothelial proliferations are listed in Table 16.4, and malignant features are illustrated in Fig. 16.5.

A large number of markers tested for their potential to aid in the differentiation between benign and malignant mesothelial proliferations have given inconsistent results in

Table 16.4 Histological features of mesothelial hyperplasia and epithelioid malignant mesothelioma

Feature	Mesothelial hyperplasia	Epithelioid malignant mesothelioma
Invasion	No	Yes
	Entrapment or tissue cut *en face* may simulate invasion	True invasion of underlying tissue
Full-thickness cellularity and cellular nodules	Rare	Common
	Apparent zonation with mesothelial hyperplasia on surface and fibrosis in deeper tissue	Full thickness of atypical cells without zonation
		Cellular nodules
Tubular and papillary structures	Simple nonbranching structures	Complex
		Papillary structures with fibrovascular core and branching tubular structures
Cellular atypia	Common	Often mild atypia in a monotonous cell population
	Often accompanied by fibrin deposition and active inflammation	Sometimes remarkable pleomorphism
Mitotic figures	Common	Rare or frequent
		Sometimes atypical
Necrosis	Rare	Bland necrosis
	Necrosis with cellular debris and inflammation	

Data modified from Refs. [54, 55]

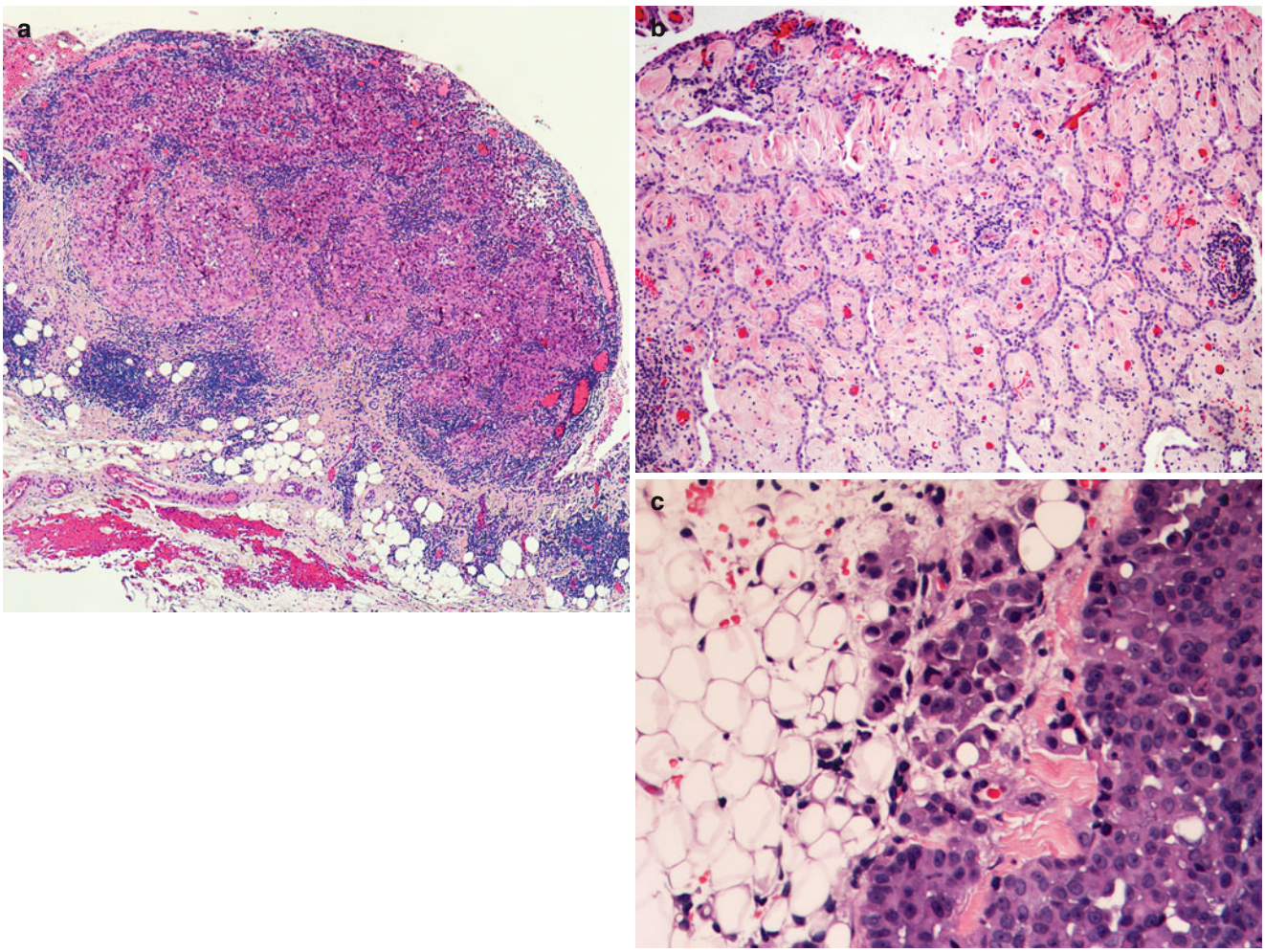


Fig. 16.5 Features of malignancy in the epithelioid mesothelial lesion. Large cellular nodules on the serosal surface (**a**), branching tubular structures (**b**), and invasion of parietal pleural fat layer (**c**) (H&E; **a**, **b**, low magnification; **c**, medium magnification)

different studies. Attanoos et al. studied the use of desmin, epithelial membrane antigen (EMA), p53 protein, bcl-2, P-glycoprotein, and a platelet-derived growth factor receptor (PDGF-R) in distinguishing reactive from neoplastic mesothelium and reviewed previous studies concerning these markers [56]. According to their study and the review of the literature, desmin and EMA were the most useful markers: combined results from this and previous studies showed diffuse cytoplasmic staining for desmin in 86 % of reactive proliferations and 18 % of epithelioid MMs and strong membranous staining for EMA in 15 % of reactive lesions and 75 % of epithelioid MMs [56]. King et al. performed a systematic review of literature on markers used to distinguish between benign and malignant mesothelial proliferations, including p53, desmin, EMA, bcl-2, and p-170, and the counting of argyrophilic nucleolar organizer regions (AgNOR, silver-stained nucleolar organizer regions, which are loops of DNA encoding ribosomal RNA and associating with argyrophilic nonhistone proteins) [57]. Also in this review, desmin and EMA were most useful, with a sensitivity of 83 and 74 % and specificity of 83 % and 89 %, respectively [57]. A few newer markers of malignant transformation, such as XIAP (X-linked inhibitor of apoptosis protein) and GLUT-1 (glucose transporter isoform-1), and the homozygous deletion of chromosomal region 9p21 have shown promising results in initial studies [58–63]. No results from previously mentioned studies can be applied to clinical practice as such, but each laboratory should study the performance of the markers in their reference materials. Furthermore, the diagnosis of malignancy cannot be based on markers, but positive markers together with morphological features of atypical mesothelial hyperplasia may be used as a warning sign inducing follow-up or a new biopsy, depending on the clinician's judgment.

Biphasic Malignant Mesothelioma

Biphasic MM contains epithelioid and sarcomatoid or desmoplastic components, each covering at least 10 % of the tumor area. The diagnosis of biphasic MM is greatly benefitted by immunohistochemistry as the epithelioid component is always positive with several mesothelial markers and cytokeratins, whereas the sarcomatoid or desmoplastic component may be either positive or negative (see below). Differential diagnosis includes other biphasic tumors, such as metastatic carcinosarcomas, pleomorphic carcinomas with better differentiated components, pulmonary blastoma, and biphasic synovial sarcoma [64]. Sometimes a stromal reaction may simulate a sarcomatoid tumor component [64]. Cytokeratins are not very useful in differentiating between biphasic MM and synovial sarcoma, because cytokeratins 5/6, 7, 8, 18, and 19 are positive in the epithelial components and occasionally in the sarcomatous components of both tumors [35, 65]. Synovial sarcoma may express "mesothelial" markers calretinin and D2-40 [35, 66], whereas bcl-2 and Ber-EP4 are commonly positive in synovial sarcoma and seldom in MM [35, 67–69]. The most reliable marker is the t(X;18) chromosomal translocation of a synovial sarcoma resulting in either a SYT-SSX1 or SYT-SSX2 chimeric fusion transcript, which does not occur in MM [67, 70].

Sarcomatoid Malignant Mesothelioma

Sarcomatoid MM is a subtype of MM in which 90 % or more of the tumor tissue consists of sarcomatoid cell type. Sarcomatoid MM constitutes approximately 10 % of all pleural MM [14–17]. The proportion of sarcomatoid MM seems to be highest in the pleura, but it is not known whether this is influenced by selection bias in some materials or diagnostic difficulties in body cavities other than the pleura. In the study of Klebe et al., only 2 % of sarcomatoid MMs were of peritoneal origin [37]. The diagnosis of sarcomatoid MM requires information regarding the typical gross features of MM, i.e., marked diffuse thickening of the serosal surface with encasement of the visceral organs. The presence of intrapulmonary mass suggests a diagnosis of a primary lung tumor rather than MM [64].

The morphology of sarcomatoid MM is variable, and it may resemble any sarcoma or be a mixture of several morphological types (Fig. 16.6). Klebe et al. [37] analyzed 326 sarcomatoid MMs: 44 % of them represented the conventional type without any special subtype, 21 % were sarcomatoid with desmoplastic features, 34 % fulfilled the criteria of desmoplastic MM, 1 % had osteosarcomatous and/or chondrosarcomatous differentiation, and less than 1 % were of the lymphohistiocytoid subtype [37]. The most common growth pattern of sarcomatoid MM is a fibrosarcoma-like or malignant fibrous histiocytoma-like pattern where spindle cells are arranged in storiform, haphazard, or fascicular patterns (Fig. 16.6a) [13, 67]. Some sarcomatoid MMs resemble pleomorphic malignant fibrous histiocytomas with tumor giant cells [37]. Sarcomatoid MM may also have leiomyoid features [37]. A very rare variant is sarcomatoid MM with heterologous elements which is characterized by malignant osteosarcomatous, chondrosarcomatous, or rhabdomyoblastic elements (Fig. 16.6b) [13]. This entity does not include MM with areas of metaplastic ossification or MM with rhabdoid features, which are commonly observed in epithelioid and sarcomatoid MM [13, 71]. Lymphohistiocytoid MM consists of discohesive proliferation of histiocytoid malignant cells with a marked infiltration of reactive lymphocytes and plasma cells (Fig. 16.6c) [72].

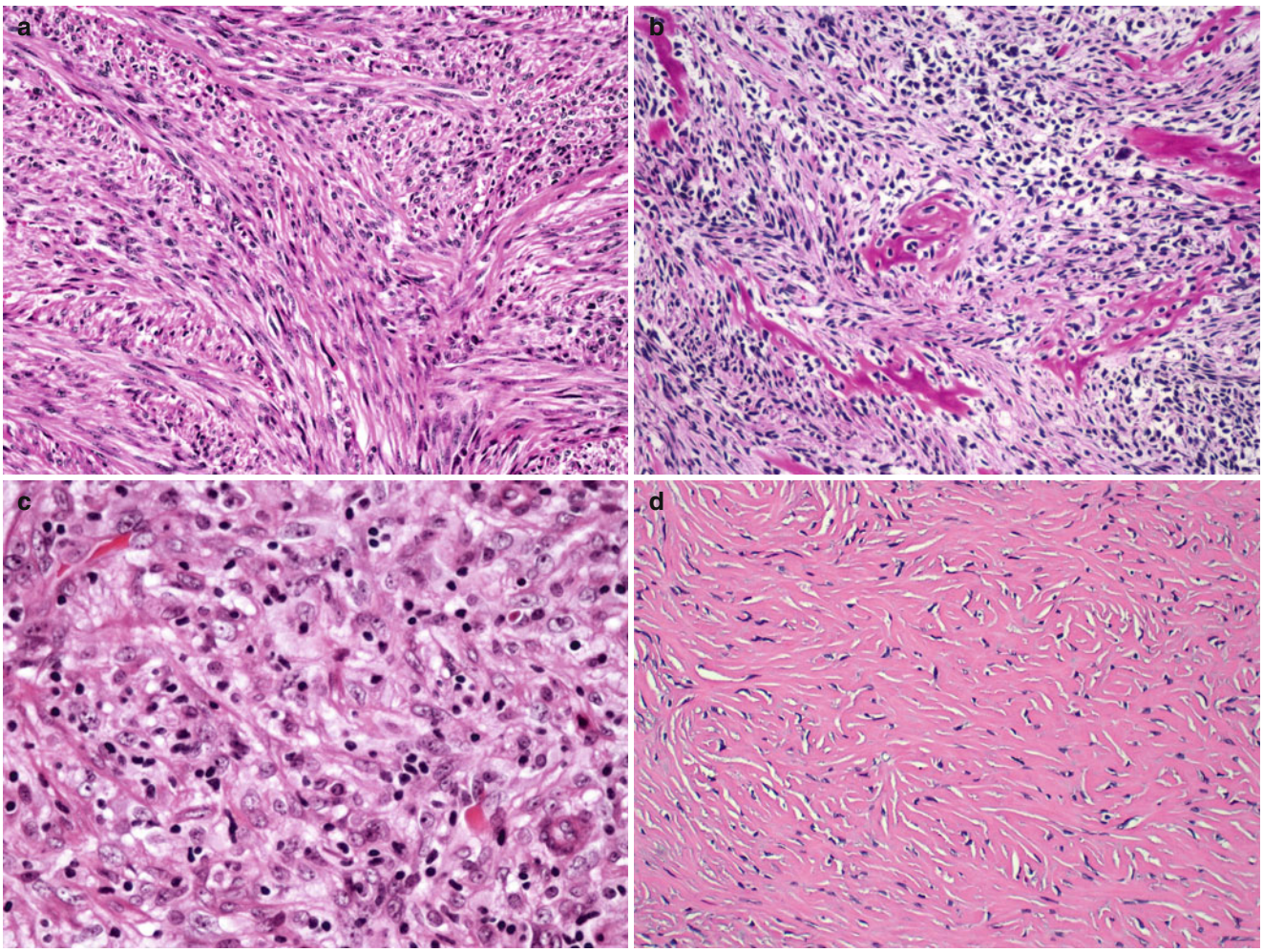


Fig. 16.6 Sarcomatoid malignant mesothelioma. Bundles of spindle cells arranged in fibrosarcomatous pattern (**a**), heterologous mesothelioma with osteoid formation (**b**), lymphohistiocytoid malignant mesothelioma (**c**) and desmoplastic malignant mesothelioma (**d**) (H&E; medium magnification)

Desmoplastic Malignant Mesothelioma

Desmoplastic morphology in MM is observed if malignant tissue forms acellular or paucicellular hyalinized bundles of collagen arranged in a storiform pattern. Small, hyperchromatic spindle cell nuclei with minimal or no atypia are seen between the bundles of collagen (Figs. 16.6d and 16.7a) [4, 64, 73, 74]. Desmoplastic features are common in sarcomatoid MM [37] and may occur in the sarcomatoid component of biphasic mesotheliomas [74–76]. Desmoplastic MM is diagnosed if more than 50 % of the tumor tissue exhibits a desmoplastic pattern. This morphological pattern is often difficult to distinguish from fibrous pleuritis, and differential diagnosis may require extensive sampling and examination of several tissue blocks. The criteria of desmoplastic MM defined by Mangano et al. (1998) include a paucicellular lesion with a storiform pattern or a "patternless pattern" and one or more of the following: foci of bland necrosis, invasion of chest wall or lung tissue, identification of marked cellular atypia in non-desmoplastic areas of the tumor, or distant metastases [64, 73]. Necrosis foci have not been identified in all cases, and necrosis should be distinguished from fibrin depositions. Invasion of lung tissue may be mistaken for organizing pneumonia because of the intra-alveolar accumulation of spindle cells [4]. Immunostaining with pancytokeratins is often helpful as invasive fibrous tumor tissue is usually cytokeratin positive, whereas the deep fibrous tissue of chronic pleuritis is negative with pancytokeratins (Fig. 16.7b). In contrast, myofibroblastic cells of fibrous pleuritis located close to the pleural surface stain with cytokeratins [64, 77]. No immunohistochemical markers, other than cytokeratins, have any feasibility in the differential diagnosis of desmoplastic MM and fibrous pleuritis. The morphological features separating desmoplastic MM from fibrous pleuritis are listed in Table 16.5.

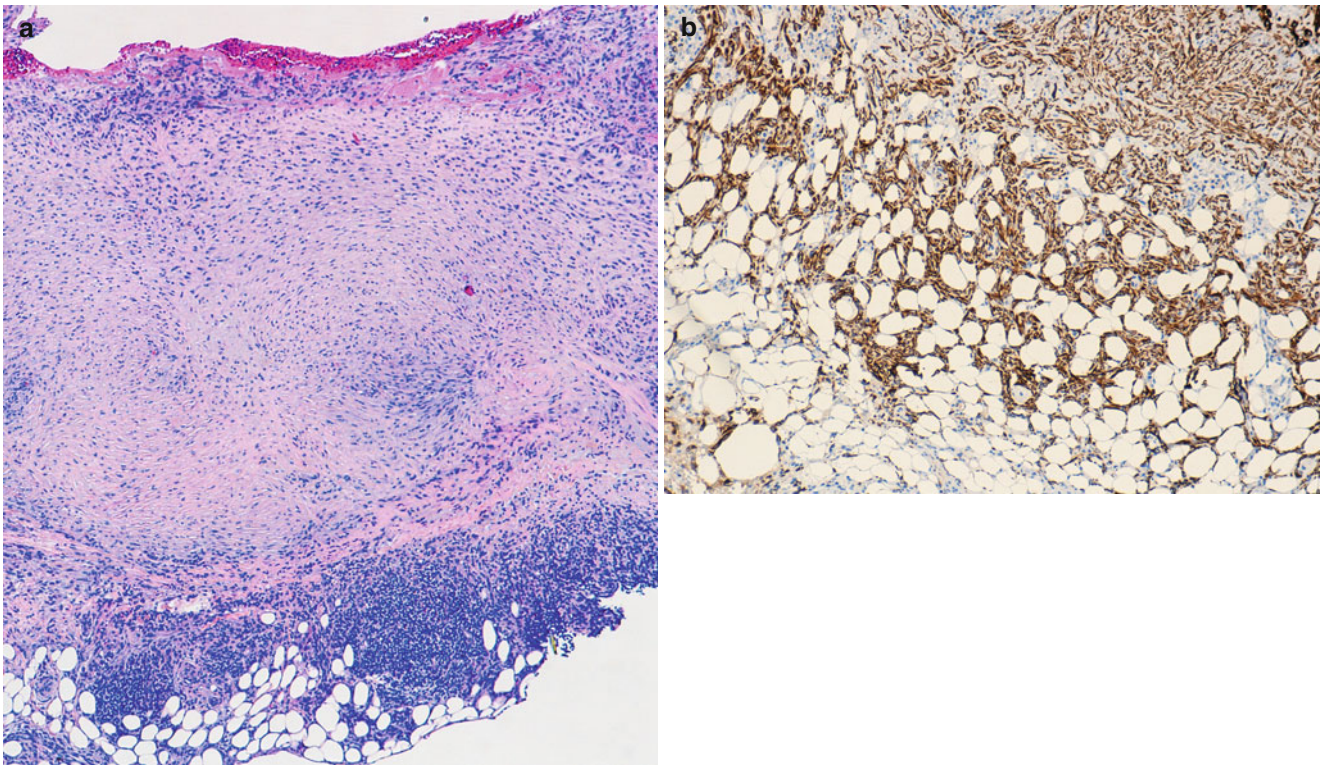


Fig. 16.7 Features of malignancy in mesothelial spindle cell lesion. Haphazard arrangement of cellular and acellular regions in sarcomatoid/desmoplastic malignant mesothelioma (**a**). Parietal pleural fat-invading cytokeratin-positive spindle cells in sarcomatoid malignant mesothelioma (**b**) (H&E; **b**, pancytokeratin immunostaining; (**a**) low magnification; (**b**) medium magnification)

Table 16.5 Differential diagnosis between desmoplastic malignant mesothelioma and fibrous pleuritis

Feature	Fibrous pleuritis	Desmoplastic mesothelioma
Invasion	No	Invasion of adjacent tissue present
Morphological pattern	Typical layering of organizing fibrinous exudates: granulation tissue close to the surface and fibrosis in deeper tissue	Random distribution of cellular and fibrous regions
	Capillaries arranged perpendicular to the pleural surface	Storiform pattern or haphazard arrangement of collagenous tissue
		Capillaries inconspicuous
Cellular atypia	No sarcomatoid foci	Sarcomatoid foci present – may not be found in small biopsies
Necrosis	No	Bland necrosis may occur
	Fibrin deposits should not be mistaken as necrosis	
Pancytokeratins	Positive myofibroblastic cells close to pleural surface – no positivity in deeper fibrous tissue	Demonstrate storiform or fascicular growth pattern
		Invasive tumor tissue usually positive
Mesothelial markers	Positivity in reactive mesothelial cells	Usually negative
		Help to detect a small epithelioid component – if found, confirms diagnosis of malignant mesothelioma

Data modified from Refs. [73] and [54]

Differential Diagnosis of Sarcomatoid/ Desmoplastic MM

The differential diagnosis of sarcomatoid MM includes sarcomatoid carcinomas, especially those originating from the lung or kidney, sarcomas, and benign and malignant solitary fibrous tumors. Desmoplastic MM should be distinguished from fibrous pleuritis and desmoid tumor in particular.

Immunohistochemical markers are less useful in the diagnosis of sarcomatoid and desmoplastic MM than in the diagnosis of epithelioid MM. “Mesothelial” markers, such as calretinin and cytokeratin 5/6, are often negative in sarcomatoid MM, although they may be helpful in the identification

of a small epithelioid component and thus help to confirm the diagnosis of MM. The percentage of calretinin-positive cases among sarcomatoid MMs and the sarcomatoid components of biphasic MM has varied from 30 to 100 % in different studies, often with a focal or patchy staining pattern [13, 35, 37, 78–81]. The positivity for calretinin in sarcomatoid tumors of the serosa appears to be nonspecific, as about 50 % of synovial sarcomas and 60–80 % of pulmonary sarcomatoid carcinomas have shown at least focal positivity for calretinin [79, 81, 82]. The other markers of epithelioid MM, such as CK5/6, thrombomodulin, WT-1, and podoplanin, have been either negative or positive in a minority of sarcomatoid MM, depending on the study [35, 78, 80, 81, 83], but positive immunostaining for thrombomodulin, WT-1, and podoplanin may also occur in sarcomatoid carcinomas [81, 82]. Tsuta et al. studied the sensitivity and specificity of two antibody clones of WT-1, namely, 6F-H2 and WT49, in the diagnosis of MM [83]. Immunostaining with the antibody clones 6F-H2 and WT49 demonstrated nuclear positivity in 71 and 79 % of epithelioid MM, 8 and 42 % of sarcomatoid MM, 0 and 13 % of pulmonary pleomorphic carcinomas, and 0 and 10 % of synovial sarcomas [83]. Markers of pulmonary and kidney carcinomas may sometimes be useful for the differential diagnosis of sarcomatoid tumors. Unfortunately, less than half of pulmonary sarcomatoid carcinomas express carcinoma markers, such as TTF-1, p63, CEA, or MOC31 [84–88]. Immunohistochemistry is even less useful in the differentiation between sarcomatoid MM and sarcomatoid renal cell carcinomas metastatic to pleura, as only up to 28 % of sarcomatoid renal cell carcinomas are positive with RCC or PAX8. Furthermore, positive immunostaining is frequently observed in MM with renal cell marker CD10 and less often with PAX8 and RCC [89–91].

The use of several different cytokeratins or pancytokeratins has been recommended for the diagnosis of sarcomatoid and desmoplastic MM. Recent studies have reported the percentage of sarcomatoid MM with positive immunostaining for cytokeratins to be from 70 to over 90 % [13, 37, 78, 81]. The proportion of cytokeratin-positive sarcomatoid MM is influenced by the fixation and processing of tissue samples, and the recent development of pancytokeratin cocktails and pretreatments for immunostaining has increased the percentage of positive samples [13, 37, 78, 81]. However, it is generally accepted that completely cytokeratin-negative sarcomatoid and desmoplastic MMs exist [37]. Cytokeratins are not helpful in the differentiation between sarcomatoid carcinomas and sarcomatoid MM, because both tumors may express low-molecular-weight cytokeratins or be completely cytokeratin negative [37, 64, 88]. Pancytokeratins help in the differential diagnosis between desmoplastic MM and fibrous pleuritis, because they aid in the recognition of the storiform and fascicular growth pattern of MM and the invasion of the chest wall structures or the lung [64].

Conclusion

MM is divided into four main histological subtypes, i.e., epithelioid, biphasic, sarcomatoid, and desmoplastic, each of which has distinctive morphological and immunohistochemical features, differential diagnosis, and a slightly divergent prognosis. Immunohistochemistry with a panel of antibodies including the positive and negative markers of MM is of great aid in the differential diagnosis of epithelioid MM and carcinomas infiltrating body cavities. The pathologist involved in the diagnosis of MM requires information regarding previous malignant diseases, imaging, and the clinical findings of the patient, as a number of both benign and malignant and primary and secondary neoplastic diseases may arise in or invade the body cavities. Furthermore, in the case of sarcomatoid MM, the characteristic gross finding may be the only distinguishing feature between MM and sarcomatoid carcinomas, as immunohistochemical markers only have a limited value in the differential diagnosis of the sarcomatoid and pleomorphic tumors of the body cavities. Reactive lesions, especially atypical mesothelial hyperplasia and fibrous pleuritis, are important to consider in the differential diagnosis of epithelioid and sarcomatoid MM, respectively.

References

1. Allen TC, Cagle PT, Churg AM, Colby TV, Gibbs AR, Hammar SP, Corson JM, Grimes MM, Ordonez NG, Roggli V, Travis WD, Wick MR. Localized malignant mesothelioma. Am J Surg Pathol. 2005;29:866–73.
2. Renshaw AA, Dean BR, Antman KH, Sugarbaker DJ, Cibas ES. The role of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma. Chest. 1997;111:106–9.
3. Butnor KJ. My approach to the diagnosis of mesothelial lesions. J Clin Pathol. 2006;59:564–74.
4. Galateau-Salle F, editor. Pathology of malignant mesothelioma. London: Springer; 2006.
5. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, editors. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2004.
6. Gorini G, De Gregorio G, Silvestri S, Chellini E, Cupelli V, Seniori Costantini A. Survival of malignant pleural mesothelioma cases in the Tuscan Mesothelioma Register, 1988–2000: a population-based study. Eur J Cancer Prev. 2005;14:195–9.
7. Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J Clin Oncol. 1998;16:145–52.
8. Ceresoli GL, Locati LD, Ferreri AJ, Cozzarini C, Passoni P, Melloni G, Zannini P, Bolognesi A, Villa E. Therapeutic outcome according to histologic subtype in 121 patients with malignant pleural mesothelioma. Lung Cancer. 2001;34:279–87.
9. Neragi-Miandoab S, Richards WG, Sugarbaker DJ. Morbidity, mortality, mean survival, and the impact of histology on survival after pleurectomy in 64 patients with malignant pleural mesothelioma. Int J Surg. 2008;6:293–7.
10. Balduyck B, Trousse D, Nakas A, Martin-Ucar AE, Edwards J, Waller DA. Therapeutic surgery for nonepithelioid malignant

pleural mesothelioma: is it really worthwhile? Ann Thorac Surg. 2010;89:907–11.
11. Churg A, Cagle PT, Roggli VL, editors. Tumors of the serosal membranes. Silver Spring: ARP Press; 2006.
12. Allen TC. Recognition of histopathologic patterns of diffuse malignant mesothelioma in differential diagnosis of pleural biopsies. Arch Pathol Lab Med. 2005;129:1415–20.
13. Klebe S, Mahar A, Henderson DW, Roggli VL. Malignant mesothelioma with heterologous elements: clinicopathological correlation of 27 cases and literature review. Mod Pathol. 2008;21:1084–94.
14. Van Gelder T, Damhuis RA, Hoogsteden HC. Prognostic factors and survival of malignant pleural mesothelioma. Eur Respir J. 1994;7:1035–8.
15. Yates DH, Corrin B, Stidolph PN, Browne K. Malignant mesothelioma in south east England: clinicopathological experience of 272 cases. Thorax. 1997;52:507–12.
16. Britton M. The epidemiology of mesothelioma. Semin Oncol. 2002;29:18–25.
17. Neumann V, Gunthe S, Mulle KM, Fischer M. Malignant mesothelioma – German mesothelioma register 1987–1999. Int Arch Occup Environ Health. 2001;74:383–95.
18. Kadota K, Suzuki K, Sima CS, Rusch VW, Adusumilli PS, Travis WD. Pleomorphic epithelioid diffuse malignant pleural mesothelioma: a clinicopathological review and conceptual proposal to reclassify as biphasic or sarcomatoid mesothelioma. J Thorac Oncol. 2011;6:896–904.
19. McCaughey WT, Colby TV, Battifora H, Churg A, Corson JM, Greenberg SD, Grimes MM, Hammar S, Roggli VL, Unni KK. Diagnosis of diffuse malignant mesothelioma: experience of a US/Canadian mesothelioma panel. Mod Pathol. 1991;4:342–53.
20. Dardick I, Jabi M, McCaughey WT, Deodhare S, van Nostrand AW, Srigley JR. Diffuse epithelial mesothelioma: a review of the ultrastructural spectrum. Ultrastruct Pathol. 1987;11:503–33.
21. Oury TD, Hammar SP, Roggli VL. Ultrastructural features of diffuse malignant mesotheliomas. Hum Pathol. 1998;29:1382–92.
22. MacDougall DB, Wang SE, Zidar BL. Mucin-positive epithelial mesothelioma. Arch Pathol Lab Med. 1992;116:874–80.
23. Bedrossian CW. Diagnostic problems in serous effusions. Diagn Cytopathol. 1998;19:131–7.
24. Rao R. Mesothelioma. In: Shidham V, Atkinson BF, editors. Cytopathologic diagnosis of serous fluids. Philadelphia: Saunders; 2007. p. 107–13.
25. Ylagan LR, Zhai J. The value of ThinPrep and cytospin preparation in pleural effusion cytological diagnosis of mesothelioma and adenocarcinoma. Diagn Cytopathol. 2005;32:137–44.
26. Sherman ME, Mark EJ. Effusion cytology in the diagnosis of malignant epithelioid and biphasic pleural mesothelioma. Arch Pathol Lab Med. 1990;114:845–51.
27. Rakha EA, Patil S, Abdulla K, Abdulkader M, Chaudry Z, Soomro IN. The sensitivity of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma. Diagn Cytopathol. 2010;38:874–9.
28. Pereira TC, Saad RS, Liu Y, Silverman JF. The diagnosis of malignancy in effusion cytology: a pattern recognition approach. Adv Anat Pathol. 2006;13:174–84.
29. Nguyen GK, Akin MR, Villanueva RR, Slatnik J. Cytopathology of malignant mesothelioma of the pleura in fine-needle aspiration biopsy. Diagn Cytopathol. 1999;21:253–9.
30. Butnor KJ, Sporn TA, Ordonez NG. Recommendations for the reporting of pleural mesothelioma. Hum Pathol. 2007;38:1587–9.
31. Husain AN, Colby TV, Ordonez NG, Krausz T, Borczuk A, Cagle PT, Chirieac LR, Churg A, Galateau-Salle F, Gibbs AR, Gown AM, Hammar SP, Litzky LA, Roggli VL, Travis WD, Wick MR. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2009;133:1317–31.
32. King JE, Thatcher N, Pickering CA, Hasleton PS. Sensitivity and specificity of immunohistochemical markers used in the diagnosis of epithelioid mesothelioma: a detailed systematic analysis using published data. Histopathology. 2006;48:223–32.
33. Ordonez NG. Immunohistochemical diagnosis of epithelioid mesotheliomas: a critical review of old markers, new markers. Hum Pathol. 2002;33:953–67.
34. Blobel GA, Moll R, Franke WW, Kayser KW, Gould VE. The intermediate filament cytoskeleton of malignant mesotheliomas and its diagnostic significance. Am J Pathol. 1985;121:235–47.
35. Miettinen M, Limon J, Niezabitowski A, Lasota J. Calretinin and other mesothelioma markers in synovial sarcoma: analysis of antigenic similarities and differences with malignant mesothelioma. Am J Surg Pathol. 2001;25:610–7.
36. Attanoos RL, Webb R, Dojcinov SD, Gibbs AR. Malignant epithelioid mesothelioma: anti-mesothelial marker expression correlates with histological pattern. Histopathology. 2001;39:584–8.
37. Klebe S, Brownlee NA, Mahar A, Burchette JL, Sporn TA, Vollmer RT, Roggli VL. Sarcomatoid mesothelioma: a clinical-pathologic correlation of 326 cases. Mod Pathol. 2010;23:470–9.
38. Attanoos RL, Galateau-Salle F, Gibbs AR, Muller S, Ghandour F, Dojcinov SD. Primary thymic epithelial tumours of the pleura mimicking malignant mesothelioma. Histopathology. 2002;41:42–9.
39. Pan CC, Chen PC, Chou TY, Chiang H. Expression of calretinin and other mesothelioma-related markers in thymic carcinoma and thymoma. Hum Pathol. 2003;34:1155–62.
40. Fukunaga M. Expression of D2-40 in lymphatic endothelium of normal tissues and in vascular tumours. Histopathology. 2005;46:396–402.
41. Breiteneder-Geleff S, Soleiman A, Kowalski H, Horvat R, Amann G, Kriehuber E, Diem K, Weninger W, Tschachler E, Alitalo K, Kerjaschki D. Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries: podoplanin as a specific marker for lymphatic endothelium. Am J Pathol. 1999;154:385–94.
42. Fujii T, Zen Y, Sato Y, Sasaki M, Enomae M, Minato H, Masuda S, Uehara T, Katsuyama T, Nakanuma Y. Podoplanin is a useful diagnostic marker for epithelioid hemangioendothelioma of the liver. Mod Pathol. 2008;21:125–30.
43. Zhang PJ, Goldblum JR, Pawel BR, Fisher C, Pasha TL, Barr FG. Immunophenotype of desmoplastic small round cell tumors as detected in cases with EWS-WT1 gene fusion product. Mod Pathol. 2003;16:229–35.
44. Granville L, Laga AC, Allen TC, Dishop M, Roggli VL, Churg A, Zander DS, Cagle PT. Review and update of uncommon primary pleural tumors: a practical approach to diagnosis. Arch Pathol Lab Med. 2005;129:1428–43.
45. Foyle A, Al-Jabi M, McCaughey WT. Papillary peritoneal tumors in women. Am J Surg Pathol. 1981;5:241–9.
46. Sane AC, Roggli VL. Curative resection of a well-differentiated papillary mesothelioma of the pericardium. Arch Pathol Lab Med. 1995;119:266–7.
47. Xiao SY, Rizzo P, Carbone M. Benign papillary mesothelioma of the tunica vaginalis testis. Arch Pathol Lab Med. 2000;124:143–7.
48. Butnor KJ, Sporn TA, Hammar SP, Roggli VL. Well-differentiated papillary mesothelioma. Am J Surg Pathol. 2001;25:1304–9.
49. Galateau-Salle F, Vignaud JM, Burke L, Gibbs A, Brambilla E, Attanoos R, Goldberg M, Launoy G. Well-differentiated papillary mesothelioma of the pleura: a series of 24 cases. Am J Surg Pathol. 2004;28:534–40.
50. Asioli S, Dal Piaz G, Damiani S. Localised pleural malignant mesothelioma. Report of two cases simulating pulmonary carcinoma and review of the literature. Virchows Arch. 2004;445:206–9.
51. Onat A, Berktin K, Kapanci Y. Localized pleural mesothelioma of epithelial type and malignant nature. Report of a case. Dis Chest. 1963;44:649–52.

52. Sasaki M, Araki I, Yasui T, Kinoshita M, Itatsu K, Nojima T, Nakanuma Y. Primary localized malignant biphasic mesothelioma of the liver in a patient with asbestosis. World J Gastroenterol. 2009;15:615–21.
53. Espinal-Witter R, Servais EL, Klimstra DS, Lieberman MD, Yantiss RK. Localized intrapancreatic malignant mesothelioma: a rare entity that may be confused with other pancreatic neoplasms. Virchows Arch. 2010;456:455–61.
54. Churg A, Colby TV, Cagle P, Corson J, Gibbs AR, Gilks B, Grimes M, Hammar S, Roggli V, Travis WD. The separation of benign and malignant mesothelial proliferations. Am J Surg Pathol. 2000;24:1183–200.
55. Cagle PT, Churg A, editors. Differential diagnosis of benign and malignant mesothelial proliferations on pleural biopsies. 2005.
56. Attanoos RL, Griffin A, Gibbs AR. The use of immunohistochemistry in distinguishing reactive from neoplastic mesothelium. A novel use for desmin and comparative evaluation with epithelial membrane antigen, p53, platelet-derived growth factor-receptor, P-glycoprotein and Bcl-2. Histopathology. 2003;43:231–8.
57. King J, Thatcher N, Pickering C, Hasleton P. Sensitivity and specificity of immunohistochemical antibodies used to distinguish between benign and malignant pleaural disease: a systematic review of published reports. Histopathology. 2006;49:561–8.
58. Kato Y, Tsuta K, Seki K, Maeshima AM, Watanabe S, Suzuki K, Asamura H, Tsuchiya R, Matsuno Y. Immunohistochemical detection of GLUT-1 can discriminate between reactive mesothelium and malignant mesothelioma. Mod Pathol. 2007;20:215–20.
59. Chiosea S, Krasinskas A, Cagle PT, Mitchell KA, Zander DS, Dacic S. Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas. Mod Pathol. 2008;21:742–7.
60. Shen J, Pinkus GS, Deshpande V, Cibas ES. Usefulness of EMA, GLUT-1, and XIAP for the cytologic diagnosis of malignant mesothelioma in body cavity fluids. Am J Clin Pathol. 2009;131:516–23.
61. Wu M, Yuan S, Szporn AH, Gan L, Shtilbans V, Burstein DE. Immunocytochemical detection of XIAP in body cavity effusions and washes. Mod Pathol. 2005;18:1618–22.
62. Wu M, Sun Y, Li G, Desman G, Wang B, Gil J, Burstein DE. Immunohistochemical detection of XIAP in mesothelium and mesothelial lesions. Am J Clin Pathol. 2007;128:783–7.
63. Takeda M, Kasai T, Enomoto Y, Takano M, Morita K, Kadota E, Nonomura A. 9p21 deletion in the diagnosis of malignant mesothelioma, using fluorescence in situ hybridization analysis. Pathol Int. 2010;60:395–9.
64. Travis WD. Sarcomatoid neoplasms of the lung and pleura. Arch Pathol Lab Med. 2010;134:1645–58.
65. Miettinen M, Limon J, Niezabitowski A, Lasota J. Patterns of keratin polypeptides in 110 biphasic, monophasic, and poorly differentiated synovial sarcomas. Virchows Arch. 2000;437:275–83.
66. Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol. 2005;36:372–80.
67. Litzky LA. Pulmonary sarcomatous tumors. Arch Pathol Lab Med. 2008;132:1104–17.
68. Gaertner E, Zeren EH, Fleming MV, Colby TV, Travis WD. Biphasic synovial sarcomas arising in the pleural cavity. A clinicopathologic study of five cases. Am J Surg Pathol. 1996;20:36–45.
69. Aubry MC, Bridge JA, Wickert R, Tazelaar HD. Primary monophasic synovial sarcoma of the pleura: five cases confirmed by the presence of SYT-SSX fusion transcript. Am J Surg Pathol. 2001;25:776–81.
70. de Leeuw B, Balemans M, Olde Weghuis D, Geurts van Kessel A. Identification of two alternative fusion genes, SYT-SSX1 and SYT-SSX2, in t(X;18)(p11.2;q11.2)-positive synovial sarcomas. Hum Mol Genet. 1995;4:1097–9.
71. Ordonez NG. Mesothelioma with rhabdoid features: an ultrastructural and immunohistochemical study of 10 cases. Mod Pathol. 2006;19:373–83.
72. Khalidi HS, Medeiros LJ, Battifora H. Lymphohistiocytoid mesothelioma. An often misdiagnosed variant of sarcomatoid malignant mesothelioma. Am J Clin Pathol. 2000;113:649–54.
73. Mangano WE, Cagle PT, Churg A, Vollmer RT, Roggli VL. The diagnosis of desmoplastic malignant mesothelioma and its distinction from fibrous pleurisy: a histologic and immunohistochemical analysis of 31 cases including p53 immunostaining. Am J Clin Pathol. 1998;110:191–9.
74. Stout A. Tumors of the pleura. Harlem Hosp Bull. 1971;5:54–7.
75. Wilson GE, Hasleton PS, Chatterjee AK. Desmoplastic malignant mesothelioma: a review of 17 cases. J Clin Pathol. 1992;45:295–8.
76. Cantin R, Al-Jabi M, McCaughey WT. Desmoplastic diffuse mesothelioma. Am J Surg Pathol. 1982;6:215–22.
77. Addis B, Roche H. Problems in mesothelioma diagnosis. Histopathology. 2009;54:55–68.
78. Attanoos RL, Dojcinov SD, Webb R, Gibbs AR. Anti-mesothelial markers in sarcomatoid mesothelioma and other spindle cell neoplasms. Histopathology. 2000;37:224–31.
79. Kushitani K, Takeshima Y, Amatya VJ, Furonaka O, Sakatani A, Inai K. Differential diagnosis of sarcomatoid mesothelioma from true sarcoma and sarcomatoid carcinoma using immunohistochemistry. Pathol Int. 2008;58:75–83.
80. Hinterberger M, Reineke T, Storz M, Weder W, Vogt P, Moch H. D2-40 and calretinin – a tissue microarray analysis of 341 malignant mesotheliomas with emphasis on sarcomatoid differentiation. Mod Pathol. 2007;20:248–55.
81. Lucas DR, Pass HI, Madan SK, Adsay NV, Wali A, Tabaczka P, Lonardo F. Sarcomatoid mesothelioma and its histological mimics: a comparative immunohistochemical study. Histopathology. 2003;42:270–9.
82. Kenmotsu H, Ishii G, Nagai K, Nakao M, Kawase A, Kojika M, Murata Y, Nishiwaki Y, Ochiai A. Pleomorphic carcinoma of the lung expressing podoplanin and calretinin. Pathol Int. 2008;58:771–4.
83. Tsuta K, Kato Y, Tochigi N, Hoshino T, Takeda Y, Hosako M, Maeshima AM, Asamura H, Kondo T, Matsuno Y. Comparison of different clones (WT49 versus 6F-H2) of WT-1 antibodies for immunohistochemical diagnosis of malignant pleural mesothelioma. Appl Immunohistochem Mol Morphol. 2009;17:126–30.
84. Koss MN, Hochholzer L, Frommelt RA. Carcinosarcomas of the lung: a clinicopathologic study of 66 patients. Am J Surg Pathol. 1999;23:1514–26.
85. Lewis JS, Ritter JH, El-Mofty S. Alternative epithelial markers in sarcomatoid carcinomas of the head and neck, lung, and bladder-p63, MOC-31, and TTF-1. Mod Pathol. 2005;18:1471–81.
86. Pelosi G. The new taxonomy of lung adenocarcinoma stemming from a multidisciplinary integrated approach: novel pathology concepts and perspectives. J Thorac Oncol. 2011;6:241–3.
87. Rossi G, Cavazza A, Sturm N, Migaldi M, Facciolongo N, Longo L, Maiorana A, Brambilla E. Pulmonary carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements: a clinicopathologic and immunohistochemical study of 75 cases. Am J Surg Pathol. 2003;27:311–24.
88. Pelosi G, Sonzogni A, De Pas T, Galetta D, Veronesi G, Spaggiari L, Manzotti M, Fumagalli C, Bresaola E, Nappi O, Viale G, Rosai J. Review article: pulmonary sarcomatoid carcinomas: a practical overview. Int J Surg Pathol. 2010;18:103–20.
89. Laury AR, Hornick JL, Perets R, Krane JF, Corson J, Drapkin R, Hirsch MS. PAX8 reliably distinguishes ovarian serous tumors from malignant mesothelioma. Am J Surg Pathol. 2010;34:627–35.
90. Truong LD, Shen SS. Immunohistochemical diagnosis of renal neoplasms. Arch Pathol Lab Med. 2011;135:92–109.
91. Butnor KJ, Nicholson AG, Allred DC, Zander DS, Henderson DW, Barrios R, Haque AK, Allen TC, Killen DE, Cagle PT. Expression of renal cell carcinoma-associated markers erythropoietin, CD10, and renal cell carcinoma marker in diffuse

malignant mesothelioma and metastatic renal cell carcinoma. Arch Pathol Lab Med. 2006;130:823–7.
92. Padgett DM, Cathro HP, Wick MR, Mills SE. Podoplanin is a better immunohistochemical marker for sarcomatoid mesothelioma than calretinin. Am J Surg Pathol. 2008;32:123–7.
93. Yaziji H, Battifora H, Barry TS, Hwang HC, Bacchi CE, McIntosh MW, Kussick SJ, Gown AM. Evaluation of 12 antibodies for distinguishing epithelioid mesothelioma from adenocarcinoma: identification of a three-antibody immunohistochemical panel with maximal sensitivity and specificity. Mod Pathol. 2006;19:514–23.
94. Miettinen M, Sarlomo-Rikala M. Expression of calretinin, thrombomodulin, keratin 5, and mesothelin in lung carcinomas of different types: an immunohistochemical analysis of 596 tumors in comparison with epithelioid mesotheliomas of the pleura. Am J Surg Pathol. 2003;27:150–8.
95. Lugli A, Forster Y, Haas P, Nocito A, Bucher C, Bissig H, Mirlacher M, Storz M, Mihatsch MJ, Sauter G. Calretinin expression in human normal and neoplastic tissues: a tissue microarray analysis on 5233 tissue samples. Hum Pathol. 2003;34:994–1000.
96. Ordonez NG. The diagnostic utility of immunohistochemistry in distinguishing between epithelioid mesotheliomas and squamous carcinomas of the lung: a comparative study. Mod Pathol. 2006;19:417–28.
97. Ordonez NG. The diagnostic utility of immunohistochemistry in distinguishing between mesothelioma and renal cell carcinoma: a comparative study. Hum Pathol. 2004;35:697–710.
98. Ordonez NG. The diagnostic utility of immunohistochemistry and electron microscopy in distinguishing between peritoneal mesotheliomas and serous carcinomas: a comparative study. Mod Pathol. 2006;19:34–48.
99. Ordonez NG. Role of immunohistochemistry in distinguishing epithelial peritoneal mesotheliomas from peritoneal and ovarian serous carcinomas. Am J Surg Pathol. 1998;22:1203–14.
100. Barnetson RJ, Burnett RA, Downie I, Harper CM, Roberts F. Immunohistochemical analysis of peritoneal mesothelioma and primary and secondary serous carcinoma of the peritoneum: antibodies to estrogen and progesterone receptors are useful. Am J Clin Pathol. 2006;125:67–76.
101. Attanoos RL, Webb R, Dojcinov SD, Gibbs AR. Value of mesothelial and epithelial antibodies in distinguishing diffuse peritoneal mesothelioma in females from serous papillary carcinoma of the ovary and peritoneum. Histopathology. 2002;40:237–44.
102. Chu PG, Weiss LM. Expression of cytokeratin 5/6 in epithelial neoplasms: an immunohistochemical study of 509 cases. Mod Pathol. 2002;15:6–10.
103. Ordonez NG. Value of thyroid transcription factor-1, E-cadherin, BG8, WT1, and CD44S immunostaining in distinguishing epithelial pleural mesothelioma from pulmonary and nonpulmonary adenocarcinoma. Am J Surg Pathol. 2000;24:598–606.
104. Ordonez NG. Value of mesothelin immunostaining in the diagnosis of mesothelioma. Mod Pathol. 2003;16:192–7.
105. Comin CE, Dini S, Novelli L, Santi R, Asirelli G, Messerini L. h-Caldesmon, a useful positive marker in the diagnosis of pleural malignant mesothelioma, epithelioid type. Am J Surg Pathol. 2006;30:463–9.
106. Chu AY, Litzky LA, Pasha TL, Acs G, Zhang PJ. Utility of D2-40, a novel mesothelial marker, in the diagnosis of malignant mesothelioma. Mod Pathol. 2005;18:105–10.
107. Di Loreto C, Publisi F, Di Laurio V, Damani G, Beltrami A. TTF-1 protein expression in pleural malignant mesotheliomas and adenocarcinomas of the lung. Cancer Lett. 1998;124:72–8.
108. Khoor A, Whitsett JA, Stahlman MT, Olson SJ, Cagle PT. Utility of surfactant protein B precursor and thyroid transcription factor 1 in differentiating adenocarcinoma of the lung from malignant mesothelioma. Hum Pathol. 1999;30:695–700.
109. Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol. 2005;36:372–80.
110. Anttila S. Epithelioid lesions of the serosa. Arch Pathol Lab Med. 2012;136:241–52.
111. Comin CE, Saieva C, Messerini L. h-caldesmon, calretinin, estrogen receptor, and Ber-EP4: a useful combination of immunohistochemical markers for differentiating epithelioid peritoneal mesothelioma from serous papillary carcinoma of the ovary. Am J Surg Pathol. 2007;31:1139–48.
112. Ordonez NG. Value of estrogen and progesterone receptor immunostaining in distinguishing between peritoneal mesotheliomas and serous carcinomas. Hum Pathol. 2005;36:1163–7.

Malignant Mesothelioma: Mechanism of Carcinogenesis

17

Agnes B. Kane, Didier Jean, Sakari Knuutila, and Marie-Claude Jaurand

Keywords
Malignant mesothelioma • Mesothelial carcinogenesis • Asbestos • Pleural carcinogenesis • Genomic changes • Epigenetic changes • Signaling pathways

Introduction

Our present knowledge of the mechanism of mesothelial carcinogenesis results from pathophysiological and toxicological research carried out in vivo in rodents and in mammalian cells in culture and from biological and molecular studies of malignant mesothelioma (MM) tissue samples and cell lines from humans and experimental animals. In this latter context, most experimental studies have been based on the cellular and/or animal responses to asbestos fibers and in genetically modified mice. These investigations have provided a body of data on the cellular and molecular effects of asbestos fibers on mesothelial cells and the mesothelium, including genomic and genetic changes and alterations of regulatory and signaling pathways. Human MM has been characterized at the genomic, genetic, epigenetic, and physiological levels, with the development of large-scale analyses allowing global integration of the networks involved in the transformation of the mesothelial cell. The aim of the present work is to propose a potential mechanism of mesothelial carcinogenesis by integrating data based on cellular and molecular effects of asbestos fibers on mesothelial cells, with altered physiological and molecular features of malignant mesothelioma cells.

A.B. Kane, MD, PhD
Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, USA

D. Jean, PhD
INSERM UMR-S 1162. Functional Genomics of Solid Tumors, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France

S. Knuutila, PhD
Department of Pathology and Genetics, HUSLAB, Helsinki University Central Hospital, Haartmaninkatu 3, 400, Helsinki, HUS 00029, Finland

M.-C. Jaurand, DrSc, PhD (✉)
UMR-S1162. Functional Genomics of Solid Tumors, Institut National de la Santé et de la Recherche Médicale (INSERM), 27, Rue Juliette Dodu, Paris 75010, France
e-mail: marie-claude.jaurand@inserm.fr

Mechanism of Action of Asbestos Fibers

Translocation

The initial route of entry of asbestos fibers is by inhalation and deposition in the tracheobronchial regions, distal airways, and alveolar spaces of the lungs [1]. While particles and fibers are readily cleared from the tracheobronchial airways by mucociliary transport, clearance from distal airways and alveoli is slower and mediated by phagocytosis by alveolar macrophages. Fiber length impairs macrophage-mediated clearance, especially for fibers that exceed the diameter of alveolar macrophages (10–25 μm). Impaired clearance may result in penetration of fibers through the alveolar epithelium and subsequent translocation to the pleura and distant sites [2]. Fibers that enter the interstitium may cross the visceral pleural by paracellular migration or by direct penetration [3]. An alternative route of translocation to the pleural space is transport via lymphatics or the bloodstream [4].

The parietal pleura lines the chest wall and the superior surface of the diaphragm, and the visceral pleura covers the lungs. The pleural space in humans is lined by a single layer of mesothelial cells approximately 1 μm thick resting on a basement membrane and underlying connective tissue and blood vessel [5]. The major route of drainage of fluid,

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_17, © Springer-Verlag London 2014

protein, particulates, and cells from the pleural space is lymphatic stomata that open between mesothelial cells on the parietal pleural lining [6, 7]. The diameter of lymphatic stomata (~10–12 μm) limits the clearance of long fibers from the pleural space [4].

Systemic dissemination of fibers through lymphatics and the bloodstream has been described in humans following autopsy [8–10]. Asbestos fibers and asbestos bodies have been noted in the liver, mesentery, spleen, and abdominal lymph nodes [11, 12]. Diffuse peritoneal malignant mesothelioma is also associated with exposure to asbestos fibers [13, 14]; fibers may reach the peritoneal mesothelial lining via diaphragmatic lymphatics that connect the pleura and peritoneal spaces or following systemic vascular and lymphatic dissemination. Another route of entry may be via swallowing of expectorated mucus and penetration of fibers through gastrointestinal walls.

Experimental Studies on Biological Effects of Asbestos Fibers

As this volume is devoted to occupational cancer, the studies reported here will focus on asbestos as the only known etiological factor associated with MM. However, other types of fibers are associated with MM following environmental exposure, and other fibers used for industrial or commercial applications have been found to produce MM in animals, including man-made mineral fibers and more recently carbon nanotubes. Their effects will be discussed separately in subsequent paragraphs related to the fiber parameters related to carcinogenicity (see paragraphs in 22-2.c).

Effects of Asbestos Fibers in Animals

Epidemiological studies have clearly linked mesothelial carcinogenesis with asbestos exposure. Nevertheless, no history of exposure can be found in about 10–20 % of MM cases [15–18]. This relationship between mesothelioma and asbestos has also been well demonstrated by numerous experimental studies carried out in rodents. It must be noted that in animals, other types of fibers also induce MM. Some samples of asbestos fiber substitutes, refractory ceramic fibers (RCF) and glass fibers, have induced MM after inhalation by rats or hamsters. These data have been described in detail in several IARC monographs and summarized in peer reviews [19]. Other routes of exposure by intracavitary pleural or peritoneal injection have illustrated the carcinogenic potency of these mineral fibers. Both types of exposure have been used to assess fiber parameters modulating the oncogenic response in the pleura. It can be emphasized here that fiber-induced MM show similar morphological features in rodents as in humans [20–23].

Some studies have investigated pleural responses to asbestos fibers after deposition in the lung. An inflammatory reaction characterized by the recruitment of inflammatory cells and the presence of growth factors in the pleural fluid was demonstrated [24]. These growth factors were able to induce proliferation of mesothelial cells in culture. This inflammatory response may be triggered by fiber translocation to the pleura as demonstrated in rodents exposed to glass fibers or to RCF [25, 26]. Several studies have demonstrated the presence of asbestos fibers in the human pleura [9, 10, 27]. Hypotheses on the mechanism of asbestos translocation have been recently discussed [3, 4]

Several fiber parameters are of importance in the mechanism of asbestos toxicity. In animal experiments, it was generally found that the fiber dimensions were important, with a greater carcinogenic potency of long and thin fibers in comparison with shorter fibers.

Mutations in malignant mesotheliomas have been investigated in animals after in vivo exposure to asbestos fibers. Table 17.1 summarizes genomic alterations in MM identified in asbestos-exposed animals. Although few studies have been performed, these results are consistent with observations made in human MM. Chromosome rearrangements were observed in wild-type animals exposed to asbestos. Mutations and base hydroxylation have been detected within several weeks after asbestos administration. At the gene level, no or few mutations were found in the tumor suppressor gene (TSG) tumor protein p53 (*Trp53*), both in wild-type rats and heterozygous *NF2* mice. Interestingly, genes at the *Ink4a* locus were deleted, as found in human MM. In MM from genetically modified mice, gene inactivation occurred by loss of heterozygosity (LOH). These studies suggest that asbestos fibers are genotoxic and can produce DNA strand breaks and chromosomal recombination.

Effects of Asbestos Fibers on Mesothelial Cells in Culture

While early studies have been carried out with cells of different species and tissues, rat and human mesothelial cells have been most widely used to study the response of mesothelial cells to asbestos fibers. Detailed data can be found in several reviews [37, 38].

Various types of asbestos fibers have been found to cause cytotoxic and genotoxic defects in primary cell cultures and in animals exposed to fibers [39]. Typically, chromosomal breaks, centromeric and telomeric alterations, and aneuploidy (a lower number of chromosomes in comparison with normal cells), polyploidy (twice or several times the normal number of chromosomes), and heteroploidy (an abnormal number of chromosomes) due to spindle defects are seen. Because of chromosomal breaks, as well as spindle and centrosomal damage, micronucleus formation is a

Table 17.1 Molecular alterations in mesothelial tissue and malignant mesothelioma developed in asbestos-exposed animals

Reference	Animal, type of experiment	Fiber type	Molecular alteration
	Rat		
Libbus et al. [28]	Rat, i.p. administration. Chromosome analysis in MM	Crocidolite Chrysotile	Loss of chromosomes X, 8, 16, 18, and 20. Translocations involving 5, 10, and 13, repeated points
Ni et al. [29]	Rat, i.p. administration. Investigation of p53 (exons 5–8) and *K-ras* (exons 1, 2) mutations in MM	Crocidolite	No mutation detected
Unfried et al. [30]	Rat, i.p. administration. Investigation of p53 mutations in MM	Crocidolite	No mutation detected in p53, while numerous base substitution were found in B[a]P-treated animals
Unfried et al. [31]	Big Blue rat, i.p. administration	Crocidolite	Significantly enhanced mutation rate of *lacI* gene from omenta 12 and 24 weeks postexposure[a]
Schürkes et al. [32]	Rat, i.p. administration	Crocidolite	Significantly enhanced level of 8-OH-dG in DNA from *omenta* 10–20 weeks posttreatment
	Mice		
Vaslet et al. [33]	Mice, *Trp53* heterozygous, i.p. administration. Gene analysis	Crocidolite	LOH at the *Trp53* locus
Fleury-Feith et al. [23]	Mice, *Nf2* heterozygous, i.p. administration. Gene analysis	Crocidolite	LOH at the *Nf2* locus
Altomare et al. [34]	Mice, *Nf2* heterozygous, i.p. administration. Gene analysis	Crocidolite	LOH at the *Nf2* locus. Deletion *INK4* locus
Lecomte et al. [35]	Mice, *Nf2* heterozygous, i.p. administration. Gene analysis	Crocidolite	LOH at the *Nf2* locus. Deletion *INK4* locus
Altomare et al. [36]	Mice, *Arf* heterozygous, i.p. administration. Gene analysis	Crocidolite	LOH at the *Arf* locus. Hemizygous loss of *Faf1* (Fas-associated factor 1)

i.p. intraperitoneal, *LOH* loss of heterozygosity
[a]G to T predominant (29 %) followed by deletion (26 %), G to A (20 %), G to C (12 %), A to T (6 %), A to G, and insertion (3 %), while controls' spontaneous mutations were G to T (19 %), deletion (5 %), G to A (57 %), G to C (14 %), A to T and A to G (0 %), and insertion (5 %)

typical feature of asbestos-induced genotoxicity, whereby genotoxic endpoints are quantitated by scoring the number micronuclei [40].

Table 17.2 summarizes genomic alterations in mesothelial cells in culture treated with asbestos fibers. Briefly, when exposed to asbestos fibers, mesothelial cells demonstrate phagocytic properties. Within hours, responses to oxidant stress, activation of the mitogen-activated protein kinase (MAPK) pathway, and induction of transcription factors are detected. Table 17.3 summarizes the activation of various signaling pathways in mesothelial cells in culture exposed to asbestos fibers. When incubated in the absence of serum or in low levels of serum concentration, cell proliferation was observed [65, 66]. In proliferating mesothelial cells, asbestos provoked a p53- and p21-dependent cell cycle arrest consistent with the induction of a DNA damage-induced response [58]. P53 was also induced in serum-deprived G0-synchronized mesothelial cells exposed to asbestos but failed to block cell cycle progression [67]. However, genotoxicity was also found, suggesting that the DNA repair mechanism was incomplete, error-prone, or impaired.

Several types of genetic damage have been found in asbestos-exposed mesothelial cells (Table 17.2). Briefly, DNA damage was demonstrated directly by the occurrence of DNA breakage [60, 68–70] and indirectly by the induction of DNA repair [55, 56]. Oxidation of deoxyguanosine has been reported in several studies. Notably, recurrent chromosome abnormalities have been reported. These consist in numerical and structural changes, including aneuploidy and polyploidy, micronucleus formation, and chromosomal missegregation [43, 45, 51, 52, 54, 57, 71]. Comparison between different studies showed that significant effects were found with doses of 0.5–1 μg/cm^2 [38]. These studies demonstrate that asbestos fibers are genotoxic for mesothelial cells, able to produce base hydroxylation, DNA breakage, and numerical and structural chromosomal changes in mesothelial cells. DNA repair processes are stimulated in asbestos-treated mesothelial cells. The consequences of DNA damage will be dependent on the efficiency and fidelity of repair. When genomic damage is extensive, an apoptotic program should be induced. As discussed previously, life-or-death decisions may be at the heart of malignant transformation, and defective mechanisms of arrest or apoptosis may be critical to the development of malignancy [72]. Several studies with mesothelial cells in culture have emphasized the occurrence of apoptosis, which should be beneficial for the

Table 17.2 Molecular alterations in mesothelial cells in culture treated with asbestos fibers

Reference	Cells, type of experiment	Fiber type	Molecular alteration in comparison with untreated or sham cells
	Human		
Lechner et al. [41]	Normal cells. Karyotype analysis of cells after several passages	Amosite	Numerical and structural chromosomal abnormalities from passage 5
Olofsson et al. [42]	Normal cells. Karyotype analysis (G banding)	Crocidolite Chrysotile Amosite	Nonrandom aneuploidy, deletion, translocations, inversions (but not breaks, dicentrics, fragments, polyploidization)
Pelin et al. [43]	Normal cells from different donors[a]. Chromosomal aberrations in metaphases in six donors	Amosite	Increased chromosome breakage in four cases. Independent of *GSTM1* status
Burmeister et al. [44]	Normal cells and human MeT-5A. DNA breakage (comet assay, quantification of DNA strand breaks and Fpg-sensitive sites by alkaline unwinding[b])	Crocidolite Chrysotile	DNA breakage in both assays, but no increase in Fpg-sensitive sites No effect on MeT-5A cells
Poser et al. [45]	Normal cells. Micronucleus assay and kinetochore analysis	Crocidolite Chrysotile	Micronucleus formation, chromosome breakage. Role of ROS[c] and metals
Chen et al. [46]	MeT-5A. Formation of 8-oxo-2′-deoxyguanosine released in the culture medium (HPLC)	Crocidolite	Increased level of 8-oxo-2′-deoxyguanosine
Fung et al. [47]	MeT-5A. Formation of 8-OH-dG in DNA (HPLC)	Crocidolite	Decreased level of 8-OH-dG
Jensen and Watson [48]	MeT-5A. High-resolution time-lapse microscopy	Crocidolite Chrysotile	Delayed cytokinesis. Formation of bi- and multinucleated cells
Nygren et al. [49]	MeT-5A. DNA breakage (comet assay)	Crocidolite	Increased DNA breakage, more pronounced in cells associated with fibers than in cells without fibers
	Rat		
Jaurand et al. [50]	Pleural mesothelial cells. Morphological study of metaphases	Chrysotile	Increased chromosome breakage
Achard et al. [51]	Pleural mesothelial cells. Sister chromatid exchanges	Crocidolite	Increased sister chromatid exchanges
Wang et al. [52]	Pleural mesothelial cells. Ultrastructural study of metaphases	Crocidolite Chrysotile	Polyploidization, chromosome deformities (vacuolization)
Renier et al. [53]	Pleural mesothelial cells. DNA repair (unscheduled DNA synthesis)	Chrysotile	Increased DNA repair
Yegles et al. [54]	Pleural mesothelial cells. Morphological study of mitotic cells	Crocidolite Chrysotile	Increased aneuploidy and few structural chromosomal abnormalities. Increased anaphase/telophase abnormalities
Dong et al. [55]	Pleural mesothelial cells. DNA repair (unscheduled DNA synthesis)	Crocidolite Chrysotile	Increased DNA repair. Partial involvement of ROS
Dong et al. [56]	Pleural mesothelial cells. DNA repair (poly(ADP-ribose) synthesis)	Crocidolite Chrysotile	Increased DNA repair. Partial involvement of ROS
Yegles et al. [57]	Pleural mesothelial cells. Morphological study of mitotic cells	Crocidolite Chrysotile Amosite	Induction of abnormal anaphases and telophases
Fung et al. [47]	Pleural mesothelial cells. Formation of 8-OH-dG in DNA (HPLC)	Crocidolite	Increased level of 8-OH-dG
Levresse et al. [58]	Pleural mesothelial cells. Cell cycle analysis	Crocidolite Chrysotile	G2/M accumulation. G0/G1 accumulation and time-dependent p53 and p21 expression (chrysotile). Delay in the G1/S transition paralleling a low rate of p53 expression (crocidolite)
Fung et al. [59]	Pleural mesothelial cells, induction of the enzyme apurinic/apyrimidinic endonuclease	Crocidolite	Increased level (mRNA and protein)

(continued)

Table 17.2 (continued)

Reference	Cells, type of experiment	Fiber type	Molecular alteration in comparison with untreated or sham cells
	Rabbit		
Liu et al. [60]	Pleural mesothelial cells. DNA breakage (alkaline unwinding ethidium bromide fluorometric assay)	Crocidolite	DNA breakage. Cell cycle arrest in G2/M. Phagocytosis reduction by cytochalasin reduces DNA breakage

Met-5A: an SV40-transformed human mesothelial cell line
ROS reactive oxygen species
[a]The glutathione S-transferase M1 (GSTM1) genotypes of the patients were determined
[b]Fpg protein, which recognizes oxidized bases such as 8-oxo-guanine, is used as indicative of oxidative DNA-base modifications
[c]Reduction of micronucleus formation by antioxidants (metal chelators and ROS scavengers). ROS produced by fibers (crocidolite) and phagocytosis

Table 17.3 Activation of signaling pathways in mesothelial cells in culture exposed to asbestos fibers

Reference	Cells/experiment	Fiber type	Signaling response in comparison with untreated cells
Janssen et al. [61]	Pleural mesothelial cells from rat	Crocidolite Chrysotile	Increased mRNA expression of c-*fos* and c-*jun*
Timblin et al. [62]	Pleural mesothelial cells from rat	Crocidolite	Increased mRNA and protein expression of c-*fos* and c-*jun*
Zanella et al. [63]	Pleural mesothelial cells from rat	Crocidolite	Increased expression of mRNA c-*fos* via enhancement of EGFR level
Berken et al. [64]	Pleural mesothelial cell line nontumorigenic (4/4) from rat	Crocidolite	Activation of Erk1/2 and Akt in a β-integrin-dependent manner
Altomare et al. [36]	Culture of mesothelioma cells from mesothelioma form heterozygous *Arf* $^{+/-}$mice i.p. administration	Crocidolite	Regulation of NF-κB dependent on *Faf1* expression in response to TNF-α. Upregulated in cell showing loss of *Faf1* (see Table 17.1)

Met-5A: an SV40-transformed human mesothelial cell line

mesothelium. However, some cells can survive with gene alterations that can be inherited in daughter cells. In that context, it is remarkable that mesothelial cells show both cell cycle arrest and mitotic abnormalities, suggesting that the cells could pass through cell cycle checkpoints with unrepaired DNA and chromosomal damage.

According to our knowledge, no data on epigenetic changes in asbestos-exposed cells in culture or in animals have been reported. Further investigations would be of great interest for our understanding of the mechanism of action of asbestos fibers in carcinogenesis.

MM in Genetically Modified Mice

Several models of MM have been developed using genetically modified mice exposed to mineral fibers. One study was based on mice carrying a heterozygous mutation in the TSG *Trp53* (*Trp53*$^{+/-}$), and others on mice heterozygous for a mutation on the neurofibromin 2 gene (*NF2*), a TSG known to be inactivated in human MM (*Nf2*$^{+/-}$mice). Interestingly MM cells obtained from *Trp53*$^{+/-}$mice exhibited *Trp53* LOH and polyploidy [73]. LOH of the *Nf2* gene was found in *Nf2*$^{+/-}$mice, suggesting a common mechanism for loss of the wild-type (WT) allele [23, 34]. Moreover, in *NF2*$^{+/-}$mice, two other TSG, cyclin-dependent kinase inhibitor 2a (*p16*/*cdkn2a*) and cyclin-dependent kinase inhibitor 2b (*p15*/*cdkn2b*), were deleted at a high rate, similar to human MM, while *Trp53* was mutated at a much lower rate [34, 35]. In studies carried out by one of us (MCJ), *Nf2* and *Trp53* were exclusively inactivated. Spontaneous MM in the absence of asbestos exposure have been generated in double mutants *Nf2*$^{+/-}$;*Trp53*$^{-/-}$ and *Nf2*$^{+/-}$; *Ink4a*/*Arf*$^{-/-}$ mice. MM developed rapidly and at a high incidence [74]. These results suggest that MM development can be associated with the inactivation of TSG involving several pathways including *Trp53* or *Nf2* and genes at the *Ink4a* locus, the two latter genes being more specific targets of asbestos effects. Murine MM closely mimicked the human disease characterized by peritoneal ascites, a long latency between fiber injection and MM development, and histological subtypes, epithelioid, sarcomatoid, and biphasic, similar to human MM. The results obtained with genetically modified mice show that MM progression could follow several routes involving different TSG and are in good agreement with (i) specific clinical features and molecular alterations in human MM and (ii) the role of tobacco smoke in cancer development. It is generally accepted that MM is not related to smoking and that p53 mutation is a signature of tobacco smoke, consistent with no signature of tobacco smoke in MM development. Nevertheless, this strongly suggests that other carcinogens targeting p53 that could reach the pleura would be able to induce MM.

Fiber Properties in Relation to the Biological Effects and Carcinogenic Potency

This chapter will discuss the biological mechanisms leading to the development of diffuse malignant mesothelioma, focusing on the physiochemical properties of asbestos fibers, carbon nanotubes, and other engineered high-aspect-ratio nanomaterials relevant for the pathogenesis of this cancer. The reader is referred to the comprehensive reviews cited above for a detailed summary of the toxicological studies related to biological activity of carbon nanotubes.

Mineral Fibers

Asbestos and erionite are naturally occurring fibrous minerals that have been associated with the development of diffuse malignant mesothelioma in epidemiological studies [75, 76]. Asbestos fibers are fibrous silicates and are classified into two groups based on their crystal structure and chemical composition: serpentine asbestos which is called chrysotile and amphibole asbestos which includes crocidolite, amosite, tremolite, actinolite, and anthophyllite [77, 78]. Erionite fibers are a form of the mineral zeolite characterized by a high internal surface area [79]. These naturally occurring fibrous minerals are variable with respect to chemical composition, associated minerals, and trace contaminants depending on their geographic origin [80]. Asbestos fibers may contaminate other mineral deposits, for example, talc [75, 81] and vermiculite from Libby, Montana [81, 82], and exposure to these mixed materials has also been linked with diffuse malignant mesothelioma [79, 83]. The physiochemical properties of mineral fibers associated with biological activity include shape and dimensions, surface chemistry and reactivity, and biopersistence [19].

Shape and Dimensions

Elongated fibers with a high aspect ratio, defined as a length/diameter ratio of 3:1 or greater, are characteristic of the crystalline structure of the mineral. Asbestos fibers occur as bundles of individual crystals or fibrils that split longitudinally at the silicate layers. Fiber length and diameter determine the respirability and site of deposition in the lungs, and fiber length is related to efficiency of phagocytosis by alveolar macrophages and rate of clearance from the lungs [19].

Titanium dioxide nanorods have been shown to induce frustrated phagocytosis and activation of the Nalp3 inflammasome [84] similar to asbestos fibers [85]. Carbon nanotubes have also been shown to induce frustrated phagocytosis by macrophages in vitro [86]. In rodents, long rigid carbon nanotubes have been shown to translocate to the subpleural regions of the lungs [87–90] and to induce inflammation, frustrated phagocytosis, and granulomas similar to asbestos fibers following intraperitoneal injection [86]. Direct intraperitoneal [91] or intrascrotal injection [92] of some commercial carbon nanotubes induced diffuse malignant mesothelioma in heterozygous p53-deficient mice and wild-type rats, respectively. However, short multiwalled carbon nanotubes (<1 μm long) did not induce mesotheliomas in rodents following intraperitoneal injection [93].

Surface Chemistry and Reactivity

Serpentine or chrysotile asbestos is a magnesium silicate (Mg_3 $Si_2O_5(OH)_4$); Al^{3+} or Fe^{2+} may substitute for Si^{4+} or Mg^{2+}. Amphibole asbestos fibers are double-chain silicates containing a variety of cations including Fe^{2+}, Fe^{3+}, Mg^{2+}, Al^{3+}, Ca^{2+}, and Na^{+}. Surface chemistry determines interactions between the fiber, physiological fluids, and cells with possible proton transfer, oxidation-reduction reactions, and adsorption of biological macromolecules [79]. Broken chemical bonds at the fiber surface are highly reactive with molecular oxygen and can generate free radicals in aqueous fluid [94]. Surface Fe^{2+} and Fe^{3+} ions on amphibole asbestos fibers are bioavailable and catalyze formation of reactive oxygen species (ROS) [95]. Erionite fibers can acquire Fe^{2+} and Fe^{3+} ions and become redox active in the presence of intracellular chelators or reductants such as citrate or ascorbate [96]. Iron-catalyzed redox activity has been associated with biological effects of mineral fibers including lipid peroxidation, oxidative DNA damage, and activation of intracellular signaling pathways [97, 98].

Genotoxicity of natural and man-made fibers has been linked with surface reactivity, especially redox activity, as detected using acellular assays for free radical generation [99], induction of micronuclei [37], and mutagenicity using a hamster-human hybrid cell line [100]. Amphibole and chrysotile asbestos fibers show strong activity using these assays, while silicon carbide fibers show no free radical activity [99]. Refractory ceramic fibers contain bioavailable iron and are active in the salicylate assay to detect release of hydroxyl radicals [99]. Chrysotile asbestos fibers, tremolite (an amphibole fiber that contaminates chrysotile deposits), and erionite are mutagenic in the hamster-human hybrid cell line, while refractory ceramic fibers are non-mutagenic [100].

The ability of carbon nanotubes to generate free radicals is controversial. Some commercial carbon nanotube samples have not been shown to generate carbon- or oxygen-centered free radicals using spin-trapping and electron spin resonance [89, 101]. In fact, carbon nanotubes can scavenge hydroxyl and superoxide radicals which has been attributed to defects in the graphene sidewalls creating gaps in the carbon lattice and dangling bonds [102]. Multiwalled carbon nanotubes are not directly mutagenic in bacterial reverse mutation assays [103]. Agglomerated multiwalled carbon nanotubes are also negative in this assay and do not induce chromosome aberrations in the V79 cell assay [104]. Long multiwalled carbon nanotubes, but not short multiwalled carbon nanotubes or long single-walled carbon nanotubes, induced DNA strand

breaks in human lung epithelial cells [105]. Multiwalled carbon nanotubes also induced micronuclei in rat lung epithelial cells in culture and in animals [106]. Single-walled carbon nanotubes, carbon nanofibers, and graphite nanofibers induced micronuclei in V79 cells [107] and human bronchial epithelial cells [108]. Both single-walled and multiwalled carbon nanotubes have been shown to induce oxidative stress, DNA damage, and activation of intracellular signaling pathways in cultures of human mesothelial cells [109, 110].

Direct generation of ROS at the surface of asbestos or erionite fibers may be amplified by secondary generation of reactive oxygen and nitrogen species by target cells, including inflammatory cells and mesothelial cells in the pleural lining [97, 111]. Target cells generate endogenous ROS and reactive nitrogen species during the process of phagocytosis [112], disruption of mitochondrial electron transport [98], and activation of inducible nitric oxide synthase generating nitrogen-derived radicals [113]. These exogenous and endogenous reactive oxygen and nitrogen species have multiple effects on target cells in the pleura that amplify the inflammatory response; activate inflammatory cells to release chemokines, cytokines, and other mediators; stimulate cell proliferation; and induce cell injury and apoptosis [85, 97].

Fiber length has also been associated with the induction of aneuploidy and chromosomal damage due to direct physical interference with the mitotic apparatus [37, 114] or by binding to cell cycle regulatory proteins [115]. The induction of chromosomal breaks and aneuploidy has been shown for single-walled carbon nanotubes and carbon nanofibers in V79 cells [107] and for single-walled and multiwalled carbon nanotubes in rat [106] and human [108] lung epithelial cells. These direct physical effects of long, thin fibers on target cells in the lungs and pleura raise concern about the potential carcinogenicity of man-made mineral fibers that have been developed as asbestos substitutes [19] or engineered fibrous nanomaterials including carbon nanotubes [4, 116] and metal and metal oxide nanorods or nanowires [84]. Although these man-made fibers and engineered nanomaterials may not have intrinsic redox activity, other surface properties (e.g., structural defects or carbonaceous residues on the surface of carbon nanotubes) may generate oxygen-derived radicals.

Biopersistence

A major determinant of fiber pathogenicity is biopersistence in the lungs [19]. If long fibers are not efficiently cleared or destroyed by physical breakage, splitting, or chemical dissolution in the lungs, they are called biopersistent [19]. Differences in biopersistence of asbestos fibers have been linked with carcinogenic potency, as biopersistent fibers could sustain a local inflammatory response [117]. Amphibole asbestos fibers are more potent than chrysotile asbestos fibers due to their increased biopersistence in the lungs. However, fiber biopersistence in the pleura is not documented; in particular, there are no data on the relationship between biopersistence in the lung and translocation of fibers from the lung to the pleura, nor on the pleural clearance of fibers following inhalation [118, 119].

Biopersistence of natural and man-made fibers in the lungs [120] or peritoneal cavity [121] is an important characteristic of fibrous materials that induce lung cancer and diffuse malignant mesothelioma in rodents following inhalation [19]. Man-made mineral fibers developed as asbestos fiber substitutes, especially refractory ceramic fibers [26] and silicon carbide whiskers, have been shown to be biopersistent [122] following inhalation by rodents. Following inhalation by hamsters, refractory ceramic fibers translocated to the pleura and induced mesothelial cell proliferation and fibrosis [26]. Refractory ceramic fibers also induced pleural malignant mesotheliomas after chronic inhalation by rats and hamsters [19]. Intrapleural [123] or intraperitoneal injection of silicon carbide whiskers [124] also induced diffuse malignant mesothelioma in rats. Although no malignant mesotheliomas have been reported in worker cohorts involved in manufacturing and application of refractory ceramic fibers, the rodent carcinogenicity assays raise concern that long thin biopersistent mineral fibers may be carcinogenic [125]. Erionite fibers are very potent in the induction of malignant mesotheliomas following intrapleural injection [126] or inhalation [127].

Natural and man-made fibers are not unique in the induction of rodent malignant mesotheliomas following intraperitoneal or intrapleural injection. A variety of chemicals, radionuclides, SV40 virus, and metallic nickel particles are also carcinogenic in this rodent bioassay [128]. From a mechanistic viewpoint, ferric saccharate, nitrilotriacetic acid, nickel particles, and alpha- or beta-emitting radionuclides are notable in their abilities to generate reactive oxygen species [129].

Unfunctionalized carbon nanotubes are bioperistent when assessed in acellular assays [130]; however, carboxylated single-walled carbon nanotubes are susceptible to enzymatic [131] or oxidative degradation [132]. In principle, carbon nanotubes could be engineered to alter their physiochemical properties in order to decrease their biological reactivity and potential carcinogenicity.

High aspect ratio and biopersistence [4, 133] have been hypothesized to be important properties of engineered nanomaterials that raise concern about their potential to be translocated to and retained in the pleura following inhalation. So far, this hypothesis has not been tested in any long-term inhalation studies of high-aspect-ratio engineered nanomaterials in rodents.

Unique Characteristics of Nanomaterials

Additional features of engineered carbon nanomaterials that may alter their biological activity include their purity, rigidity, hydrophobicity, and agglomeration state. Carbon

nanotubes are frequently produced commercially in the presence of metal catalysts including nickel, iron, cobalt, and yttrium [134]. Other potential contaminants include combustion-derived products such as polycyclic aromatic hydrocarbons [134]. Amorphous carbon residues at the graphenic surface of carbon nanotubes may also contribute to surface reactivity [106]. The bioavailability of metal catalyst residues is variable depending on the purity of carbon nanotubes; redox-active metal catalyst residues can generate reactive oxygen species leading to cell toxicity, inflammation, activation of intracellular signaling pathways involving the MAPK and the nuclear factors NF-KB and AP-1 [97], and genotoxicity [116]. Carbon nanotubes can be highly variable in length ranging from 1 nm to 1 mm. Although short nanotubes and nanofibers less than 5 μm in length should be more easily phagocytized and cleared following inhalation [4], they may behave as needles and penetrate into cells and the nucleus where they could directly damage chromosomes and DNA [116]. Unfunctionalized carbon nanomaterials are very hydrophobic and tend to form agglomerates or bundles called nanoropes, although individual carbon nanotubes have been detected in aerosols [135]. Hydrophobic nanomaterials may interact differently with biological macromolecules in comparison with hydrophilic crystalline mineral fibers [136]. Very thin, hydrophobic carbon nanotubes may bend and agglomerate to form spherical aggregates that are more readily phagocytized than long, rigid multiwalled carbon nanotubes that have been shown to induce frustrated phagocytosis resulting in impaired clearance and translocation to the pleura [4, 137]. The extent of agglomeration has also been shown to influence cell toxicity: ropelike agglomerates of carbon nanotubes were shown to be more toxic than crocidolite asbestos fibers using a mesothelioma cell line [136]. Finally, structural defects at carbon nanotube surfaces attributed to imperfections in the graphene lattice or defects leading to surface oxidation and increased hydrophilicity have been shown to contribute to acute toxicity and genotoxicity of even short multiwalled carbon nanotubes [106].

The potential of engineered carbon nanotubes to induce pathological reactions (lung inflammation, fibrosis, and diffuse malignant mesothelioma) similar to asbestos fibers has generated significant controversy and concern for occupational safety and health [133, 138]. Occupational exposures via inhalation, skin contact, and ingestion are possible during the synthesis, handling, and fabrication steps of engineered carbon nanotubes; airborne mass concentrations in the range of 0.7–430 μg/m^3 have been detected at eight worksites and research laboratories [139]. Several recent reviews have summarized the numerous in vitro cellular and rodent toxicology studies investigating biological activity and potential toxicity of carbon nanotubes [111, 135, 137, 139].

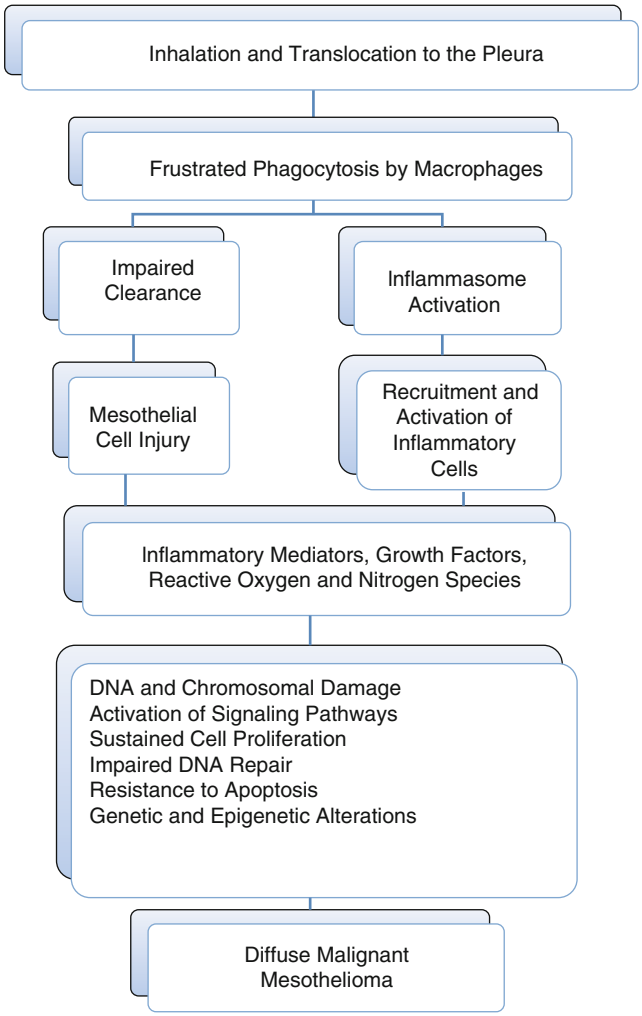


Fig. 17.1 Multistage development of asbestos-induced mesothelioma (Adapted from Shukla et al. [97]; Nymark et al. [140]; Pacurari et al. [135]; and Broaddus et al. [141])

Summary Hypotheses on the Mechanism of Action of Asbestos Fibers to Generate Mesothelioma

The development of diffuse malignant mesothelioma is a complex, multistage process that is governed by the physicochemical properties of crystalline mineral fibers and their propensity to migrate to the pleural and peritoneal linings as summarized in Fig. 17.1. The most important properties of asbestos fibers related to carcinogenicity are fibrous shape and dimensions, surface chemistry and reactivity, and biopersistence [19]. Long, rigid biopersistent fibers that are translocated to the pleura are trapped on the parietal pleura lining at the sites of lymphatic openings [27] and incite a persistent inflammatory response [4]. The pleura is covered by a thin, single layer of mesothelial cells that have lower antioxidant defenses than lung epithelial cells [142].

Interactions between mesothelial cells and fibers can cause genetic and chromosomal changes. There is a great body of evidence (1) that asbestos fibers can directly interfere with chromosomes and the mitotic spindle [41, 143, 144] and (2) that they induce the formation of reactive oxygen species (ROS) resulting in DNA breaks, oxidation, and mutations [145]. Further, (3) the physical interaction of fibers with target cells causes persistent inflammation and, consequently, modulation of inflammatory and immune responses.

ROS have been clearly indicated to cause genetic damage including chromosomal breaks and mutations [145]; and they are well shown to initiate signal transduction pathways that are, in turn, linked to inflammation, proliferation, and apoptosis [146]. Free radical scavengers have been reported to decrease genotoxic endpoints such as micronucleus formation induced by fibers [147]. Further, there is clear-cut evidence that antioxidant enzymes can protect cells against genotoxicity induced by chrysotile fibers [148].

Prolonged interaction between pleural inflammatory cells and adjacent mesothelial cells causes persistent release of chemokines and cytokines, inflammatory mediators, reactive oxygen and nitrogen species, and growth factors that trigger repeated episodes of inflammation resulting in mesothelial cell injury, death, and proliferation [149]. In this chronic inflammatory microenvironment, genomic instability and acquired genetic and chromosomal alterations in mesothelial cells may lead to altered cell cycle and growth regulation, resistance to apoptosis [150], impaired repair of DNA and chromosomal damage induced directly or indirectly by asbestos fibers [37, 114], and activation of oncogenes and inactivation of tumor suppressor genes [151]. Persistent inflammation has also been linked with altered gene methylation patterns identified in diffuse pleural malignant mesotheliomas in humans [152]. DNA methylation leads to epigenetic gene silencing and has been linked to inflammation-mediated damage to cytosine [153] or endogenous generation of methyl radicals [154]. This persistent inflammatory microenvironment in combination with oxidative stress generates a strong selective force for mesothelial cells that have acquired genetic and epigenetic changes that promote their survival, proliferation, and tumor progression [155].

Mesothelial Cells and Malignant Mesothelioma

The Mesothelial Cell In Situ: Normal Cells

The mesothelium consists of a monolayer of mesothelial cells lying on a basement membrane and supported by connective tissue stroma containing fibroblasts. Mesothelial cells provide a protective barrier for frictionless interface for the free movement of apposing organs and tissues and in fluid transport across the pleura [156]. Mesothelial cells may have specialized functions at different anatomical sites, as demonstrated by morphological studies at the ultrastructural level [157]. Mesothelial cells play a role in the resolution of inflammation and tissue repair after pleural injury. Fibrosis is a potential outcome of chronic inflammation. These processes are of particular interest in investigating the mechanism of action of asbestos fibers in the pleura.

So far, the mechanism of mesothelial cell regeneration is poorly understood, mostly in the context of serosal injury following dialysis; however, some controversial hypotheses have been formulated. Recent comprehensive reviews summarize our present knowledge of these potential mechanisms [158, 159]. The regeneration process has been studied experimentally following mechanical, chemical, or heat injury of the peritoneal serosa. Briefly, six mechanisms have been suggested to replace the injured mesothelial cells: (1) centripetal migration of adjacent mesothelial cells, (2) exfoliation of mature or proliferating mesothelial cells that replicate on the wound surface, (3) preexisting free-floating serosal cells having the capability to differentiate into new mesothelium, (4) macrophage transformation into mesothelial cells, (5) submesothelial mesenchymal precursors that migrate to and differentiate at the mesothelium surface, and (vi) bone marrow-derived circulating precursors [159].

The origin of these new mesothelial cells has not yet been confirmed, but according to Mutsaers et al. [158], mesothelial regeneration is not dependent on subserosal cells, but more likely results from implantation, proliferation, and incorporation of free-floating mesothelial cells [160].

The Malignant Mesothelioma Cell

Role of Gene Mutations in the Neoplastic Transformation of Mesothelial Cells

Carcinogens provoke several types of somatic gene mutations, consisting of DNA and chromosome alterations. Some mutations are the signature of past exposure to one or several given carcinogens. Somatic mutations in tumors are of interest both to determine the mechanism of action of carcinogens and to elucidate their adverse consequences on cellular homeostasis.

In malignant pleural mesothelioma (MPM), there are a limited number of genes known to be recurrently mutated. Mutations in TSG cyclin-dependent kinase inhibitor 2A (*P16*/*CDKN2A*), an alternative open reading frame of *CDKN2A* generating a distinct protein (*P14*/*ARF*); cyclin-dependent kinase inhibitor 2B (*P15*/*CDKN2B*); and *NF2* have been reported in a high percentage of MM, and *TP53* (tumor protein p53) has been found mutated at a lower rate in comparison with other human cancers [161–163]. These

genes play a role in cell cycle regulation at different levels. The *CDKN2A* locus encodes two different proteins, $p16^{INK4A}$ and $p14^{ARF}$, while *P15/CDKN2B* encodes one protein $p15^{INK4B}$. Both $p16^{INK4A}$ and $p15^{INK4B}$ are inhibitors of the kinase function of cyclin/cdk complexes involved in cell cycle progression. *TP53* encodes a protein, p53, which is activated in response to DNA damage and is a regulator of apoptosis. The protein $p14^{ARF}$ has an indirect function on cell cycle regulation, by positively regulating the level of p53 through interaction with p53 inhibitors. Consequently, cells with damaged DNA can proliferate and survive in the absence of $p14^{ARF}$. Interestingly, all of these genes carry different types of mutations. The most frequent alteration at the *P16/CDKN2A* and *P15/CDKN2B* loci is homozygous deletion in about 70 % of MM cases [163]. In murine models of asbestos-induced mesothelioma, the orthologous genes, *p16/Cdkn2a* and *p15/Cdkn2b*, were also inactivated by deletion [34, 35, 164]. It can be also noted that *P16/CDKN2A* deletions have been considered as a marker of asbestos exposure in a study of non-small cell carcinomas [165]. However, in MM, DNA methylation of *P16/CDKN2A* and *P15/CDKN2B* has been reported at a frequency of 13 % (nine patients) and 4 % (three patients), respectively, and positively correlated with asbestos body counts in the lung [152, 166]. The average methylation frequency of these genes in the literature is about 10 % [35, 166–171]. It was also suggested that mesotheliomas express microRNA (miRNA) that could inhibit *P16/CDKN2A* expression, based on in silico analysis for miRNA target gene prediction [172].

Point mutations are the main types of alterations of *TP53* in MM. Six point mutations are indicated in the IARC p53 database, five missense mutations and one stop mutation [173]. So far, no specific type of mutation in *TP53* has been related to asbestos exposure. In lung cancer, G:C-to-T:A transversions are generally interpreted as mutagenic fingerprints of tobacco smoke [174]. This base substitution can be due to the formation of 8-OH-deoxyguanosine generated by oxidative damage, which in turn causes primarily G-to-T transversions. A few studies have reported *TP53* mutations in relation to asbestos exposure. In lung cancer, the frequency of mutations was diminished in lung adenocarcinomas of asbestos-exposed subjects in comparison with unexposed patients, but the difference was not significant [175]. G-to-T transversions in asbestos-exposed lung cancers have been reported, but not in all studies, and G:C-to-A:T transitions are rare [175].

TP53 mutations reported in MM consisted of different types of base substitution and base deletion, but G:C-to-A:T transitions seem to be the most frequent [173] (unpublished data from MCJ). In animal models of MM, the mutated status of *Trp53* was investigated in mice exposed to mineral fibers by intraperitoneal inoculation. In C57Bl/6 $p53^{+/-}$mice, a strain having one allele mutated in the gene *Trp53*, loss of the wild-type allele was found at a high rate in MM induced by asbestos fibers [33]. In $Nf2^{WT}$ and $Nf2^{+/-}$FVB mice, *Trp53* alterations were infrequent. Two point mutations, A:T to C:G, were detected in mice exposed to asbestos, and two point mutations, A:T to G:C and A:T to T:A, and a duplication of 12 bases in MM were found in mice exposed to ceramic fibers [35, 164]. Alteration in the chromosomal region of the *Trp53* locus was infrequent [176]. These results suggest that deletions would be more likely a consequence of the mechanism of action of asbestos, while p53 point mutations could be related to "spontaneous" gene alterations in this model.

The alterations of *NF2* TSG are frequently found in about 50 % of MPM [177, 178]. This gene encodes merlin, a protein found in cell-cell junctions and microvilli and regulating contact-dependent cell proliferation [179, 180]. *NF2* has pleiotropic functions, being involved in regulation in cell proliferation, apoptosis, and endocytic trafficking and acting upstream of the Hippo signaling pathway [181]. Mutations in *NF2* consist of both point mutations and deletions [151]. So far, there is no explanation for the high level of alterations in *NF2* in MPM. However, some hypotheses can be formulated and will be discussed below (see section "Conclusion").

Role of Genomic Alterations in the Neoplastic Transformation of Mesothelial Cells

Chromosome banding, fluorescence in situ hybridization, flow cytometry, Southern blotting and chromosome and array comparative genomic hybridization, single-nucleotide polymorphism (SNP) array, and representational oligonucleotide microarray analysis (ROMA) as well as second-generation sequencing analyses all indicate complex genomic alterations in MM [182–192]. Typically, chromosomal abnormalities are very complex, even chaotic, that is, involving alterations both in chromosome structure and number [182, 184–186, 193–195]. It is characteristic for this disease that the chromosome number is mostly hypodiploid (less than 46 chromosomes, the normal number of chromosomes in human), but it varies greatly within a specimen, as a given tumor can exhibit a variety of hypodiploid metaphases [182]. Similarly, polyploid forms (with a number of chromosomes twice or more the number of chromosomes present in the parental cell) of the hypodiploid clone are commonly encountered. Other cytogenetic alterations may be observed such as diplochromosomes of endoreduplication which are a signature of alteration of the mitotic process. The polyploidization and nondisjunction type of aneuploidy are due to fiber-induced damages to the structures involved in cell division, i.e., the middle spindle, centrosome, centriole, cleavage furrow, and cell membrane.

Similar to numerical chromosomal aberrations, structural aberrations in MM are highly variable. Typically, translocations, deletions, insertions, and inversions are seen.

Occasionally, double minutes and a homogenously staining region, representing cytological manifestations of gene amplification, are also observed. So far, translocations are mainly unbalanced, and no recurrent chromosomal translocations with known fusion genes have been reported. Due to the chaotic nature of these aberrations and methodological difficulties, the detection of specific chromosomal aberrations has been very difficult in karyotypic analysis. Novel next-generation sequencing methods, such as exome sequencing, have facilitated overcoming the abovementioned problems, and for the first time, fusion genes have been described in MM [190].

These described structural changes are mainly due to DNA breaks. The mechanism known as breakage-fusion-bridge phenomenon nicely explains severe chromosomal imbalances and intratumoral heterogeneity in MM [196]. As already mentioned, asbestos fibers are capable of causing DNA breaks either directly or indirectly through ROS generation. Whether there are hot spots in the genome for DNA breaks caused by fibers is still largely an open question. However, experiments with cells in culture have indicated that chromosome aberrations induced by fibers may be recurrent. Certain numerical chromosomal abnormalities have been reported to be overrepresented in human pleural cell cultures exposed to asbestos [42]. Even though no distinct hot spots were seen in this study, chromosome 1 seemed to be involved more often than other chromosomes. Interestingly, we have previously reported that structural aberrations in the short arm of chromosome 1 and loss of material in the short arm of chromosomes 1 and 4 were associated with high asbestos fiber burden in MM [197, 198]. More recently, one of us (DJ) identified a recurrent region of chromosome loss, 14q11.2-q21, in MM from asbestos-exposed patients that was not found in unexposed patients. The syntenic region was also lost in fiber-induced MM in mice, suggesting that this region might be a target of the action of mineral fibers [176].

Very recent experiments from one of us (SK), carried out with cell lines and with lung tumor tissues (not mesotheliomas) of patients who had been either exposed or unexposed to asbestos fibers, indicated a couple of asbestos-associated chromosomal areas. These findings are described in detail in Chap. XX. Even though chromosomal aberrations in MM are complex, they are not random and they are clonal in nature, originating from one cell. Chapter XX describes, in more detail, these recurrent aberrations and their clinical significance.

The chromosomal alterations characteristic of MM, such as hypodiploid chromosome number as well as deletions and losses in chromosomes 14 and 10, are not seen in lung adenocarcinoma, which helps in differential diagnosis of these malignancies [199, 200]. Interestingly, chromosomal aberrations in gastrointestinal stromal tumors (GIST) resemble those seen in MM [201]. To our knowledge, GIST is not, however, an asbestos-related tumor, but the similarities of chromosomal alterations may, instead, be related to similarities in mesenchymal stem cells from which the tumors originate.

To conclude, asbestos fibers cause a wide variety of chromosomal imbalances. Even though some of these changes may be recurrent, most of them are random. Various genetic changes caused by asbestos fibers offer a versatile genomic aberration reservoir, from which the aberrations promoting uncontrolled growth and malignant transformation are selected during the long initiation and progression (latency) period before tumor diagnosis. Variable chromosomal aberrations together with multifocal clonal evolution are consistent with this mechanism.

Role of Epigenetic Alterations in the Neoplastic Transformation of Mesothelial Cells

Altered gene expression in MPM could also be due to epigenetic mechanisms. MPM show specific patterns of gene methylation as compared to normal pleura or other tumors [152, 167, 170, 202, 203]. Data on methylation profiles of MPM will be described in detail in Chap. 24. Several studies suggested that DNA methylation at specific gene loci could be correlated with asbestos exposure. Significant associations between asbestos exposure and DNA methylation were first described in genes encoding heavy metal-binding proteins, *MT1A* and *MTA2*, with a positive association for *MT1A*, but not for *MT2A*. Asbestos exposure does not seem to be an independent variable in this study [204]. A trend toward an increasing number of methylated cell cycle control genes (*APC*, *CCND2*, *CDKN2A*, *CDKN2B*, *HPPBP1*, and *RASSF1*) and increasing asbestos body counts was observed [166]. These findings were confirmed in a more recent high-throughput methylation analysis underlining distinct methylation profiles between MPM from asbestos-exposed and unexposed patients and a significant positive association between asbestos fiber burden and methylation status of *CDKN2A*, *CDKN2B*, *RASSF1*, and *MT1A* and about 100 other loci [152].

MiRNAs are small (around 22 base pairs in size) RNAs that have a crucial role in posttranscriptional gene regulation. Their biosynthesis and functions have been described in more detail in Chaps. X and XX. It has been demonstrated that MPM has a characteristic miRNA profile and that different MPM histopathological subtypes can be discriminated according to their profiles (see Chap. XX). Even though significantly differentially expressed miRNAs discriminated MPM patients according to smoking habit, this did not significantly discriminate asbestos-exposed patients versus unexposed [172]. The reason for this may be the low number of nonsmoking patients. On the other hand, it is possible that patients classified into the unexposed category were actually

exposed to asbestos fibers. Recent results provide evidence that a group of miRNAs differentiates asbestos-associated lung adenocarcinomas from the nonassociated tumors [205]. The results of these lung carcinoma studies are presented in detail. As the mechanisms of the miRNA regulation are yet poorly understood, it is premature to speculate how asbestos fibers cause miRNA dysregulation seen in MM and in lung carcinomas. Nevertheless, some of them could be lost, as their loci are located in chromosomal regions frequently altered in MPM, and possibly linked to asbestos exposure, as was demonstrated for miR31 which is close to the *CDKN2A* locus [206]. So far, no experiments using cell cultures or experimental animals have been published that investigate miRNA profiles in asbestos-exposed cells or animals. Further investigations are needed to elucidate the mechanisms responsible for miRNA dysregulation and function in MM. In two MPM cell lines lacking either miR31 or miR29C, overexpression by transfection of these miRNAs decreased proliferation, migration, invasion, and colony formation [206, 207].

The molecular mechanisms responsible for epigenetic changes in MPM are poorly understood, and it is not known whether they are directly induced by asbestos or they are indirect effects. Nevertheless, as with chromosomal imbalances, they most likely play a role in mesothelial carcinogenesis.

Pathways Involved in the Neoplastic Transformation of Mesothelial Cells

Constitutive activation of several signaling pathways has been demonstrated in MPM by the occurrence of mutations and/or deregulated expression of specific regulators in comparison with normal mesothelial cells. These studies have been carried out in primary tumor samples but also in malignant mesothelial cell cultures developed from tissue samples. Pathway activation in MM has been shown by gene expression profiling. So far, the relationship between pathway activation and asbestos exposure has not been specifically investigated in MM. The effects of asbestos on mesothelial cells are discussed in paragraph 22-2.b.ii.

The Hippo Pathway. The Hippo pathway is of special interest regarding the high frequency of mutations detected in merlin encoded by the *NF2* gene. Merlin negatively regulates cell proliferation. Its activity is affected by interaction between extracellular signals and membrane proteins, and activated merlin transduces signals suppressing the transcriptional activity of YAP coactivator [163]. In a recent study, another negative regulator of the hippo pathway, *LATS2*, was found to be deleted in three out of six MM cell lines and in one out of 25 tumors by DNA sequencing analyses [208]. Merlin exists in two forms, active unphosphorylated or inactive phosphorylated. This later form is found in MPM cells possibly accounting for another mechanism for the deregulation of the hippo pathway in these cells [209].

Cell Cycle. The alteration of CDK inhibitor genes located at the *INK4* (*CDKN2A* and *CDKN2B*) locus, as mentioned above, contributes to uncontrolled cell proliferation. However, cell cycle control can be affected in MM cells not only by the loss of other negative regulators but also by the overexpression of cyclin-dependent kinases (CDKs), cyclins (CCNs), and regulators of the mitotic checkpoints. These alterations have been shown by gene profiling analyses using microarrays [210–212]. Overexpressed genes were involved in the regulation of all phases of the cell cycle and cell replication and control of cell cycle progression: cyclin-dependent kinase 1 (*CDK1*/*CDC2*); cell division cycle 6 (*CDC6*), a regulator of replication; cyclin-dependent kinase inhibitor 2C, p18 (*CDKN2C*); cyclin H (*CCNH*); cyclin B1 (*CCNB1*), controlling the cell cycle at the G2/M transition; and forkhead box M1 transcription factor (*FOXM1*), a regulator of gene expression in the G2 phase. Others are more specific of a response to DNA damage such as checkpoint kinase 1 (*CHEK1*). The protein encoded by this gene, Chk1, is required for checkpoint-mediated cell cycle arrest in response to DNA damage. Underexpression of cyclin D2 (*CCND2*), a regulator of Cdk4 and Cdk6, which controls the cell cycle at the G1/S transition, was also detected [210].

Several genes involved in the control of entry in mitosis and mitosis progression were also detected. Overexpression of aurora kinases has been reported in several studies [211, 213]. Stathmin, a gene involved in the regulation of the microtubule dynamics by inhibiting the formation of microtubules and/or promoting their depolymerization, was strongly overexpressed in MPM, resulting in protein overexpression [214, 215].

These results can account for the complex, even chaotic, chromosomal alterations mentioned above, as a result of defective control of cell cycle progression through different phases of the cell cycle, including dysregulation of mitosis.

Signaling Pathways. The MAPK signaling pathway controls cell proliferation and differentiation, survival, apoptosis, and Wnt signaling [216]. In normal cells, the MAPK pathway is triggered by the activating phosphorylation of tyrosine kinase receptors (RTKs), followed by a protein kinase cascade. Downstream networks from RTKs can be activated by RTK mutation or sustained signaling through autocrine or paracrine mechanisms.

The MAPK signaling pathway is constitutively activated in MM as demonstrated by the phosphorylation and activation of downstream proteins of the MAPK cascade, extracellular-regulated kinases (ERKs), Jun amino-terminal kinases/stress-activated kinases (JNKs/SAPKs), and p38 MAPK [217, 218] and inhibition of cell proliferation and induction of apoptosis by inhibitors of the pathway [219]. RTK activation can be achieved by a variety of growth factors, such as EGF family, PDGF, FGF, and HGF/SF, and cytokines such as TGF-ß, TNF, and IL1. In a recent study,

the relative levels of tyrosine phosphorylation of 42 distinct RTKs were determined in MM cell lines established from surgical specimens. Coordinated activation of several RTKs – EGFR, ERBB3, AXL, and MET – was found [220].

MPM cells express both vascular endothelial growth factor (VEGF) and the VEGF receptors (fms-related tyrosine kinases, *FLT1* and *FLT4*, and fetal liver kinase, *KDR*/*FLK1*) [221–224]. VEGF expression was enhanced in a large proportion of MPM in comparison with nonneoplastic specimens [225]. An autocrine role for VEGF in cell proliferation has been suggested [223, 226].

MM cell growth may also be linked to autocrine or paracrine stimulation by platelet-derived growth factor (PDGF), and the regulation by PDGF appears to be complex in MM cells. PDGF has been suggested as a regulatory factor for proliferation of MM cells, either directly or indirectly via the hyaluronan/CD44 pathway [227, 228]. Human MM cells express high levels of PDGF-A, PDGF-B, and PDGFR-B, while normal human mesothelial cells express low levels of PDGF-A mRNA chain and PDGFR-A [229, 230]. PDGF-A could contribute to tumor formation via a paracrine mechanism [231, 232].

Epidermal growth factor receptor (EGFR) is overexpressed in 44–97 % of MM as found by immunohistochemical studies, but no mutation was detected in contrast with others types of cancer [233].

Human MM cells express insulin growth factor (IGF) and insulin growth factor receptors (IGFR), and the activation of IGFR activates downstream signaling [234, 235]. IGF-I appears to function as an autocrine growth factor in human mesothelial cells [236]. IGFBPs also regulate IGF-dependent growth [235, 237, 238].

Hepatocyte growth factor receptor (MET) is a proto-oncogene. It is the receptor for the ligand hepatocyte growth factor/scattering factor (HGF/SF). Mutation in the *MET* gene has been detected in a few MM cell lines [239, 240]. Both MET and HGF/SF proteins are expressed in some MPM [241, 242]. In vitro HGF/SF increases spreading, motility, and/or invasiveness of mesothelial cell lines and inhibition of MET reduced cell proliferation [239, 243, 244]. The activation status of MET and other RTKs, EGFR family (Erb1, Erb2, Erb3), PDGF-A, and PDGFR-B, has been investigated in 20 MPM cell lines and 23 primary specimens of MPM, and the effect of MET-specific inhibitors (MET-shRNA interference vector and RTK inhibitors) was investigated on cell lines [240]. The results showed that inhibition of a single RTK was not sufficient to obtain a tumor suppressor effect but that inhibition of multiple RTK was required [240].

The activation of RTKs also induces activation of other downstream signaling cascades including phosphatidylinositol-3-kinase (PI3K-AKT) pathway, regulating cell survival and proliferation, cell migration, and apoptosis. The phosphorylation of AKT protein, the active form of the protein, and the activation of the Akt pathway have been demonstrated in MM cells [245, 246]. In *PTEN*, a TSG and negative regulator of the PI3K-AKT pathway, homozygous deletion has been reported in a small subset of MPM cell lines [247, 248].

The Wnt signaling pathway regulates developmental processes, cell proliferation, and cell polarity, and its activation prevents beta-catenin inactivation, a coactivator of transcription, allowing the expression of a variety of genes exerting pleiotropic effects [249]. However, cell growth inhibition and apoptosis of MPM cells was observed according to a beta-catenin-independent inhibition of Wnt signaling [250, 251]. In MPM, the Wnt pathway could be altered as a result of promoter hypermethylation of regulatory genes [250, 252, 253]. Gene expression profiling of MM cell lines, primary MPM tumors, and normal pleural tissue demonstrated that numerous Wnt and Wnt-related genes were upregulated and that some WNT antagonists were downregulated [254]. These results suggest that deregulation of the Wnt signaling pathway is involved in mesothelial carcinogenesis.

Apoptosis. The deregulation of signaling pathways likely plays an important role in the dysfunction of apoptosis in MPM. Moreover, specific regulators can contribute to MM resistance to apoptosis. In MM cells, apoptosis alteration can be due to the overexpression of the caspase-8 inhibitor, *FLIP*/*CFLAR*; the methylation of cell death agonist TRAIL receptors; and/or the low expression of proapoptotic proteins (Bax, Bak, Bad, Bid, or Bim) and high levels or activity of antiapoptotic proteins (Bcl-2, Bcl-xL, and Mcl-1) regulating mitochondrial function [246, 255–258].

Conclusion

Several hallmarks of cancer have been considered to contribute to neoplastic transformation [259]. These include direct molecular damage induced by carcinogens that alter the genome and induce dysregulated cellular functions and resistance to apoptosis. Neoplastic progression is associated with genetic and chromosomal instability. Genetic instability reflects unrepaired DNA damage which may arise from either increased rates of damage or defective mechanisms responsible for genetic integrity. Chromosomal instability arises from the dysregulation of mitotic checkpoints. As a consequence, cancer cells fail to control the cell cycle and to correct error-free DNA and to repair chromosome damage. Investigation of the mechanism of asbestos carcinogenicity has focused on interactions between asbestos and target cells, especially mesothelial cells, and early responses of lung and pleural cells to asbestos exposure. Studies of human MM cells provide the opportunity to identify the cellular and molecular changes that have accumulated over the latent period of 30–40 years since the beginning of asbestos exposure. However, the body of data obtained by these mechanistic

studies using cells and experimental animals reveal that all types of asbestos fibers induce early genetic changes directly and also indirectly due to the early recruitment of macrophages and inflammatory cells. These early genetic changes cause molecular alterations that perturb cell cycle control giving rise to sustained cell proliferation and additional genetic and chromosomal instability. Early activation of proliferation and survival pathways has been shown in asbestos-exposed mesothelial cells in culture in short-term experiments. The relationship between these early effects and the characteristics of MM cells studied 30–40 years after the beginning of exposure remains to be explored.

When the molecular status of human MM is placed in the context of results from studies with cells in culture and in animals, consistent mechanisms emerge. Among genes inactivated in MM, those at the *INK4* locus control the cell cycle, and loss of their function results in failure of cell cycle control. The functional consequences of *P14/ARF* loss are more complex. This does not seem to be associated with p53 degradation, as expected from the known negative regulation of p53 stability by $p14^{ARF}$ loss. In contrast, p53 appears to be stabilized in MM, suggesting basal overexpression and/or another type of dysregulation. The p53 protein is constitutively expressed, not only in MM cells in culture but also in immunohistological sections of primary tumors [260–263]. Candidates for p53 activation could be upregulation of IGF-1/AKT/mTOR pathway and altered energy metabolism, which have been identified as additional functions of p53, as recently reviewed [264]. The AKT/mTOR cell survival and growth pathway is activated in MM and linked to apoptosis resistance. It is remarkable that current approaches to control MM proliferation have focused on the resistance of MM cells to apoptosis [265, 266]. Energy metabolism of MM cells is characterized as aerobic glycolysis (the Warburg effect), and the p53 protein could be induced to shut down this pathway [264, 267]. The low rate of p53 mutations found in asbestos-induced MM in both humans and mice and the functional response of p53 in asbestos-exposed cells are consistent with these observations.

Transcriptional analyses suggest that cell cycle checkpoints are compromised in MM. Differential expression of genes encoding proteins involved in the control of mitosis, *AURKA*, *AURKB*, and *CHEK1*, has been reported in comparison with normal mesothelium or normal mesothelial cells. Aurora B (encoded by *AURKB*) is localized in the internal part of kinetochore and is the enzymatic component of the "chromosome passenger complex," which also includes the internal protein of the centromere, and is involved in mitotic spindle organization, chromosome segregation, and cytokinesis [268]. Those events are compromised in cells that have internalized asbestos fibers as demonstrated using different target cells, including mesothelial cells [48, 269, 270]. In their review, Lampson and Cheeseman [268] suggest Aurora B activity to be modulated by tension forces. Chromosome segregation is controlled at several levels, and chromosome movement is driven by motors that are linked to kinetochore-associated microtubules and the centrosome. Tensile strengths are developed during this process. So far, mechanical properties of carcinogenic fibers have not been taken into consideration, but it would be of interest to consider this parameter in the context of fiber interactions with the mitotic apparatus during cell division. Tensile strengths induce tissue and cell deformation. In a recent study carried out with nanoparticles, Mijailovich et al. [271] investigated the mechanisms by which deposited particles exert mechanical forces and provoke the particle indentation into the alveolar tissue. They found that these mechanisms are centered on a mechanical balance between surface tension forces and tissue elastic forces. These concepts should be considered to account for the effects of fibers on cells and tissues, especially during cytoskeleton remodeling and mitosis progression.

The alteration of *NF2* is also consistent with a physical mechanism of action of asbestos fibers with mesothelial cells. The encoded protein, merlin, is a regulator involved in signaling pathways that control, among other parameters, cell shape, proliferation (involving the hyaluronic acid receptor, CD44, which is important for proliferation of MM cells), survival, and motility [181]. Merlin is a component of the adherens junctions and other types of cell-to-cell contacts [179, 180]. As cell division is mechanically impaired by the presence of asbestos fibers, mutation of *NF2* could be responsible for enhanced proliferation as well as impaired mitotic control.

The overall consequences of these effects would be genetic and chromosomal instability and, possibly, evasion from apoptosis. It would be important to investigate the repair processes induced by exposure to asbestos and whether these processes are impaired, leading to additional damage such as gene deletions. So far, we do not know which gene(s) is initiator(s) of the asbestos-induced neoplastic transformation of mesothelial cells. An activated oncogene has not clearly been identified yet. From studies carried out in genetically modified mice, it seems that NF2 could facilitate tumor progression, but Nf2 deficiency does not act as an initiator, as the latent period for development of MM is similar in WT and heterozygous $Nf2^{+/-}$crocidolite-exposed mice [23]. In "spontaneous" MM that develops in double mutants $Nf2^{-/-}$;$p14/ARF^{-/-}$, the first MM develops at 3 months, confirming the role of null status of both genes in mesothelial cell transformation [74]. Further studies will improve our knowledge of the nature and relative role of gene alterations in MM.

In human epidemiological studies, pleural fibrosis and pleural plaques are a marker of past exposure. The consequences of the interaction between a mesothelial cell and asbestos fibers toward a fibrotic or a neoplastic pathway are dependent on several parameters as discussed above. Other important variables could include the anatomical location of the mesothelial cell injured by asbestos, the severity of injury, and the dose of fibers. Knowledge of these variables is important in understanding the mechanisms of asbestos carcinogenesis and in assessing the carcinogenic potential of other particles or chemicals that may reach the pleura.

References

1. Lippmann M, Yeates DB, Albert RE. Deposition, retention and clearance of inhaled particles. Br J Industr Med. 1980;37: 337–62.
2. Oberdorster G. Evaluation and use of animal models to assess mechanisms of fibre carcinogenicity. IARC Sci Publ.1996;107–25.
3. Miserocchi GA, Sancini GA, Mantegazza F, Chiappino G. Translocation pathways for inhaled asbestos fibers. Environ Health. 2008;7:4.
4. Donaldson K, Murphy FA, Duffin R, Poland CA. Asbestos, carbon nanotubes and the pleural mesothelium: a review and the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. Part Fibre Toxicol. 2010;7:5.
5. Wang NS. Anatomy of the pleura. Clin Chest Med. 1998;19: 229–40.
6. Wang NS. The preformed stomas connecting the pleural cavity and the lymphatics in the parietal pleura. Am Rev Respir Dis. 1975;111:12–20.
7. Hammar SP. The pathology of benign and malignant pleural disease. Chest Surg Clin N Am. 1994;4:405–30.
8. Holt PF. Transport of inhaled dust to extrapulmonary sites. J Pathol. 1981;133:123–9.
9. Muller KM, Schmitz I, Konstantinidis K. Black spots of the parietal pleura: morphology and formal pathogenesis. Respiration. 2002;69:261–7.
10. Mitchev K, Dumortier P, De Vuyst P. 'Black Spots' and hyaline pleural plaques on the parietal pleura of 150 urban necropsy cases. Am J Surg Pathol. 2002;26:1198–206.
11. Pooley FD. Proceedings: the recognition of various types of asbestos as minerals, and in tissues. Clin Sci Mol Med. 1974;47: 11P–2.
12. Dodson RF, O'Sullivan MF, Huang J, Holiday DB, Hammar SP. Asbestos in extrapulmonary sites: omentum and mesentery. Chest. 2000;117:486–93.
13. Boffetta P. Epidemiology of peritoneal mesothelioma: a review. Ann Oncol. 2007;18:985–90.
14. Price B, Ware A. Time trend of mesothelioma incidence in the United States and projection of future cases: an update based on SEER data for 1973 through 2005. Crit Rev Toxicol. 2009;39: 576–88.
15. Albin M, Magnani C, Krstev S, Rapiti E, Shefer I. Asbestos and cancer: an overview of current trends in Europe. Environ Health Perspect. 1999;107 Suppl 2:289–98.
16. Kishimoto T, Ozaki S, Kato K, Nishi H, Genba K. Malignant pleural mesothelioma in parts of Japan in relationship to asbestos exposure. Ind Health. 2004;42:435–9.
17. Goldberg M, Imbernon E, Rolland P, et al. The French national mesothelioma surveillance program. Occup Environ Med. 2006;63:390–5.
18. Park EK, Hannaford-Turner KM, Hyland RA, Johnson AR, Yates DH. Asbestos-related occupational lung diseases in NSW, Australia and potential exposure of the general population. Ind Health. 2008;46:535–40.
19. Bernstein D, Castranova V, Donaldson K, et al. Testing of fibrous particles: short-term assays and strategies. Inhal Toxicol. 2005;17:497–537. of an ILSI Risk Science Institute Working Group.
20. Wagner JC, Berry G. Mesotheliomas in rats following inoculation with asbestos. Br J Cancer. 1969;23:567–81.
21. Davis JM. Structural variations between pleural and peritoneal mesotheliomas produced in rats by the injection of crocidolite asbestos. Ann Anat Pathol (Paris). 1976;21:199–210.
22. Davis JM. The histopathology and ultrastructure of pleural mesotheliomas produced in the rat by injections of crocidolite asbestos. Br J Exp Pathol. 1979;60:642–52.
23. Fleury-Feith J, Lecomte C, Renier A, et al. Hemizygosity of N*f*2 is associated with increased susceptibility to asbestos-induced peritoneal tumours. Oncogene. 2003;22:3799–805.
24. Adamson IYR, Bakowska J. KGF and HGF are growth factors for mesothelial cells in pleural lavage fluid after intratracheal asbestos. Exp Lung Res. 2001;27:605–16.
25. Gelzleichter TR, Bermudez E, Mangum JB, Wong BA, Moss OR, Everitt JI. Pulmonary and pleural responses in Fischer 344 rats following short-term inhalation of a synthetic vitreous fiber. 2. Pathobiologic responses. Fund Appl Toxicol. 1996;30:39–46.
26. Everitt JI, Gelzleichter TR, Bermudez E, et al. Comparison of pleural responses of rats and hamsters to subchronic inhalation of refractory ceramic fibers. Environ Health Perspect. 1997;105 Suppl 5:1209–13.
27. Boutin C, Dumortier P, Rey F, Viallat JR, Devuyst P. Black spots concentrate oncogenic asbestos fibers in the parietal pleura: thoracoscopic and mineralogic study. Am J Respir Crit Care Med. 1996;153:444–9.
28. Libbus BL, Craighead JE. Chromosomal translocations with specific breakpoints in asbestos-induced rat mesotheliomas. Cancer Res. 1988;48:6455–61.
29. Ni Z, Liu YQ, Keshava N, Zhou G, Whong WZ, Ong TM. Analysis of K-ras and p53 mutations in mesotheliomas from humans and rats exposed to asbestos. Mutat Res. 2000;468:87–92.
30. Unfried K, Kociok N, Roller M, Friemann J, Pott F, Dehnen W. P53 mutations in tumours induced by intraperitoneal injection of crocidolite asbestos and benzo[a]pyrene in rats. Exp Toxicol Pathol. 1997;49:181–7.
31. Unfried K, Schürkes C, Abel J. Distinct spectrum of mutations induced by crocidolite asbestos: clue for 8-hydroxydeoxyguanosine-dependent mutagenesis in vivo. Cancer Res. 2002;62:99–104.
32. Schurkes C, Brock W, Abel J, Unfried K. Induction of 8-hydroxydeoxyguanosine by man made vitreous fibres and crocidolite asbestos administered intraperitoneally in rats. Mutat Res. 2004;553:59–65.
33. Vaslet CA, Messier NJ, Kane AB. Accelerated progression of asbestos-induced mesotheliomas in heterozygous p53 (+/−) mice. Toxicol Sci. 2002;68:331–8.
34. Altomare DA, Vaslet CA, Skele KL, et al. A mouse model recapitulating molecular features of human mesothelioma. Cancer Res. 2005;65:8090–5.
35. Lecomte C, Andujar P, Renier A, et al. Similar tumor suppressor gene alteration profiles in asbestos-induced murine and human mesothelioma. Cell Cycle. 2005;4:1862–9.
36. Altomare DA, Menges CW, Pei J, et al. Activated TNF-alpha/NF-kappaB signaling via down-regulation of Fas-associated factor 1 in asbestos-induced mesotheliomas from Arf knockout mice. Proc Natl Acad Sci U S A. 2009;106:3420–5.

37. Jaurand MC. Use of in-vitro genotoxicity and cell transformation assays to evaluate potential carcinogenicity of fibres. In: Kane AB, Boffetta P, Sarracci R, Wilbourn JD, editors. Mechanisms in fiber carcinogenesis, vol. 140. 1996. p. 55–72.
38. Huang SXL, Jaurand MC, Kamp DW, Whysner J, Hei T. Role of mutagenicity in asbestos fiber-induced carcinogenicity and other diseases. J Toxicol Environ Health Part B. 2011;14:1–67.
39. Jaurand MC. Mechanisms of fiber-induced genotoxicity. Environ Health Perspect. 1997;105:1073–84.
40. Ruosaari ST, Nymark PE, Aavikko MM, et al. Aberrations of chromosome 19 in asbestos-associated lung cancer and in asbestos-induced micronuclei of bronchial epithelial cells in vitro. Carcinogenesis. 2008;29:913–7.
41. Lechner JF, Tokiwa T, LaVeck M, et al. Asbestos-associated chromosomal changes in human mesothelial cells. Proc Natl Acad Sci U S A. 1985;82:3884–8.
42. Olofsson K, Mark J. Specificity of asbestos-induced chromosomal aberrations in short-term cultures human mesothelial cells. Cancer Genet Cytogenet. 1989;41:33–9.
43. Pelin K, Hirvonen A, Taavitsainen M, Linanainmaa K. Cytogenetic response to asbestos fibers in cultured human primary mesothelial cells from 10 different donors. Mutat Res. 1995;334:225–33.
44. Burmeister B, Schwerdtle T, Poser I, et al. Effects of asbestos on initiation of DNA damage, induction of DNA-strand breaks, P53-expression and apoptosis in primary, SV40-transformed and malignant human mesothelial cells. Mutat Res. 2004;558:81–92.
45. Poser I, Rahman Q, Lohani M, et al. Modulation of genotoxic effects in asbestos-exposed primary human mesothelial cells by radical scavengers, metal chelators and a glutathione precursor. Mutat Res. 2004;559:19–27.
46. Chen Q, Marsh J, Ames B, Mossman B. Detection of 8-oxo-2′-deoxyguanosine, a marker of oxidative DNA damage, in culture medium from human mesothelial cells exposed to crocidolite asbestos. Carcinogenesis. 1996;17:2525–7.
47. Fung H, Kow YW, Van Houten B, Mossman BT. Patterns of 8-hydroxydeoxyguanosine formation in DNA and indications of oxidative stress in rat and human pleural mesothelial cells after exposure to crocidolite asbestos. Carcinogenesis. 1997;18:825–32.
48. Jensen CG, Watson M. Inhibition of cytokinesis by asbestos and synthetic fibres. Cell Biol Intl. 1999;23:829–40.
49. Nygren J, Suhonen S, Norppa H, Linnainmaa K. DNA damage in bronchial epithelial and mesothelial cells with and without associated crocidolite asbestos fibers. Environ Mol Mutagen. 2004;44:477–82.
50. Jaurand MC, Kheuang L, Magne L, Bignon J. Chromosomal changes induced by chrysotile fibres or benzo(3–4)pyrene in rat pleural mesothelial cells. Mutat Res. 1986;169:141–8.
51. Achard S, Perderiset M, Jaurand MC. Sister chromatid exchanges in rat pleural mesothelial cells treated with crocidolite, attapulgite or benzo 3–4 pyrene. Br J Ind Med. 1987;44:281–3.
52. Wang NS, Jaurand MC, Magne L, Kheuang L, Pinchon MC, Bignon J. The interactions between asbestos fibers and metaphase chromosomes of rat pleural mesothelial cells in culture. A scanning and transmission electron microscopic study. Am J Pathol. 1987;126:343–9.
53. Renier A, Levy F, Pilliere F, Jaurand MC. Uncheduled DNA synthesis in rat pleural mesothelial cells treated with mineral fibres or benzo[a]pyrene. Mutat Res. 1990;241:361–7.
54. Yegles M, Saint-Etienne L, Renier A, Janson X, Jaurand MC. Induction of metaphase and anaphase/telophase abnormalities by asbestos fibers in rat pleural mesothelial cells in vitro. Am J Respir Cell Mol Biol. 1993;9:186–91.
55. Dong HY, Buard A, Renier A, Levy F, Saint-Etienne L, Jaurand MC. Role of oxygen derivatives in the cytotoxicity and DNA damage produced by asbestos on rat pleural mesothelial cells in vitro. Carcinogenesis. 1994;15:1251–5.
56. Dong HY, Buard A, Levy F, Renier A, Laval F, Jaurand MC. Synthesis of poly(ADP-ribose) in asbestos treated rat pleural mesothelial cells in culture. Mutat Res. 1995;331:197–204.
57. Yegles M, Janson X, Dong HY, Renier A, Jaurand MC. Role of fibre characteristics on cytotoxicity and induction of anaphase/telophase aberrations in rat pleural mesothelial cells in vitro. Correlations with in vivo animal findings. Carcinogenesis. 1995;16:2751–8.
58. Levresse V, Renier A, Fleury-Feith J, et al. Analysis of cell cycle disruptions in cultures of rat pleural mesothelial cells exposed to asbestos fibres. Am J Respir Cell Mol Biol. 1997;17:660–71.
59. Fung H, Kow YW, Van Houten B, et al. Asbestos increases mammalian AP-endonuclease gene expression, protein levels, and enzyme activity in mesothelial cells. Cancer Res. 1998;58:189–94.
60. Liu W, Ernst JD, Broaddus VC. Phagocytosis of crocidolite asbestos induces oxidative stress, DNA damage, and apoptosis in mesothelial cells. Am J Respir Cell Mol Biol. 2000;23:371–8.
61. Janssen YMW, Heintz NH, Marsh JP, Borm PJA, Mossman BT. Induction of c-fos and c-jun proto-oncogenes in target cells of the lung and pleura by carcinogenic fibers. Am J Respir Cell Mol Biol. 1994;11:522–30.
62. Timblin CR, Janssen YWM, Mossman BT. Transcriptional activation of the proto-oncogene c-jun by asbestos and H2O2 is directly related to increased proliferation and transformation of tracheal epithelial cells. Cancer Res. 1995;55:2723–6.
63. Zanella CL, Timblin CR, Cummins A, et al. Asbestos-induced phosphorylation of epidermal growth factor receptor is linked to c-fos and apoptosis. Am J Physiol. 1999;277:L684–93.
64. Berken A, Abel J. Unfried K. beta1-integrin mediates asbestos-induced phosphorylation of AKT and ERK1/2 in a rat pleural mesothelial cell line. Oncogene. 2003;22:8524–8.
65. Zanella CL, Posada J, Tritton TR, Mossman BT. Asbestos causes stimulation of the extracellular signal-regulated kinase 1 mitogen-activated protein kinase cascade after phosphorylation of the epidermal growth factor receptor. Cancer Res. 1996;56:5334–8.
66. Faux SP, Houghton CE, Hubbard A, Patrick G. Increased expression of epidermal growth factor receptor in rat pleural mesothelial cells correlates with carcinogenicity of mineral fibres. Carcinogenesis. 2001;12:2275–80.
67. Kopnin PB, Kravchenko IV, Furalyov VA, Pylev LN, Kopnin BP. Cell type-specific effects of asbestos on intracellular ROS levels, DNA oxidation and G1 cell cycle checkpoint. Oncogene. 2004;23:8834–40.
68. Levresse V, Renier A, Levy F, Broaddus VC, Jaurand MC. DNA breakage in asbestos-treated normal and transformed (TSV40) rat pleural mesothelial cells. Mutagenesis. 2000;15:239–44.
69. Puhakka A, Ollikainen T, Soini Y, et al. Modulation of DNA single-strand breaks by intracellular glutathione in human lung cells exposed to asbestos fibers. Mutat Res. 2002;514:7–17.
70. Pietruska JR, Kane AB. SV40 oncoproteins enhance asbestos-induced DNA double-strand breaks and abrogate senescence in murine mesothelial cells. Cancer Res. 2007;67:3637–45.
71. Pelin K, Kivipensas P, Linnainmaa K. Effects of asbestos and man-made vitreous fibers on cell division in cultured human mesothelial cells in comparison to rodent cells. Environ Mol Mutag. 1995;25:118–25.
72. Broaddus VC. Asbestos, the mesothelial cell and malignancy: a matter of life or death. Am J Respir Cell Mol Biol. 1997;17:657–9.
73. Marsella JM, Liu BL, Vaslet CA, Kane AB. Susceptibility of p53-deficient mice to induction of mesothelioma by crocidolite asbestos fibers. Environ Health Perspect. 1997;105(supp 5):1069–72.
74. Jongsma J, van Montfort E, Vooijs M, et al. A conditional mouse model for malignant mesothelioma. Cancer Cell. 2008;13:261–71.

75. Merchant JA. Human epidemiology: a review of fiber type and characteristics in the development of malignant and nonmalignant disease. Environ Health Perspect. 1990;88:287–93.
76. Baris YI, Grandjean P. Prospective study of mesothelioma mortality in Turkish villages with exposure to fibrous zeolite. J Natl Cancer Inst. 2006;98:414–7.
77. Coin PG, Roggli VL, Brody AR. Persistence of long, thin chrysotile asbestos fibers in the lungs of rats. Environ Health Perspect. 1994;102 Suppl 5:197–9.
78. Greillier L, Astoul P. Mesothelioma and asbestos-related pleural diseases. Respiration. 2008;76:1–15.
79. IOM. Asbestos: selected cancers. Washington, DC: The National Academies Press; 2006.
80. Fubini B. Surface reactivity in the pathogenic response to particulates. Environ Health Perspect. 1997;105:1013–20.
81. McDonald JC. Epidemiology of malignant mesothelioma – an outline. Ann Occup Hyg. 2010;54:851–7.
82. McDonald JC, Harris J, Armstrong B. Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. Occup Environ Med. 2004;61:363–6.
83. IARC. Silica and some silicates. In: IARC Press G, editors. Monographs on the evaluation of carcinogenic risk of chemical to humans. vol. 42. 1987. p. 39–143.
84. Hamilton RF, Wu N, Porter D, Buford M, Wolfarth M, Holian A. Particle length-dependent titanium dioxide nanomaterials toxicity and bioactivity. Part Fibre Toxicol. 2009;6:35.
85. Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science. 2008;320:674–7.
86. Poland CA, Duffin R, Kinloch I, et al. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nat Nanotechnol. 2008;3:423–8.
87. Mercer RR, Scabilloni J, Wang L, et al. Alteration of deposition pattern and pulmonary response as a result of improved dispersion of aspirated single-walled carbon nanotubes in a mouse model. Am J Physiol Lung Cell Mol Physiol. 2008;294:L87–97.
88. Ryman-Rasmussen JP, Tewksbury EW, Moss OR, Cesta MF, Wong BA, Bonner JC. Inhaled multiwalled carbon nanotubes potentiate airway fibrosis in murine allergic asthma. Am J Respir Cell Mol Biol. 2009;40:349–58.
89. Porter DW, Hubbs AF, Mercer RR, et al. Mouse pulmonary dose- and time course-responses induced by exposure to multi-walled carbon nanotubes. Toxicology. 2010;269:136–47.
90. Mercer RR, Hubbs AF, Scabilloni JF, et al. Distribution and persistence of pleural penetrations by multi-walled carbon nanotubes. Part Fibre Toxicol. 2010;7:28.
91. Takagi A, Hirose A, Nishimura T, et al. Induction of mesothelioma in p53+/– mouse by intraperitoneal application of multi-wall carbon nanotube. J Toxicol Sci. 2008;33:105–16.
92. Sakamoto Y, Nakae D, Fukumori N. Induction of mesothelioma by a single intrascrotal administration of multi-wall carbon nanotube in intact male Fischer 344 rats. J Toxicol Sci. 2009;34:65–76.
93. Muller J, Delos M, Panin N, Rabolli V, Huaux F, Lison D. Absence of carcinogenic response to multiwall carbon nanotubes in a 2-year bioassay in the peritoneal cavity of the rat. Toxicol Sci. 2009;110:442–8.
94. Fubini B, Otero-Arean C. Clinical aspects of the toxicity of inhaled mineral dusts. Chem Soc Rev. 1999;28:373–81.
95. Fubini B, Mollo L. Role of iron in the reactivity of mineral fibers. Toxicol Lett. 1995;82–3:951–60.
96. Hardy JA, Aust AE. The effect of iron binding on the ability of crocidolite asbestos to catalyze DNA single-strand breaks. Carcinogenesis. 1995;16:319–25.
97. Shukla A, Ramos-Nino M, Mossman B. Cell signaling and transcription factor activation by asbestos in lung injury and disease. Intl J Biochem Cell Biol. 2003;35:1198–209.
98. Upadhyay D, Kamp DW. Asbestos-induced pulmonary toxicity: role of DNA damage and apoptosis. Exp Biol Med (Maywood). 2003;228:650–9.
99. Brown DM, Fisher C, Donaldson K. Free radical activity of synthetic vitreous fibers: iron chelation inhibits hydroxyl radical generation by refractory ceramic fiber. J Toxicol Environ Health A. 1998;53:545–61.
100. Okayasu R, Wu L, Hei TK. Biological effects of naturally occurring and man-made fibres: in vitro cytotoxicity and mutagenesis in mammalian cells. Br J Cancer. 1999;79:1319–24.
101. Fenoglio I, Tomatis M, Lison D, et al. Reactivity of carbon nanotubes: free radical generation or scavenging activity? Free Radic Biol Med. 2006;40:1227–33.
102. Galano A, Francisco-Marquez M, Martinex A. Influence of point defects on the free-radical scavenging capability of single-walled carbon nanotubes. J Phys Chem C. 2010;114:8302.
103. Di Sotto A, Chiaretti M, Carru GA, Bellucci S, Mazzanti G. Multi-walled carbon nanotubes: lack of mutagenic activity in the bacterial reverse mutation assay. Toxicol Lett. 2009;184:192–7.
104. Wirnitzer U, Herbold B, Voetz M, Ragot J. Studies on the in vitro genotoxicity of baytubes (R), agglomerates of engineered multiwalled carbon-nanotubes (MWCNT). Toxicol Lett. 2009;186:160–5.
105. Yamashita K, Yoshioka Y, Higashisaka K, et al. Carbon nanotubes elicit DNA damage and inflammatory response relative to their size and shape. Inflammation. 2010;33:276–80.
106. Muller J, Decordier I, Hoet PH, et al. Clastogenic and aneugenic effects of multi-wall carbon nanotubes in epithelial cells. Carcinogenesis. 2008;29:427–33.
107. Kisin ER, Murray AR, Sargent L, et al. Genotoxicity of carbon nanofibers: are they potentially more or less dangerous than carbon nanotubes or asbestos? Toxicol Appl Pharmacol. 2011;252:1–10.
108. Lindberg HK, Falck GC, Suhonen S, et al. Genotoxicity of nanomaterials: DNA damage and micronuclei induced by carbon nanotubes and graphite nanofibres in human bronchial epithelial cells in vitro. Toxicol Lett. 2009;186:166–73.
109. Pacurari M, Yin XJ, Ding M, et al. Oxidative and molecular interactions of multi-wall carbon nanotubes (MWCNT) in normal and malignant human mesothelial cell. Nanotoxicology. 2008;2:155–70.
110. Pacurari M, Yin XJ, Zhao J, et al. Raw single-wall carbon nanotubes induce oxidative stress and activate MAPKs, AP-1, NF-kappaB, and Akt in normal and malignant human mesothelial cells. Environ Health Perspect. 2008;116:1211–7.
111. Sanchez VC, Pietruska JR, Miselis NR, Hurt RH, Kane AB. Biopersistence and potential adverse health impacts of fibrous nanomaterials: what have we learned from asbestos? Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2009;1:511–29.
112. Manning CB, Vallyathan V, Mossman BT. Diseases caused by asbestos: mechanisms of injury and disease development. Int Immunopharmacol. 2002;2:191–200.
113. Park SH, Aust A. Participation of iron and nitric oxide in the mutagenicity of asbestos in hgprt-, gpt + chines hamster V79 cells. Cancer Res. 1998;58:1144–8.
114. Hei T, Louie D, Zhao YL. Genotoxicity versus carcinogenicity: implications from fiber toxicity studies. Inhal Toxicol. 2000;12:141–7.
115. MacCorkle RA, Slattery SD, Nash DR, Brinkley BR. Intracellular protein binding to asbestos induces aneuploidy in human lung fibroblasts. Cell Motil Cytoskeleton. 2006;63:646–57.
116. Sargent LM, Reynolds SH, Castranova V. Potential pulmonary effects of engineered carbon nanotubes: in vitro genotoxic effects. Nanotoxicology. 2010;4:396–408.
117. Berman DW, Crump KS. A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. Crit Rev Toxicol. 2008;38 Suppl 1:49–73.

118. Suzuki Y, Yuen SR, Ashley R. Short, thin asbestos fibers contribute to the development of human malignant mesothelioma: pathological evidence. Int J Hyg Environ Health. 2005;208:201–10.
119. Dodson RF, Hammar SP. Pleural mesothelioma in a woman whose documented past exposure to asbestos was from smoking asbestos-containing filtered cigarettes: the comparative value of analytical transmission electron microscopic analysis of lung and lymph-node tissue. Inhal Toxicol. 2006;18:679–84.
120. Hesterberg TW, Chase G, Axten C, et al. Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. Toxicol Appl Pharmacol. 1998;151:262–75.
121. Miller BG, Searl A, Davis JMG, et al. Influence of fibre length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity. Ann Occup Hyg. 1999;43:155–66.
122. Akiyama I, Ogami A, Oyabu T, Yamato H, Morimoto Y, Tanaka I. Pulmonary effects and biopersistence of deposited silicon carbide whisker after 1-year inhalation in rats. Inhal Toxicol. 2007; 19:141–7.
123. Johnson NF, Hahn FF. Induction of mesothelioma after intrapleural inoculation of F344 rats with silicon carbide whiskers or continuous ceramic filaments. Occup Environ Med. 1996;53:813–6.
124. Rodelsperger K, Bruckel B. The carcinogenicity of WHO fibers of silicon carbide: SiC whiskers compared to cleavage fragments of granular SiC. Inhal Toxicol. 2006;18:623–31.
125. Mast RW, Yu CP, Oberdorster G, McConnell EE, Utell MJ. A retrospective review of the carcinogenicity of refractory ceramic fiber in two chronic fischer 344 rat inhalation studies: an assessment of the MTD and implications for risk assessment. Inhal Toxicol. 2000;12:1141–72.
126. Wagner JC, Skidmore JW, Hill RJ, Griffiths DM. Erionite exposure and mesotheliomas in rats. Br J Cancer. 1985;51:727.
127. Johnson NF, Edwards RE, Munday DE, Rowe N, Wagner JC. Pluripotential nature of mesotheliomata induced by inhalation of erionite in rats. Br J Exp Pathol. 1984;65:377–88.
128. Kane AB. Animal models of malignant mesothelioma. Inhal Toxicol. 2006;18:1001–4.
129. Pass H, Vogelzang N, Carbone M. Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis, and Translational Therapies. Springer Verlag; New York, NY. 2005.
130. Liu X, Guo L, Morris D, Kane AB, Hurt RH. Targeted removal of bioavailable metal as a detoxification strategy for carbon nanotubes. Carbon N Y. 2008;46:489–500.
131. Allen BL, Kichambare PD, Gou P, et al. Biodegradation of single-walled carbon nanotubes through enzymatic catalysis. Nano Lett. 2008;8:3899–903.
132. Liu X, Hurt RH, Kane AB. Biodurability of single-walled carbon nanotubes depends on surface functionalization. Carbon N Y. 2010;48:1961–9.
133. Nagai H, Toyokuni S. Biopersistent fiber-induced inflammation and carcinogenesis: lessons learned from asbestos toward safety of fibrous nanomaterials. Arch Biochem Biophys. 2010;502:1–7.
134. Donaldson K, Aitken R, Tran L, et al. Carbon nanotubes: a review of their properties in relation to pulmonary toxicology and workplace safety. Toxicol Sci. 2006;92:5–22.
135. Pacurari M, Castranova V, Vallyathan V. Single- and multi-wall carbon nanotubes versus asbestos: are the carbon nanotubes a new health risk to humans? J Toxicol Environ Health A. 2010;73: 378–95.
136. Wick P, Manser P, Limbach LK, et al. The degree and kind of agglomeration affect carbon nanotube cytotoxicity. Toxicol Lett. 2007;168:121–31.
137. Jaurand MC, Renier A, Daubriac J. Mesothelioma: do asbestos and carbon nanotubes pose the same health risk? Part Fibre Toxicol. 2009;6:16–29.
138. Kane AB, Hurt RH. Nanotoxicology: the asbestos analogy revisited. Nat Nanotechnol. 2008;3:378–9.
139. Aschberger K, Johnston HJ, Stone V, et al. Review of carbon nanotubes toxicity and exposure – appraisal of human health risk assessment based on open literature. Crit Rev Toxicol. 2010;40:759–90.
140. Nymark P, Wikman H, Hienonen-Kempas T, Anttila S. Molecular and genetic changes in asbestos-related lung cancer. Cancer Lett. 2008;265:1–15.
141. Broaddus VC, Everitt JI, Black B, Kane AB. Non-neoplastic and neoplastic pleural endpoints following fiber exposure. J Toxicol Environ Health B Crit Rev. 2011;14:153–78.
142. Kinnula VL, Everitt JI, Mangum JB, Chang LY, Crapo JD. Antioxidant defense mechanisms in cultured pleural mesothelial cells. Am J Respir Cell Mol Biol. 1992;7:95–103.
143. Hesterberg TW, Hart GA, Chevalier J, et al. The importance of fiber biopersistence and lung dose in determining the chronic inhalation effects of X607, RCF1, and chrysotile asbestos in rats. Toxicol Appl Pharmacol. 1998;153:68–82.
144. Kodama Y, Boreiko CJ, Maness SC, Hesterberg TW. Cytotoxic and cytogenetic effects of asbestos on human bronchial epithelial cells in culture. Carcinogenesis. 1993;14:691–7.
145. Kamp DW, Israbian VA, Yeldandi AV, Panos RJ, Graceffa P, Weitzman SA. Phytic acid, an iron chelator, attenuates pulmonary inflammation and fibrosis in rats after intratracheal instillation of asbestos. Toxicol Pathol. 1995;23:689–95.
146. Shukla A, Jung M, Stern M, et al. Asbestos induces mitochondrial DNA damage and dysfunction linked to the development of apoptosis. Am J Physiol Lung Cell Mol Physiol. 2003;285:L1018–25.
147. Srivastava RK, Lohani M, Pant AB, Rahman Q. Cyto-genotoxicity of amphibole asbestos fibers in cultured human lung epithelial cell line: role of surface iron. Toxicol Ind Health. 2010;26:575–82.
148. Hei TK, He ZY, Suzuki K. Effects of antioxidants on fiber mutagenesis. Carcinogenesis. 1995;16:1573–8.
149. Kamp DW, Weitzman SA. The molecular basis of asbestos induced lung injury. Thorax. 1999;54:638–52.
150. Heintz NH, Janssen-Heininger YM, Mossman BT. Asbestos, lung cancers, and mesotheliomas: from molecular approaches to targeting tumor survival pathways. Am J Respir Cell Mol Biol. 2010;42: 133–9.
151. Murthy SS, Testa JR. Asbestos, chromosomal deletions, and tumor suppressor gene alterations in human malignant mesothelioma. J Cell Physiol. 1999;180:150–7.
152. Christensen BC, Houseman EA, Godleski JJ, et al. Epigenetic profiles distinguish pleural mesothelioma from normal pleura and predict lung asbestos burden and clinical outcome. Cancer Res. 2009;69:227–34.
153. Valinluck V, Sowers LC. Inflammation-mediated cytosine damage: a mechanistic link between inflammation and the epigenetic alterations in human cancers. Cancer Res. 2007;67:5583–6.
154. Kasai H, Kawai K. DNA methylation at the C-5 position of cytosine by methyl radicals: a possible role for epigenetic change during carcinogenesis by environmental agents. Chem Res Toxicol. 2009;22:984–9.
155. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med. 2010;49:1603–16.
156. Mutsaers SE. The mesothelial cell. Int J Biochem Cell Biol. 2004;36:9–16.
157. Michailova KN, Usunoff KG. Serosal membranes (pleura, pericardium, peritoneum). Normal structure, development and experimental pathology. Adv Anat Embryol Cell Biol. 2006;183:i–vii. 1–144, back cover.
158. Mutsaers SE, Whitaker D, Papadimitriou JM. Mesothelial regeneration is not dependent on subserosal cells. J Pathol. 2000; 190:86–92.
159. Mutsaers SE. Mesothelial cells: their structure, function and role in serosal repair. Respirology. 2002;7:171–91.

160. Foley-Comer AJ, Herrick SE, Al-Mishlab T, Prele CM, Laurent GJ, Mutsaers SE. Evidence for incorporation of free-floating mesothelial cells as a mechanism of serosal healing. J Cell Sci. 2002;115:1383–9.
161. Mor O, Yaron P, Huszar M, et al. Absence of p53 mutations in malignant mesothelioma. Am J Respir Cell Mol Biol. 1997;16: 9–13.
162. Kitamura F, Araki S, Tanigawa T, Miura H, Akabane H, Iwasaki R. Assessment of mutations of Ha- and Ki-ras oncogenes and the p53 suppressor gene in seven malignant mesothelioma patients exposed to asbestos. PCR-SSCP and sequencing analyses of paraffin-embedded primary tumors. Ind Health. 1998;36:52–6.
163. Sekido Y. Genomic abnormalities and signal transduction dysregulation in malignant mesothelioma cells. Cancer Sci. 2010; 101:1–6.
164. Andujar P, Lecomte C, Renier A, et al. Clinico-pathological features and somatic gene alterations in refractory ceramic fibre-induced murine mesothelioma reveal mineral fibre-induced mesothelioma identities. Carcinogenesis. 2007;28:1599–605.
165. Andujar P, Wang J, Descatha A, et al. $p16^{INK4A}$ inactivation mechanisms in non small-cell lung cancer patients occupationally exposed to asbestos. Lung Cancer. 2010;67:23–30.
166. Christensen BC, Godleski JJ, Marsit CJ, et al. Asbestos exposure predicts cell cycle control gene promoter methylation in pleural mesothelioma. Carcinogenesis. 2008;29:1555–9.
167. Toyooka S, Toyooka KO, Maruyama R, et al. DNA methylation profiles of lung tumors. Mol Cancer Ther. 2001;1:61–7.
168. Hirao T, Bueno R, Chen CJ, Gordon GJ, Heilig E, Kelsey KT. Alterations of the p16INK4 locus in human malignant mesothelial tumors. Carcinogenesis. 2002;23:1127–30.
169. Wong L, Zhou J, Anderson D, Kratzke RA. Inactivation of p16INK4a expression in malignant mesothelioma by methylation. Lung Cancer. 2002;38:131–6.
170. Marsit CJ, Houseman EA, Christensen BC, et al. Examination of a CpG island methylator phenotype and implications of methylation profiles in solid tumors. Cancer Res. 2006;66: 10621–9.
171. Destro A, Ceresoli GL, Baryshnikova E, et al. Gene methylation in pleural mesothelioma: correlations with clinico-pathological features and patient's follow-up. Lung Cancer. 2008;59:369–76.
172. Guled M, Lahti L, Lindholm PM, et al. CDKN2A, NF2, and JUN are dysregulated among other genes by miRNAs in malignant mesothelioma -A miRNA microarray analysis. Gene Chromosome Cancer. 2009;48:615–23.
173. Petitjean A, Mathe E, Kato S, et al. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. Hum Mutat. 2007;28:622–9.
174. Le Calvez F, Mukeria A, Hunt JD, et al. TP53 and KRAS mutation load and types in lung cancers in relation to tobacco smoke: distinct patterns in never, former, and current smokers. Cancer Res. 2005;65:5076–83.
175. Husgafvel-Pursiainen K, Karjalainen A, Kannio A, et al. Lung cancer and past occupational exposure to asbestos. Role of p53 and K-ras mutations. Am J Respir Cell Mol Biol. 1999;20:667–74.
176. Jean D, Thomas E, Renier A, et al. Syntenic relationships between genomic profiles of fiber-induced murine and human malignant mesothelioma. Am J Pathol. 2011;176:881–94.
177. Bianchi AB, Mitsunaga S, Cheng J, et al. High frequency of inactivating mutations in the neurofibromatosis type 2 gene (NF2) in primary malignant mesothelioma. Proc Natl Acad Sci U S A. 1995;92:10854–8.
178. Sekido Y, Pass HI, Bader S, Mew DJ, Christmas MF, Gazdar AF. Neurofibromatosis type 2 (NF2) gene is somatically mutated in mesothelioma but not in lung cancer. Cancer Res. 1995;55: 1227–31.
179. Lallemand D, Curto M, Saotome I, Giovannini M, McClatchey AI. NF2 deficiency promotes tumorigenesis and metastasis by destabilizing adherens junctions. Genes Dev. 2003;17:1090–100.
180. Yi C, Troutman S, Fera D, et al. A tight Junction-associated merlin-angiomotin complex mediates Merlin's regulation of mitogenic signaling and tumor suppressive functions. Cancer Cell. 2010;19:527–40.
181. Stamenkovic I, Yu Q. Merlin, a "magic" linker between extracellular cues and intracellular signaling pathways that regulate cell motility, proliferation, and survival. Curr Protein Pept Sci. 2010; 11:471–84.
182. Tiainen M, Tammilehto L, Mattson K, Knuutila S. Nonrandom chromosomal abnormalities in malignant pleural mesothelioma. Cancer Genet Cytogenet. 1988;33:251–74.
183. Pyrhonen S, Tiainen M, Rautonen J, et al. Comparison of DNA and karyotype ploidy in malignant mesothelioma. Cancer Genet Cytogenet. 1992;60:8–13.
184. Tiainen M, Hopman A, Moesker O, et al. Interphase cytogenetics on paraffin sections of malignant pleural mesothelioma. A comparison to conventional karyotyping and flow cytometric studies. Cancer Genet Cytogenet. 1992;62:171–9.
185. Tiainen M, Kere J, Tammilehto L, Mattson K, Knuutila S. Abnormalities of chromosomes 7 and 22 in human malignant pleural mesothelioma: correlation between Southern blot and cytogenetic analyses. Gene Chromosome Cancer. 1992;4:176–82.
186. Tiainen M, Rautonen J, Pyrhonen S, Tammilehto L, Mattson K, Knuutila S. Chromosome number correlates with survival in patients with malignant pleural mesothelioma. Cancer Genet Cytogenet. 1992;62:21–4.
187. Kivipensas P, Bjorkqvist AM, Karhu R, et al. Gains and losses of DNA sequences in malignant mesothelioma by comparative genomic hybridization. Cancer Genet Cytogenet. 1996;89:7–13.
188. Lindholm PM, Salmenkivi K, Vauhkonen H, et al. Gene copy number analysis in malignant pleural mesothelioma using oligonucleotide array CGH. Cytogenet Genome Res. 2007;119:46–52.
189. Ivanov SV, Miller J, Lucito R, et al. Genomic events associated with progression of pleural malignant mesothelioma. Int J Cancer. 2009;124:589–99.
190. Bueno R, De Rienzo A, Dong L, et al. Second generation sequencing of the mesothelioma tumor genome. PLoS One. 2010;5:e10612.
191. Cheung M, Pei J, Pei Y, Jhanwar SC, Pass HI, Testa JR. The promyelocytic leukemia zinc-finger gene, PLZF, is frequently downregulated in malignant mesothelioma cells and contributes to cell survival. Oncogene. 2010;29:1633–40.
192. Christensen BC, Houseman EA, Poage GM, et al. Integrated profiling reveals a global correlation between epigenetic and genetic alterations in mesothelioma. Cancer Res. 2010;70:5686–94.
193. Hagemeijer A, Versnel MA, Van Drunen E, et al. Cytogenetic analysis of malignant mesothelioma. Cancer Genet Cytogenet. 1990;47:1–28.
194. Ribotta M, Roseo F, Salvio M, et al. Recurrent chromosome 6 abnormalities in malignant mesothelioma. Monaldi Arch Chest Dis. 1998;53:228–35.
195. Mitelman F, Johansson B, Mertens F. Database of chromosome aberrations in cancer; 2008.
196. Gisselsson D, Pettersson L, Hoglund M, et al. Chromosomal breakage-fusion-bridge events cause genetic intratumor heterogeneity. Proc Natl Acad Sci U S A. 2000;97:5357–62.
197. Tiainen M, Tammilehto L, Rautonen J, Tuomi T, Mattson K, Knuutila S. Chromosomal abnormalities and their correlations with asbestos exposure and survival in patients with mesothelioma. Br J Cancer. 1989;60:618–26.
198. Tammilehto L, Tuomi T, Tiainen M, et al. Malignant mesothelioma: clinical characteristics, asbestos mineralogy and chromosomal abnormalities of 41 patients. Eur J Cancer. 1992;28A: 1373–9.

199. Bjorkqvist AM, Tammilehto L, Nordling S, et al. Comparison of DNA copy number changes in malignant mesothelioma, adenocarcinoma and large-cell anaplastic carcinoma of the lung. Br J Cancer. 1998;77:260–9.
200. Bjorkqvist AM, Wolf M, Nordling S, et al. Deletions at 14q in malignant mesothelioma detected by microsatellite marker analysis. Br J Cancer. 1999;81:1111–5.
201. Assamaki R, Sarlomo-Rikala M, Lopez-Guerrero JA, et al. Array comparative genomic hybridization analysis of chromosomal imbalances and their target genes in gastrointestinal stromal tumors. Gene Chromosome Cancer. 2007;46:564–76.
202. Tsou JA, Shen LY, Siegmund KD, et al. Distinct DNA methylation profiles in malignant mesothelioma, lung adenocarcinoma, and non-tumor lung. Lung Cancer. 2005;47:193–204.
203. Goto Y, Shinjo K, Kondo Y, et al. Epigenetic profiles distinguish malignant pleural mesothelioma from lung adenocarcinoma. Cancer Res. 2009;69:9073–82.
204. Tsou JA, Galler JS, Wali A, et al. DNA methylation profile of 28 potential marker loci in malignant mesothelioma. Lung Cancer. 2007;58:220–30.
205. Nymark P, Guled M, Borze I, Faisal A, Lahti L. Salmenkivi K. Integrative analysis of microRNA, mRNA and acGH data reveals asbestos- and histology-related changes in lung cancer. 2011;50(8):585–97.
206. Ivanov SV, Goparaju CM, Lopez P, et al. Pro-tumorigenic effects of miR-31 loss in mesothelioma. J Biol Chem. 2010;9:2124.
207. Pass HI, Goparaju C, Ivanov S, et al. hsa-miR-29c* is linked to the prognosis of malignant pleural mesothelioma. Cancer Res. 2010;70:1916–24.
208. Murakami H, Mizuno T, Taniguchi T, et al. LATS2 is a tumor suppressor gene of malignant mesothelioma. Cancer Res. 2011;71: 873–83.
209. Thurneysen C, Opitz I, Kurtz S, Weder W, Stahel RA, Felley-Bosco E. Functional inactivation of NF2/merlin in human mesothelioma. Lung Cancer. 2009;64:140–7.
210. Romagnoli S, Fasoli E, Vaira V, et al. Identification of potential therapeutic targets in malignant mesothelioma using cell-cycle gene expression analysis. Am J Pathol. 2009;174:762–70.
211. Crispi S, Fagliarone C, Biroccio A, et al. Antiproliferative effect of Aurora kinase targeting in mesothelioma. Lung Cancer. 2010;70:271–9.
212. Roe OD, Anderssen E, Sandeck H, Christensen T, Larsson E, Lundgren S. Malignant pleural mesothelioma: genome-wide expression patterns reflecting general resistance mechanisms and a proposal of novel targets. Lung Cancer. 2010;67:57–68.
213. Lopez-Rios F, Chuai S, Flores R, et al. Global gene expression profiling of pleural mesotheliomas: overexpression of aurora kinases and P16/CDKN2A deletion as prognostic factors and critical evaluation of microarray-based prognostic prediction. Cancer Res. 2006;66:2970–9.
214. Rubin CI, Atweh GF. The role of stathmin in the regulation of the cell cycle. J Cell Biochem. 2004;93:242–50.
215. Kim JY, Harvard C, You L, et al. Stathmin is overexpressed in malignant mesothelioma. Anticancer Res. 2007;27:39–44.
216. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2010;141:1117–34.
217. Vintman L, Nielsen S, Berner A, Reich R, Davidson B. Mitogen-activated protein kinase expression and activation does not differentiate benign from malignant mesothelial cells. Cancer. 2005;103:2427–33.
218. de Melo M, Gerbase MW, Curran J, Pache JC. Phosphorylated extracellular signal-regulated kinases are significantly increased in malignant mesothelioma. J Histochem Cytochem. 2006;54: 855–61.
219. Eguchi R, Fujimori Y, Takeda H, et al. Arsenic trioxide induces apoptosis through JNK and ERK in human mesothelioma cells. J Cell Physiol. 2011;226:762–8.
220. Ou WB, Hubert C, Corson JM, et al. Targeted inhibition of multiple receptor tyrosine kinases in mesothelioma. Neoplasia. 2011; 13:12–22.
221. Ohta Y, Shridhar V, Bright RK, et al. VEGF and VEGF type C play an important role in angiogenesis and lymphangiogenesis in human malignant mesothelioma tumours. Br J Cancer. 1999; 81:54–61.
222. Konig J, Tolnay E, Wiethege T, Muller K. Co-expression of vascular endothelial growth factor and its receptor flt-1 in malignant pleural mesothelioma. Respiration. 2000;67:36–40.
223. Strizzi L, Catalano A, Vianale G, et al. Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma. J Pathol. 2001;193:468–75.
224. Filho AL, Baltazar F, Bedrossian C, Michael C, Schmitt FC. Immunohistochemical expression and distribution of VEGFR-3 in malignant mesothelioma. Diagn Cytopathol. 2007;35:786–91.
225. Lee AY, Raz DJ, He B, Jablons DM. Update on the molecular biology of malignant mesothelioma. Cancer. 2007;109:1454–61.
226. Masood R, Kundra A, Zhu S, et al. Malignant mesothelioma growth inhibition by agents that target the VEGF and VEGF-C autocrine loops. Int J Cancer. 2003;104:603–10.
227. Jacobson A, Brinck J, Briskin MJ, Spicer AP, Heldin P. Expression of human hyaluronan synthases in response to external stimuli. Biochem J. 2000;348:29–35.
228. Heldin P, Asplund T, Ytterberg D, Thelin S, Laurent TC. Characterization of the molecular mechanism involved in the activation of hyaluronan synthase by platelet-derived growth factor in human mesothelial cells. Biochem J. 1992;283(Pt 1):165–70.
229. Gerwin BI, Lechner JF, Reddel RR, et al. Comparison of production of transforming growth factor-beta and platelet-derived growth factor by normal human mesothelial cells and mesothelioma cell lines. Cancer Res. 1987;47:6180–4.
230. Versnel MA, Claessonwelsh L, Hammacher A, et al. Human malignant mesothelioma cell lines express PDGF beta-receptors whereas cultured normal mesothelial cells express predominantly PDGF alpha-receptors. Oncogene. 1991;6:2005–11.
231. Metheny-Barlow LJ, Flynn B, van Gijssel HE, Marrogi A, Gerwin BI. Paradoxical effects of platelet-derived growth factor-A overexpression in malignant mesothelioma. Antiproliferative effects in vitro and tumorigenic stimulation in vivo. Am J Respir Cell Mol Biol. 2001;24:694–702.
232. Van der Meeren A, Seddon MB, Betsholtz CA, Lechner JF, Gerwin BI. Tumorigenic conversion of human mesothelial cells as a consequence of platelet-derived growth factor-A chain overexpression. Am J Respir Cell Mol Biol. 1993;8:214–21.
233. Agarwal V, Lind MJ, Cawkwell L. Targeted epidermal growth factor receptor therapy in malignant pleural mesothelioma: where do we stand. Cancer Treat Rev. 2010;37:533–542.
234. Hoang CD, Zhang X, Scott PD, et al. Selective activation of insulin receptor substrate-1 and -2 in pleural mesothelioma cells: association with distinct malignant phenotypes. Cancer Res. 2004;64: 7479–85.
235. Whitson BA, Kratzke RA. Molecular pathways in malignant pleural mesothelioma. Cancer Lett. 2006;239:183–9.
236. Jaurand MC, Fleury-Feith J. Mesothelial cells. In: Light RW, Lee YCG, editors. Textbook of pleural diseases. 2nd ed. London: Hodder Arnold; 2008. p. 27–37.
237. Lee TC, Zhang Y, Aston C, et al. Normal human mesothelial cells and mesothelioma cell lines express insulin-like growth factor I and associated molecules. Cancer Res. 1993;53:2858–64.
238. Liu Z, Klominek J. Regulation of matrix metalloprotease activity in malignant mesothelioma cell lines by growth factors. Thorax. 2003;58:198–203.
239. Jagadeeswaran R, Ma PC, Seiwert TY, et al. Functional analysis of c-Met/hepatocyte growth factor pathway in malignant pleural mesothelioma. Cancer Res. 2006;66:352–61.

240. Kawaguchi K, Murakami H, Taniguchi T, et al. Combined inhibition of MET and EGFR suppresses proliferation of malignant mesothelioma cells. Carcinogenesis. 2009;30:1097–105.
241. Tolnay E, Kuhnen C, Wiethege T, König JE, Voss B, Müller KM. Hepatocyte growth factor/scatter factor and its receptor c-Met are overexpressed and associated with an increased microvessel density in malignant pleural mesothelioma. J Cancer Res Clin Oncol. 1998;124:291–6.
242. Thirkettle I, Harvey P, Hasleton PS, Ball RY, Warn RM. Immunoreactivity for cadherins, HGF/SF, met, and erbB-2 in pleural malignant mesotheliomas. Histopathology. 2000;36:522–8.
243. Harvey P, Warn A, Dobbin S, et al. Expression of HGF/SF in mesothelioma cell lines and its effects on cell motility, proliferation and morphology. Br J Cancer. 1998;77:1052–9.
244. Mukohara T, Civiello G, Davis IJ, et al. Inhibition of the met receptor in mesothelioma. Clin Cancer Res. 2005;11:8122–30.
245. Besson A, Robbins SM, Yong VW. PTEN/MMAC1/TEP1 in signal transduction and tumorigenesis. Eur J Biochem. 1999;263:605–11.
246. Daubriac J, Fleury-Feith J, Kheuang L, et al. Malignant pleural mesothelioma cells resist anoikis as quiescent pluricellular aggregates. Cell Death Differ. 2009;16:1146–55.
247. Altomare DA, You H, Xiao GH, et al. Human and mouse mesotheliomas exhibit elevated AKT/PKB activity, which can be targeted pharmacologically to inhibit tumor cell growth. Oncogene. 2005;24:6080–9.
248. Suzuki Y, Murakami H, Kawaguchi K, et al. Activation of the PI3K-AKT pathway in human malignant mesothelioma cells. Mol Med Rep. 2009;2:181–8.
249. Clevers H. Wnt/beta-catenin signaling in development and disease. Cell. 2006;127:469–80.
250. Lee AY, He B, You L, et al. Dickkopf-1 antagonizes Wnt signaling independent of beta-catenin in human mesothelioma. Biochem Biophys Res Commun. 2004;323:1246–50.
251. He B, Lee AY, Dadfarmay S, et al. Secreted frizzled-related protein 4 is silenced by hypermethylation and induces apoptosis in beta-catenin-deficient human mesothelioma cells. Cancer Res. 2005;65:743–8.
252. Batra S, Shi Y, Kuchenbecker KM, et al. Wnt inhibitory factor-1, a Wnt antagonist, is silenced by promoter hypermethylation in malignant pleural mesothelioma. Biochem Biophys Res Commun. 2006;342:1228–32.
253. Kohno H, Amatya VJ, Takeshima Y, et al. Aberrant promoter methylation of WIF-1 and SFRP1, 2, 4 genes in mesothelioma. Oncol Rep. 2010;24:423–31.
254. Mazieres J, You L, He B, et al. Wnt2 as a new therapeutic target in malignant pleural mesothelioma. Int J Cancer. 2005;117:326–32.
255. Soini Y, Kinnula V, Kaarteenaho-Wiik R, Kurttila E, Linnainmaa K, Paakko P. Apoptosis and expression of apoptosis regulating proteins bcl-2, mcl-1, bcl-X, and bax in malignant mesothelioma. Clin Cancer Res. 1999;5:3508–15.
256. Rippo MR, Moretti S, Vescovi S, et al. FLIP overexpression inhibits death receptor-induced apoptosis in malignant mesothelial cells. Oncogene. 2004;23:7753–60.
257. O'Kane SL, Pound RJ, Campbell A, Chaudhuri N, Lind MJ, Cawkwell L. Expression of bcl-2 family members in malignant pleural mesothelioma. Acta Oncol. 2006;45:449–53.
258. Jin L, Amatya VJ, Takeshima Y, Shrestha L, Kushitani K, Inai K. Evaluation of apoptosis and immunohistochemical expression of the apoptosis-related proteins in mesothelioma. Hiroshima J Med Sci. 2010;59:27–33.
259. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70.
260. Kafiri G, Thomas DM, Shepherd NA, Krausz T, Lane DP, Hall PA. p53 expression is common in malignant mesothelioma. Histopathology. 1992;21:331–4.
261. Ramael M, Lemmens G, Eerdekens C, et al. Immunoreactivity for p53 protein in malignant mesothelioma and non-neoplastic mesothelium. J Pathol. 1992;168:371–5.
262. Mayall FG, Goddard H, Gibbs AR. The frequency of p53 immunostaining in asbestos-associated mesotheliomas and non-asbestos-associated mesotheliomas. Histopathology. 1993;22:383–6.
263. Attanoos RL, Griffin A, Gibbs AR. The use of immunohistochemistry in distinguishing reactive from neoplastic mesothelium. A novel use for desmin and comparative evaluation with epithelial membrane antigen, p53, platelet-derived growth factor-receptor, P-glycoprotein and Bcl-2. Histopathology. 2003;43:231–8.
264. Feng Z, Levine AJ. The regulation of energy metabolism and the IGF-1/mTOR pathways by the p53 protein. Trends Cell Biol. 2010;20:427–34.
265. Leard LE, Broaddus VC. Mesothelial cell proliferation and apoptosis. Respirology. 2004;9:292–9.
266. Wilson SM, Barbone D, Yang TM, et al. mTOR mediates survival signals in malignant mesothelioma grown as tumor fragment spheroids. Am J Respir Cell Mol Biol. 2008;39:576–83.
267. Singhal S, Wiewrodt R, Malden LD, et al. Gene expression profiling of malignant mesothelioma. Clin Cancer Res. 2003;9:3080–97.
268. Lampson MA, Cheeseman IM. Sensing centromere tension: aurora B and the regulation of kinetochore function. Trends Cell Biol. 2011;21:133–40.
269. Jensen CG, Jensen LCW, Rieder CL, Cole RW, Ault JG. Long crocidolite asbestos fibers cause polyploidy by sterically blocking cytokinesis. Carcinogenesis. 1996;17:2013–21.
270. Cortez BA, Machadosantelli GM. Chrysotile effects on human lung cell carcinoma in culture: 3-D reconstruction and DNA quantification by image analysis. BMC Cancer. 2008;8:181.
271. Mijailovich SM, Kojic M, Tsuda A. Particle-induced indentation of the alveolar epithelium caused by surface tension forces. J Appl Physiol. 2010;109:1179–94.

Malignant Mesothelioma: Genetic Susceptibility

18

Ari P. Hirvonen

Keywords
Malignant mesothelioma • Genetic susceptibility • Genome-wide association studies • NAT • GST

Introduction

Although exposure to asbestos fibers is a well-known risk factor for malignant mesothelioma (MM), its mechanisms of carcinogenicity are not fully understood. Inhaled asbestos fibers penetrate the lung epithelium and irritate the pleural lining. This causes repeated cycles of damage, repair, and local inflammation. After interaction with mesothelial cells, asbestos triggers multiple cell-signaling pathways.

Asbestos fibers could also interfere with the mitotic spindle formation of cells resulting in chromosomal abnormalities. However, the most circumstantiated mechanism in this context is probably via reactive oxygen or nitrogen species (ROS/RNS). The free radicals may cause cellular toxicity and carcinogenicity by including lipid peroxidation, altering signal transduction pathway, and damaging the DNA directly [1–4].

The observation that only 5–17 % of heavily asbestos-exposed subjects develop MM [5], together with the findings on familial clustering and candidate gene association studies [6, 7], suggests a genetic component to this malignancy.

The genetic studies on MM offer us an opportunity to study the interactions between genes and environment in a complex human phenotype; the same genetic factors may confer susceptibility in sporadic and familial MM [4]. To date, however, a very limited number of studies have been conducted on individual susceptibility to MM, and they have focused on candidate genes.

A.P. Hirvonen, PhD
Finnish Institute of Occupational Health,
Topeliuksenkatu 41 a A, Helsinki, 00250, Finland
e-mail: ari.hirvonen@ttl.fi

Genetic Susceptibility to Malignant Mesothelioma

Candidate Gene Studies on Malignant Mesothelioma

The first candidate gene study was conducted in Finland on glutathione *S*-transferase M1 (GSTM1) and *N*-acetyltransferase 2 (NAT2) genotypes among highly asbestos-exposed workers [8]; the homozygous deletion of *GSTM1* gene results in total loss of GSTM1 activity, whereas variation in *NAT2* gene segregate people into fast, intermediate, and slow N-acetylator phenotypes (for more detail, see Chap. 11).

The Finnish study demonstrated an increased risk both in individuals with the *GSTM1* null genotype and the *NAT2* slow acetylator phenotype [8]; the *GSTM1* null genotype (OR 1.8, 95 % CI 1.0–3.5) and the *NAT2* slow-acetylator genotype (OR 2.1, 95 % CI 1.1–4.1) placed both individuals at about twofold increased risk of developing MM. When the patients were divided into low/moderate and high exposure groups according to their asbestos exposure histories, the effect of the at-risk genotypes was mostly attributable to the high exposure groups with ORs of 2.3 (95 % CI 1.0–5.6) and 3.7 (95 % CI 1.3–10.2), respectively.

When the gene-gene interactions were studied, the individuals with combined *GSTM1* and *NAT2* defects had about a fourfold risk of developing MM compared to those with the *GSTM1* gene and *NAT2* fast-acetylator genotype (OR 3.6, 95 % CI 1.3–9.6). Moreover, the risk among subjects highly exposed to asbestos with the double at-risk genotype was more than sevenfold compared to those with the more beneficial genotypes of both *GSTM1* and *NAT2* genes (OR 7.4, 95 % CI 1.6–34.0).

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_18, © Springer-Verlag London 2014

In an extension of the Finnish study, the effect of the homozygous deletion of the *GSTM1* gene in the risk of MM was not, however, anymore seen [9]. Neither was an association observed for the homozygous deletion of another *GST* gene, i.e., the *GSTT1* gene. However, the previously observed effect of *NAT2* slow-acetylator genotype was again observed; the risk of developing MM for carriers of *NAT2* slow-acetylator genotypes was increased to almost fourfold (OR 3.8, 95 % CI 1.2–14.3). Moreover, the previously observed combined effect of *GSTM1* and *NAT2* genotypes was seen; individuals who lacked the *GSTM1* gene and possessed a *NAT2* slow-acetylator genotype had an almost eightfold risk of developing MM (OR 7.8, 95 % CI 1.4–78.7) compared with the carriers of the combination of *GSTM1* gene and *NAT2* fast-acetylator genotype.

Subsequently Italian studies also found increased risk in asbestos-exposed individuals with the *GSTM1* null genotype [10] and with the *NAT2* slow-acetylator genotype [11]; the *GSTM1* null allele posed an almost twofold risk of MM (OR 1.69, 95 % CI 1.04–2.74) [10] and a *NAT2* slow-acetylator allele an almost fourfold risk of MM (OR 3.54, 95 % CI 1.75–7.16). However, two other Italian findings contrasted the *NAT2* results by finding increased risks with ORs of 1.74 (95 % CI 1.02–2.96) and 1.47 (95 % CI 0.96–2.26) of MM for the asbestos-exposed carriers of the *NAT2* fast-acetylator genotype [12, 13].

One of the Italian studies [10] also found an increased risk of MM among homozygous carriers of the manganese superoxide dismutase (MnSOD) wild-type allele (Ala/Ala genotype) at codon 16 (OR 3.07, 95 % CI 1.55–6.05). A polymorphism at this locus results in an Ala16Val amino acid change and a 30–40 % reduction in the respective enzyme activity (for more detail, see Chap. 11). However, an earlier Finnish study did not reveal any significant association between the *MnSOD* genotypes and risk of MM; a slightly elevated OR for malignant mesothelioma was seen for the asbestos-exposed workers with the *MnSOD* Val allele containing genotypes (OR 1.5, 95 % CI 0.4–6.7) compared with the Ala/Ala genotypes [14]. This association was, however, far from statistical significance. Furthermore, although the ORs seemed to follow the number of *MnSOD* Val alleles, being 1.4 (95 % CI 0.3–6.3) and 2.0 (95 % CI 0.3–11.9) for the *MnSOD* Ala/Val and Val/Val genotypes, respectively, the trend test revealed no significant association (*P* for trend = 0.91).

Italian studies have also implicated associations between increased risk of MM and variants of the microsomal epoxide hydrolase (EPHX1) [12], X-ray repair cross-complementing group 1 (XRCC1) and 3 (XRCC3) [6, 15], and excision repair cross-complementing rodent repair deficiency, complementation group 1 (ERCC1) [6] genes.

The genetic polymorphisms within exons 3 and 4 of the *EPHX1* gene result in His113Tyr and Arg139His amino acid substitutions, respectively. In vitro expression analyses indicated that the corresponding EPHX1 activities are decreased by approximately 40 % (Tyr113) or increased by at least 25 % (His139). A genetic variation in the 5′ flanking sequence of *EPHX1* has also been observed, which may be an additional contributing factor to the range of functional EPHX1 expression existing in human populations (for more detail, see Chap. 11).

The *XRCC1* and *XRCC3* genes, and the *ERCC1* gene, in turn, play important roles in the base excision repair (BER) and nucleotide excision repair (NER) pathways, and thus their functional polymorphisms may have important effects in development of asbestos-induced chromosomal damage (for more detail, see Chap. 11).

In one of the Italian studies [12], subjects with low EPHX1 activity-associated genotypes showed a significantly increased risk of MM (OR 2.51, 95 % CI 1.11–5.68). The association was stronger in the group with low asbestos exposure (OR 7.83, 95 % CI 0.98–62.6). In a subsequent Finnish and Italian collaborative study, however, no significant association between the *EPHX1* variant allele carrying genotypes and MM risk was observed, in contrast to the Italian findings [16].

In another Italian study [6], combining two case-control studies conducted in Casale and Turin, increased risk of MM was seen with the increasing number of *XRCC1* 399Q (OR 1.34, 95 % CI 0.98–1.84) or *XRCC1* −77T (OR 1.33, 95 % CI 0.97–1.81) alleles, when only the asbestos-exposed subjects were considered. Carriage of *ERCC1* C alleles of the polymorphic N118N site posed them also at increased risk of MM (OR 1.56, 95 % CI 1.02–2.40).

In a third Italian study [15], the carriage of *XRCC1* 399Q allele was also associated with increased risk of MM (OR 2.15, 95 % CI 1.08–4.28). Moreover, carriage of *XRCC3* 241T allele posed more than fourfold risk of MM (OR 4.09, 95 % CI 1.26–13.21).

Lastly, co-segregating germ-line mutations in BRCA1-associated protein (BAP1) gene were discovered in two families with five or more members with mesothelioma [17]; the families did not have occupational asbestos exposure, but they had modest levels of asbestos exposure from having lived in asbestos-containing houses. BAP1 is a nuclear protein that enhances BRCA1-mediated inhibition of breast cancer cell proliferation, acting as a tumor suppressor in the BRCA1 growth control pathway and regulating proliferation by deubiquitinating host cell factor-1 [18, 19].

Genome-Wide Association Studies on Malignant Mesothelioma

During recent years genome-wide association studies (GWAS), which do not require prior knowledge of the functional

significance of the variants studied, have become more and more extensively used as an alternative to the candidate gene studies. Recently, the first GWAS on MM was conducted among Italian MM cases and their controls with a complete history of asbestos exposure [20]. A replication study was also undertaken in an Australia study population.

Although no single marker reached the genome-wide significance threshold, several associations were supported by haplotype-, chromosomal region-, gene-, and gene-ontology process-based analyses. Most of these SNPs were located in regions reported to harbor aberrant alterations in mesothelioma, causing at most a two- to threefold increase in MM risk. The Australian replication study showed significant associations in five of these chromosomal regions (3q26.2, 4q32.1, 7p22.2, 14q11.2, 15q14). Multivariate analysis suggested an independent contribution of ten genetic variants, with a substantial increase of asbestos exposure risk estimation (OR 45.3, 95 % CI 21.5–95.3).

Conclusion

Although the results of the studies on individual susceptibility to MM are somewhat contradictory, they support the complementary role of genetic background in asbestos-related carcinogenesis of the pleura, indicating that genetic risk factors should be taken into account to understand MM physiopathology.

The discrepancies in the findings from the case-control studies could of course be simply due to chance. However, the different ethnic origin and habits of the study populations undoubtedly also had an important role in this, e.g., since different types of asbestos have been used in the different countries.

All of the above candidate gene studies of MM have also suffered from small sample size, population structure, and poorly characterized exposures. Large, unrelated sample set with well-defined exposure levels are therefore needed, which necessitates large international collaboration. Well-matched controls, with data recorded on similar levels of exposure, sex, and ethnicity distributions, should be used in these studies.

Additional GWAS on MM are also definitely needed. Related to this, bioinformatics tools should also be more efficiently utilized to improve the ability to find genetic risk factors and better understand the biology of MM. For example, it may be useful to identify genetic differences in individuals with MM and minimal/no asbestos exposure versus those with heavy exposure and no MM [21].

In more exploratory studies, comparisons with GWAS on MM-related phenotypes (asbestosis, pulmonary fibrosis, pleural disease, and other types of cancer) can be made to explore commonalities in germ-line genetic risk factors, and, finally, meta-analysis can be used to combine results across GWAS on MM.

References

1. Robinson BWS, Lake RA. Advances in malignant mesothelioma. N Engl J Med. 2005;353:1591–603.
2. Yang H, Testa JR, Carbone M. Mesothelioma, epidemiology, carcinogenesis, and pathogenesis. Curr Treat Opt Oncol. 2008;9:147–57.
3. Below JE, Cox NJ, Fukagawa NK, Hirvonen A, Testa JR. Factors that impact susceptibility to fiber-induced health effects. J Toxicol Environ Health B Crit Rev. 2011;14:246–66.
4. Weiner SJ, Neragi-Miandoab S. Pathogenesis of malignant pleural mesothelioma and the role of environmental and genetic factors. J Cancer Res Clin Oncol. 2009;135:15–27.
5. Neri M, Ugolini D, Dianzani I, Gemignani F, Landi S, Cesario A, Magnani C, Mutti L, Puntoni R, Bonassi S. Genetic susceptibility to malignant pleural mesothelioma and other asbestos-associated diseases. Mutat Res. 2008;659:126–36.
6. Betti M, Ferrante D, Padoan M, Guarrera S, Giordano M, Aspesi A, Mirabelli D, Casadio C, Ardissone F, Ruffini E, Betta PG, Libener R, Guaschino R, Matullo G, Piccolini E, Magnani C, Dianzani I. XRCC1 and ERCC1 variants modify malignant mesothelioma risk: a case-control study. Mutat Res. 2011;708:11–20.
7. Ugolini D, Neri M, Ceppi M, Cesario A, Dianzani I, Filiberti R, Gemignani F, Landi S, Magnani C, Mutti L, Puntoni R, Bonassi S. Genetic susceptibility to malignant mesothelioma and exposure to asbestos: the influence of the familial factor. Mutat Res. 2008;658:162–71.
8. Hirvonen A, Pelin K, Tammilehto L, Karjalainen A, Mattson K, Linnainmaa K. Inherited GSTM1 and NAT2 defects as concurrent risk modifiers in asbestos-related human malignant mesothelioma. Cancer Res. 1995;55:2981–3.
9. Hirvonen A, Saarikoski ST, Linnainmaa K, Koskinen K, Husgafvel-Pursiainen K, Mattson K, Vainio H. Glutathione *S*-transferase and *N*-acetyltransferase genotypes and asbestos-associated pulmonary disorders. J Natl Cancer Inst. 1996;88:1853–6.
10. Landi S, Gemignani F, Neri M, Barale R, Bonassi S, Bottari F, Canessa PA, Canzian F, Ceppi M, Filiberti R, Ivaldi GP, Mencoboni M, Scaruffi P, Tonini GP, Mutti L, Puntoni R. Polymorphisms of glutathione-S-transferase M1 and manganese superoxide dismutase are associated with the risk of malignant pleural mesothelioma. Int J Cancer. 2007;120:2739–43.
11. Gemignani F, Neri M, Bottari F, Barale R, Canessa PA, Canzian F, Ceppi M, Spitaleri I, Cipollini M, Ivaldi GP, Mencoboni M, Scaruffi P, Tonini GP, Ugolini D, Mutti L, Bonassi S, Landi S. Risk of malignant pleural mesothelioma and polymorphisms in genes involved in the genome stability and xenobiotics metabolism. Mutat Res. 2009;671:76–83.
12. Neri M, Filiberti R, Taioli E, Garte S, Paracchini V, Bolognesi C, Canessa PA, Fontana V, Ivaldi GP, Verna A, Bonassi S, Puntoni R. Pleural malignant mesothelioma, genetic susceptibility and asbestos exposure. Mutat Res. 2005;592:36–44.
13. Betti M, Neri M, Ferrante D, Landi S, Biava A, Gemignani F, Bertolotti M, Mirabelli D, Padoan M, Ugolini D, Botta M, Bonassi S, Magnani C, Dianzani I. Pooled analysis of NAT2 genotypes as risk factors for asbestos-related malignant mesothelioma. Int J Hyg Environ Health. 2009;212:322–9.
14. Hirvonen A, Tuimala J, Ollikainen T, Linnainmaa K, Kinnula V. Manganese superoxide dismutase genotypes and asbestos-associated pulmonary disorders. Cancer Lett. 2002;178:71–4.
15. Dianzani I, Gibello L, Biava A, Giordano M, Bertolotti M, Betti M, Ferrante D, Guarrera S, Betta GP, Mirabelli D, Matullo G, Magnani C. Polymorphisms in DNA repair genes as risk factors for asbestos-related malignant mesothelioma in a general population study. Mutat Res. 2006;599:124–34.
16. Neri M, Taioli E, Filiberti R, Ivaldi GP, Canessa PA, Verna A, Marroni P, Puntoni R, Hirvonen A, Garte S. Metabolic genotypes as modulators of asbestos-related pleural malignant mesothelioma

risk: a comparison of Finnish and Italian populations. Int J Hyg Environ Health. 2006;209:393–8.
17. Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, Cox NJ, Dogan AU, Pass HI, Trusa S, Hesdorffer M, Nasu M, Powers A, Rivera Z, Comertpay S, Tanji M, Gaudino G, Yang H, Carbone M. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet. 2011;43:1022–5.
18. Jensen DE, Proctor M, Marquis ST, Gardner HP, Ha SI, Chodosh LA, Ishov AM, Tommerup N, Vissing H, Sekido Y, Minna J, Borodovsky A, Schultz DC, Wilkinson KD, Maul GG, Barlev N, Berger SL, Prendergast GC, Rauscher 3rd FJ. BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. Oncogene. 1998;16:1097–112.
19. Ventii KH, Devi NS, Friedrich KL, Chernova TA, Tighiouart M, Van Meir EG, Wilkinson KD. BRCA1-associated protein-1 is a tumor suppressor that requires deubiquinating activity and nuclear localization. Cancer Res. 2008;68:6953–62.
20. Matullo G, Guarrera S, Betti M, Fiorito G, Ferrante D, Voglino F, Cadby G, Di Gaetano C, Rosa F, Russo A, Hirvonen A, Casalone E, Tunesi S, Padoan M, Giordano M, Aspesi A, Casadio C, Ardissone F, Ruffini E, Betta PG, Libener R, Guaschino R, Piccolini E, Neri M, Musk AW, de Klerk NH, Hui J, Beilby J, James AL, Creaney J, Robinson BW, Mukherjee S, Palmer LJ, Mirabelli D, Ugolini D, Bonassi S, Magnani C, Dianzani I. Genetic variants associated with increased risk of malignant pleural mesothelioma: a genome-wide association study. PLoS One. 2013;8:e61253.
21. Zhang GD, Nebert W, Chakraborty R, Jin L. Statistical power of association using the extreme discordant phenotype design. Pharmacogenet Genomics. 2006;16:401–13.

Malignant Mesothelioma: Molecular Markers

19

Eeva Kettunen and Sakari Knuutila

Keywords
Malignant mesothelioma • Biomarkers • Molecular markers • Cancer markers • Serum markers • Genetic markers • Genomics • Epigenetic changes • Protein markers

Introduction

During the last few years, knowledge of the molecular features has increased in neoplasias in general but especially in certain malignant diseases like malignant mesothelioma (MM) which have very high mortality. This knowledge has helped to identify biomarkers that not only facilitate early and differential diagnosis but also assist with the evaluation of the prognosis and effectiveness of the treatment provided. Similarly, these advances have also shed light on the etiology of the diseases, for example, about exposures to different environmental factors. Importantly, novel and more sensitive methods have made it possible to detect these biomarkers in effusions (pleural fluid), plasma, serum, urine, and sputum as a source of the malignant cells to achieve a fast, early, and less expensive diagnosis as well as follow-up of the disease without the need for tissue from the primary tumor for analysis.

This chapter describes genomic, proteomic, and functional changes (biomarkers) and their clinical significance in MM, while the causes of genetic changes in MM, especially the mechanisms behind the genomic alterations induced by asbestos, have been discussed in Chap. 17.

E. Kettunen, PhD
Health and Work Ability,
Finnish Institute of Occupational Health,
Helsinki, Finland

S. Knuutila, PhD (✉)
Department of Pathology and Genetics,
HUSLAB, Helsinki University Central Hospital,
Haartmaninkatu 8, P. Box 63, 00014,
The University of Helsinki, Finland
e-mail: sakari.knuutila@helsinki.fi

Methods and Materials for Studying Genetic Changes in MM

In the karyotype analysis of MM, chromosome banding is traditionally conducted on cell cultures of either primary tumor tissues or cells from pleural fluid [1, 2]. Due to the fact that cytogenetic analysis requires cell proliferation and mitotic cells, only fresh tumor cells can be used, whereas if one uses the interphase fluorescence in situ hybridization (FISH) technique with chromosome-specific probes, then uncultured cells from tumor tissue, pleural fluid, or sputum can also be utilized [3–5]. With respect to loss of heterozygosity (LOH) analysis with microsatellite markers, the chromosome and the array comparative genomic hybridization (cCGH and aCGH), as well as the next-generation sequencing and the DNA methylation studies, DNA extracted from tumor cells (and also from normal reference cells from the patient in the case of LOH) is needed [6–8]. DNA-based systems require the tumor cell proportion of at least 30 %. It is important that these systems can also utilize DNA extracted from formalin-fixed and paraffin-embedded (FFPE) tumor tissues. In contrast, as in the case for mRNA extraction and gene expression analyses, FFPE material cannot be used, although there are some exceptions, due to RNA degradation during formalin fixation. However, microRNAs (miRNA) (which will be described later in this chapter) are resistant to degradation in formalin fixation, which makes it possible to take advantage of FFPE material for analysis with miRNA microarray and PCR techniques [9].

Microarray and next-generation sequencing methods create an enormous amount of genomic and functional data. Thanks to the fast development of bioinformatics methods and to the collaboration with clinicians, molecular biologists,

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_19, © Springer-Verlag London 2014

and bioinformaticians, data from different sources can be integrated and used for mining novel genetic changes as illustrated in a recent publication revealing a novel MM-associated gene, *SIM2s* (single-minded homolog 2, short isoform) [10].

Genomic Changes as Biomarkers

Chromosomal Imbalances

Similar to malignant tumors in general, also MM displays clonal chromosomal abnormalities. Both standard chromosome banding and chromosome and array-based CGH are able to pinpoint the complex nature of these changes. Indeed, close to 100 cases with chromosomal alterations have been described [1, 2, 11–13]. The main reasons for the relatively small patient series for karyotype analyses are the necessity of cell culture, methodological difficulties encountered in chromosome preparation, as well as the chaotic nature of the aberrations.

Chromosomal abnormalities in MM are very complex, involving both chromosomal structure and number (Fig. 19.1) [1, 2]. The chromosome number varies greatly within the specimen, but it is mostly hypodiploid (less than normal diploid 46 chromosomes) even though polyploid (multiplication of the whole chromosome set) forms of hypodiploid clones are frequently observed.

There are also many different structural chromosomal aberrations, although unbalanced translocations and deletions are the characteristic abnormalities. At present, no recurrent balanced translocations have been described. The most common abnormalities are −22 (the symbol "−" means chromosome is missing); + 7 (the symbol "+" means extra chromosome); −1, −3, −4, and 6q- (the symbol "q-" means chromosomal material in the long arm is missing); and −9, +11, and 3p- (the symbol "p-" means material in the short arm is missing).

A more detailed perspective of chromosomal imbalances has emerged through chromosomal and array CGH studies as well as from LOH and FISH studies [6–8, 14].

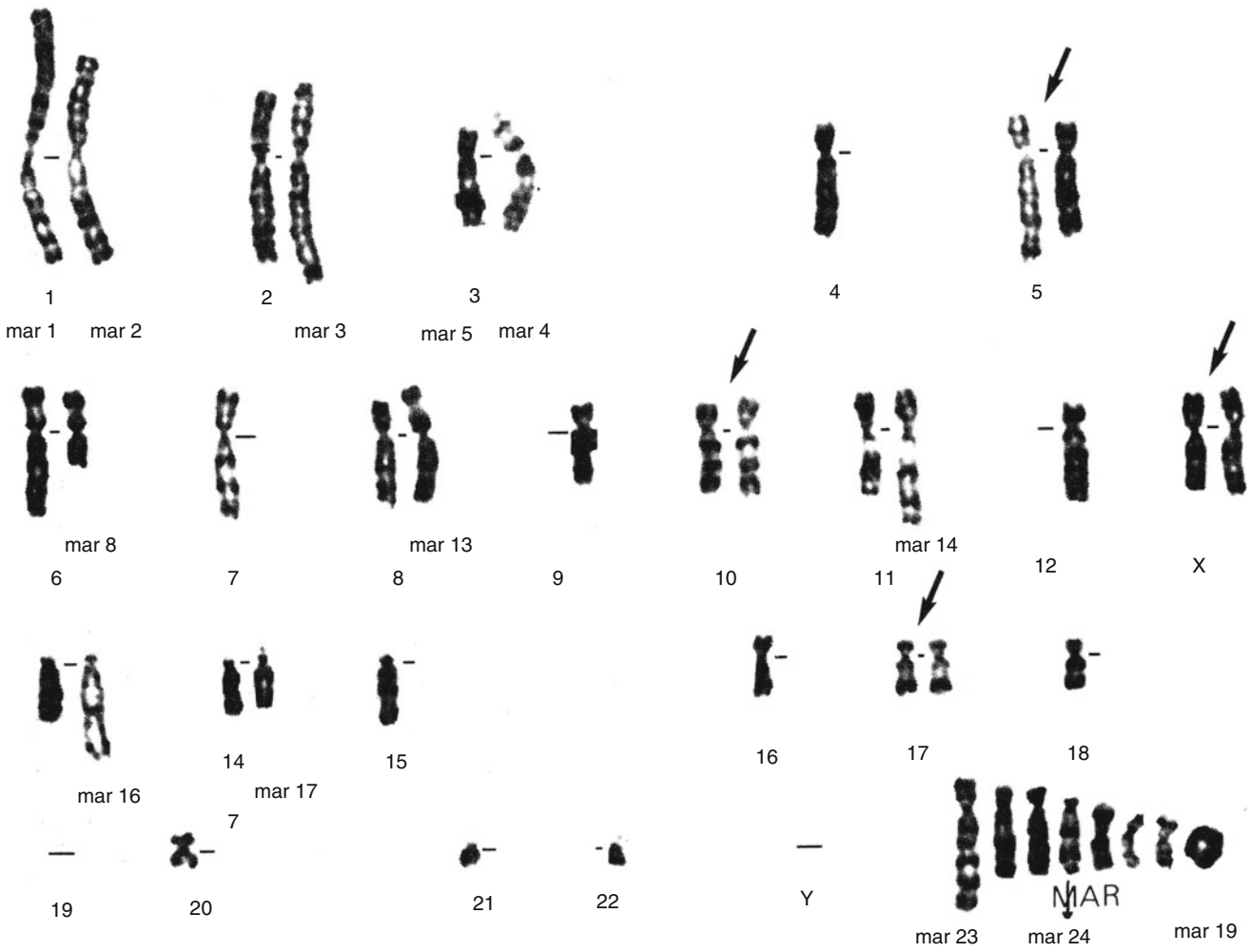


Fig. 19.1 Chaotic chromosomal aberrations in MM seen by chromosome banding analysis. *Arrows* indicate the normal chromosomes. The symbol "mar" in this context means aberrant chromosome that is seen as clonal (present at least in two metaphase cells). Descriptions of each marker chromosome are to be found in the original paper (Adapted from [1] with permission from Elsevier, Copyright 1998)

The most common gains are observed at 1q, 5p, 6p, 7, 8, 11, and 17q, whereas the most common losses are located at 1p, 12p, 6q, 9p, 10, 13, 14, and 17p. The array CGH analyses, which are more sensitive than earlier methods, have revealed novel regions of genomic losses, gains, and high-level amplifications, such as gains at 1p32 (the symbol "p32" means the chromosome band 32 in the short arm), 9p13.3, 7p22.2–p22.3, 12q13.3 (the symbol "q13.3" means the chromosome band 13.3. in the long arm), and 17q21.32-qter [8].

The most frequent aberration in MM is a homozygous deletion of 9p21.3 affecting *CDKN2A* (cyclin-dependent kinase inhibitor 2A) as well as a variable number of adjacent genes [8, 15, 16]. In pleural MM, the homozygous deletion of *CDKN2A* and the co-deletion of *MTAP* (methylthioadenosine phosphorylase) is the most common gene change which has been reported to be present in 60–74 % of primary tumors and up to 100 % in cell lines [4, 17–20]. In contrast, as for peritoneal MM, the corresponding frequency is only 35 % [21]. The deletion cases in peritoneal MM were exclusively detected in men being older than those without deletion, and, moreover, these patients had a significantly poorer prognosis than those without deletion in their tumors [21]. In fact, this deletion has also been reported to be a sign of poor prognosis in pleural MM as in peritoneal MM [22]. The fact that immunostaining revealed a loss of p16 protein coded by *CDKN2A* in peritoneal tumors even in as many as 54 % of cases may indicate that mechanisms other than deletions, for example, methylation, may be silencing the gene [21]. However, the question still remains open whether these two inactivation mechanisms (deletion vs. methylation) may be originated from different exposure status. As regards disease location, peritoneal MM have been reported to associate with heavier exposure than pleural MM [23]. In familial MM cases, 9p deletions have also been reported to be recurrent [24, 25].

In addition to *CDKN2* deletions, some other aberrations, such as at the *NF2* (neurofibromatosis 2) region at 22q together with *FHIT* (fragile histidine triad protein) region at 3p as well as deletions at 6q, 9p, and 14 have been reported by LOH analyses to be frequent [26]. Apart from the abovementioned genes (*CDKN2A*/9p, *NF2*/22q, *FHIT*/3p), the other target genes of recurrent genomic imbalances are still largely unknown. Recurrent chromosomal imbalances and the corresponding putative candidate genes are shown in Fig. 19.2 and Table 19.1. The question if some of the recurrent chromosomal abnormalities are associated with the asbestos burden will be discussed in more detail in Chap. 17, but briefly, our earlier cytogenetic analyses did reveal an association of chro-

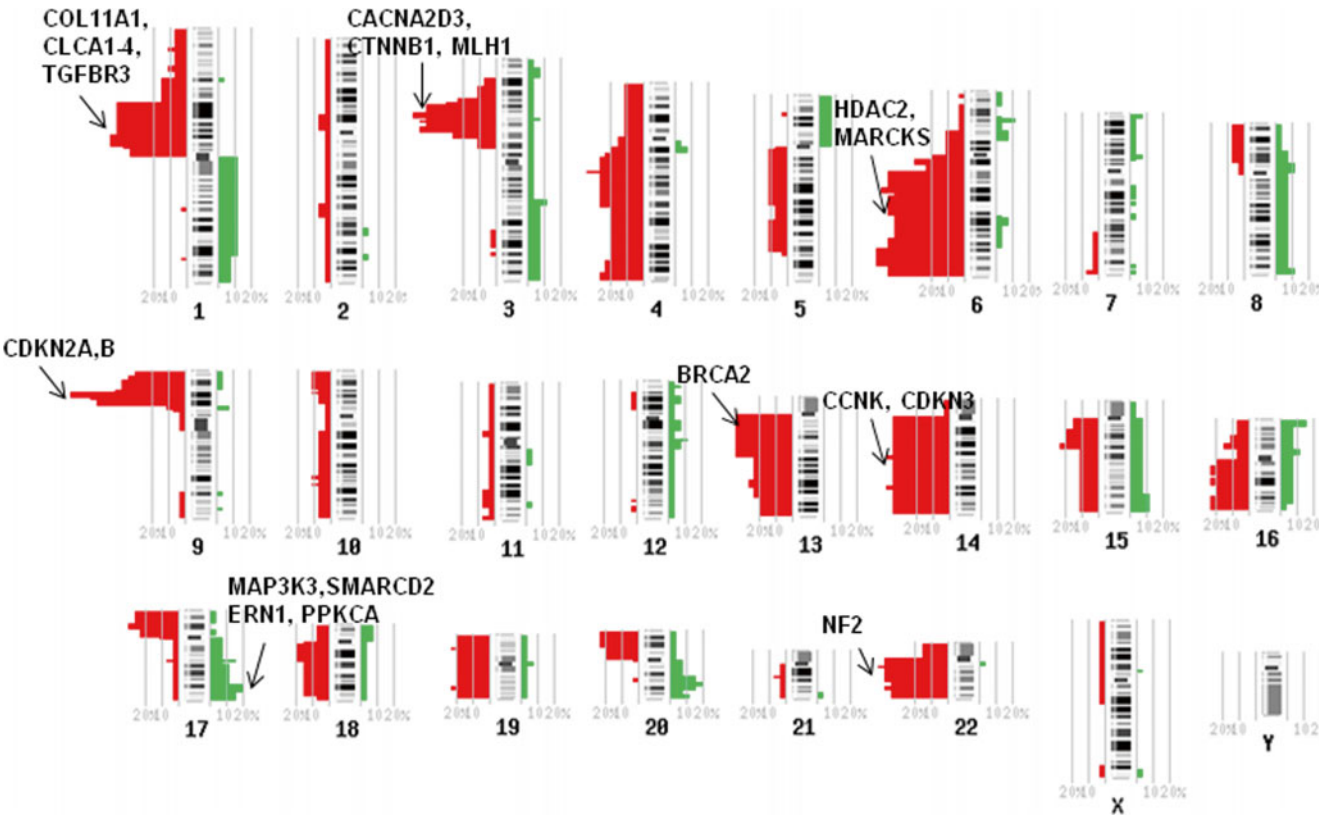


Fig. 19.2 Recurrent chromosomal imbalances and putative candidate genes in MM. Copy number losses on the left and gain on the right side of the chromosome (Modified from Lindholm et al. [8] and Baudis et al. [143])

Table 19.1 Recurrent copy number changes and putative target genes therein according to Lindholm et al. 2007

Copy number change	Genes
−1p31.1→p13.2[a]	*COL11A1*, *CLCA1*, *CLCA2*, *CLCA3*, *CLCA4*, *TGFBR3*
−3p22.1→p14.2	*CACNA2D3*, *CTNNB1*, *MLH1*
−6q22.1	*HDAC2*, *MARCKS*
−9p21.3	*CDKN2A*, *CDKN2B*, *C9Orf14*
−13cen→q14.12	*BRCA2*
−14q22.1→qter	*CCNK*, *CDKN3*
+17q21.32→qter[b]	*MAP3K3*, *SMARCD2*, *ERN1*, *PRKCA*
−22cen→q12.3	*NF2*

Modified from Lindholm et al. [8], with permission from S. Karger AG. Full names of gene symbols and their synonyms can be found at http://www.genenames.org

[a]Loss of chromosomal material (e.g., 1p31.1→p13.2 shows that the region between the chromosome band p31.1 and p13.2 is lost in the chromosome 1)

[b]Gain of chromosomal material indicated

mosome 1p deletion and monosomy 4 with a high asbestos burden [27]. Very recently, Jean et al. 2011 published evidence that a deletion at chromosome 14, one of the most recurrent alterations in MM, is also asbestos-related [28].

The histological MM subtypes (epithelioid, sarcomatoid, and biphasic) share many of the aberrations, even though partly distinct aberration patterns have been reported. A gain of 7q and losses at 3p14-p21 and 17p12-pter seem to be associated with the epithelioid MM, whereas gains at 5p and 8q and losses at 7q and 15q appear to be more related to a sarcomatoid subtype [29].

Genomic profiling of MM show clear-cut differences from the profiling of lung adenocarcinoma (Fig. 19.3). Losses at 4, 6q, 10, 14, and 9p are recurrent in MM, whereas gains at 8q, 1q, and 7p dominate in lung adenocarcinoma. The sensitivity of CGH analysis in differentiating MM from lung adenocarcinoma was 81 % with a specificity of 77 % [14].

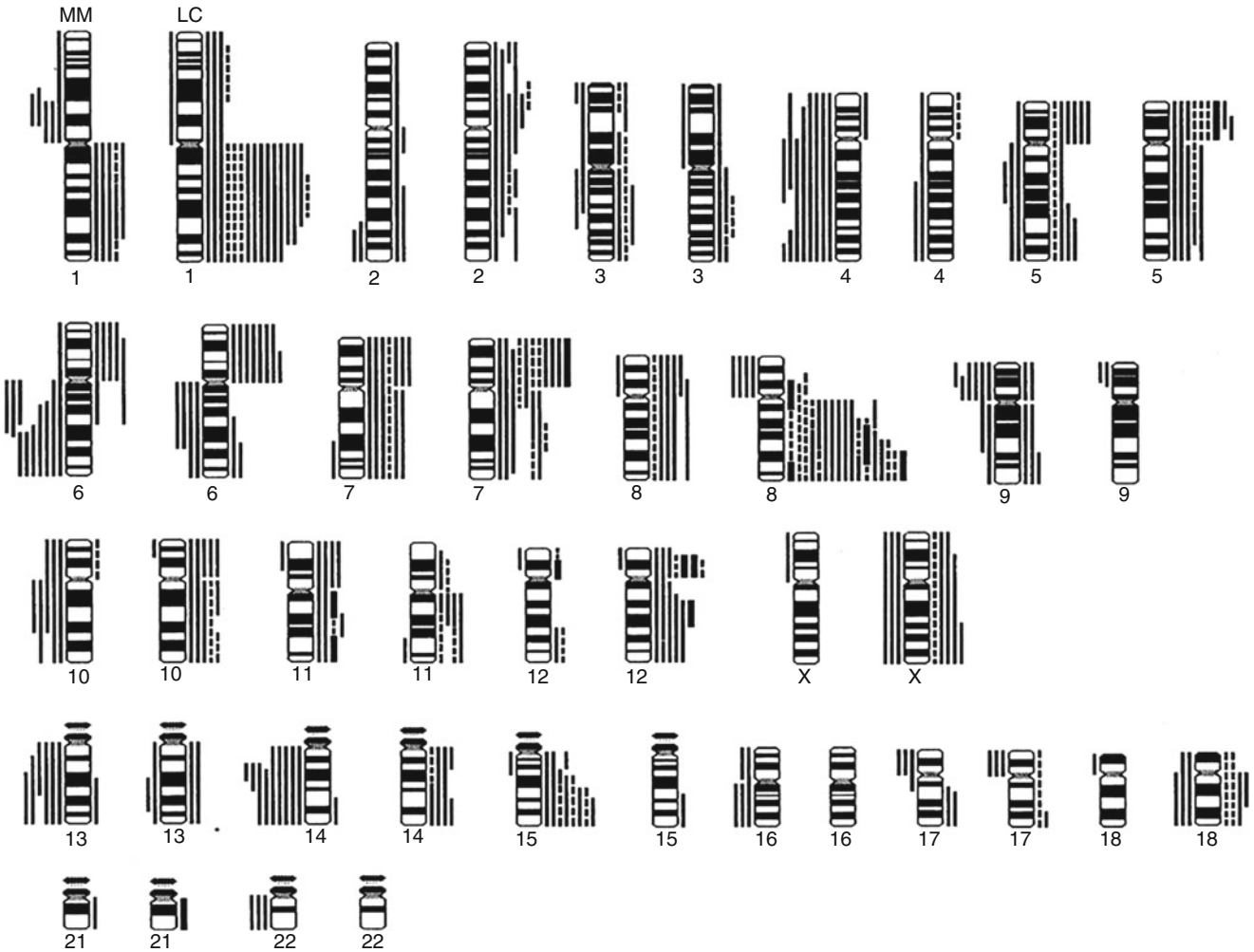


Fig. 19.3 Copy number changes in malignant mesothelioma (*MM*) and lung adenocarcinoma (*LC*) are so different that tumor type can be predicted more than 80 % (Adapted by permission from Macmillan Publishers Ltd: Björkqvist et al. [14], Copyright 1998)

Table 19.2 Genes regularly involved in MM

Downregulated
BAP1
CDKN2A, *B*
RB
NF2
WNT (*BCAT*)
RASSF1A
WT1
XRCC6 (*x-ray repair*)
Upregulated
EGFR (*ERBB2*,*3*,*4*, *JUN*, *FOS*)
VEGF (*SV-40*, *IL6*, *FLT1*, *KDR*)
BLC2 (*BAX*, *BAK*, *BAD*, *BCLXL*, *MCL1*)
IGF1
TGFB
IL6,*8*, *GMCSF*, *GCSF*, *MCSF*
COX2
IAP (*IAP1*, *IAP2*, *XIAP*, *LIVIN*, *SURVIVIN*)
TNFA
MET

Full names of gene symbols and their synonyms can be found at http://www.genenames.org

Table 19.3 Differentially expressed miRNAs and their target genes

miRNA	Overexpressed (+)/ underexpressed (–)	Target genes
hsa-miR-584	+	*RB1*
hsa-miR-30b*	+	*RB1*
hsa-miR-885-3p	+	*CDKN2A* and *NF2*
hsa-miR-345	+	
hsa-let-7b*	+	
hsa-miR-483-3p	+	*RB1 and CDKN2A*
hsa-miR-934	+	
hsa-miR-1228*	+	
hsa-miR-195*	+	
hsa-miR-32*	+	
hsa-miR-595	+	
hsa-miR-615-3p	+	
hsa-miR-144*	–	
hsa-miR-9	–	*JUN*, *YAP*, *and NFKB1*
hsa-miR-7-1*	–	*PDGFA and EGF*
hsa-miR-340*	–	
hsa-miR-34a*	–	
hsa-miR-203	–	*JUN*, *HGF, and NFKB2*
hsa-miR-582-5p	–	*HGF*
hsa-let-7e*	–	
hsa-miR-429	–	*JUN*, *TXNDC1, and ADAM28*

Modified and reprinted from Guled et al. [42]
Full names of gene symbols and their synonyms can be found at http://www.genenames.org

Mutations

Table 19.2 shows a list of genes that are regularly involved in MM. Gene copy number alterations and epigenetic regulations seem to be the main mechanisms for expression changes. Mutations in base pairs, typically seen in many tumors, are rare or perhaps simply inadequately studied so far. Next-generation sequencing has revealed a high number of novel mutations similar to the situation encountered in many other malignant tumors [30, 31].

Mutations in *NF2* have been reported in a high percentage of MM, while *TP53* (tumor protein p53) has been found to be mutated at a lower rate in comparison with other human cancers [32]. Mutations in *NF2* consist of both point mutations and deletions [33]. The EGFR (epidermal growth factor receptor) activating mutations seen in lung adenocarcinoma are infrequent in MM, and the patients are insensitive to therapy with EGFR inhibitors [34].

At present, the clinical value of the genes shown in Table 19.2 is limited. However, *CDKN2A* deletion seen at high frequency in MM offers good diagnostic marker for serous effusions by the FISH method, [35] and deletions (but not methylation) of this gene are a poor prognostic sign in peritoneal MM [21]. Among recently described mutations those in *BAP1* (*BRCA1*-associated protein 1) tumor suppressor gene are most significant as they are recurrent (30–60 %) and may be germ line in origin too, predisposing to cancer syndromes [145].

Epigenetic Changes

Epigenetic changes do not target the DNA sequence itself, instead they influence factors involved in DNA organization and the regulation of transcription and translation. Epigenetic markers consist of deregulated miRNAs, patterns of different chemical modifications of histones, and aberrant methylation of DNA at CpG islands within gene promoter regions.

MicroRNAs

MicroRNAs (miRNAs) are small, 19–25-nucleotides-long, noncoding RNAs [36]. In humans, there are more than 2,000 miRNAs [36]. Lewis et al. [37] estimated that miRNAs may regulate as many as 30 % of human genes. Most cancer-related events, such as unlimited growth, potential to replicate, evasion of apoptosis, angiogenesis, and ability to metastasize, involve changes in miRNAs [38–40]. Interestingly, miRNAs have been shown to be located in cancer-associated genomic regions [41].

So far, some ten miRNA studies have shown differentially expressed miRNAs in MM [42–48]. We first demonstrated that some of the miRNAs, such as let-7b*, miR-1228*, miR-195*, miR-30b*, miR-32*, miR-345, miR-483-3p, miR-584, miR-595, miR-615-3p, and miR-885-3p, were highly expressed, whereas others, let-7e*, miR-144*, miR-203, miR-340*, miR-34a*, miR-423, miR-582, miR-7-1*, and miR-9, were unex-

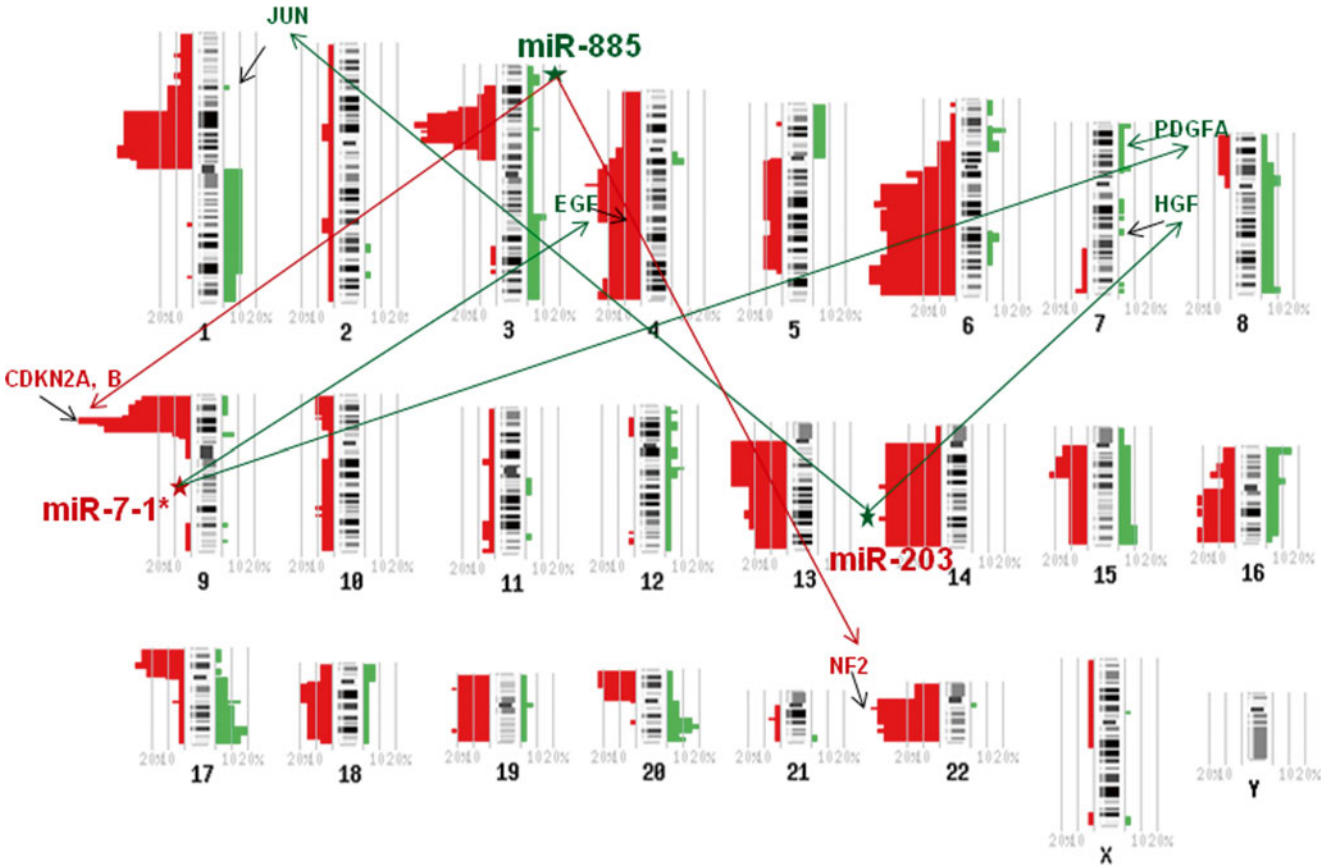


Fig. 19.4 Recurrent copy number changes, differentially expressed miRNA and putative target genes in MM. MiRNA and genes in *green* are overexpressed; miRNAs and genes in *red* are under- or non-expressed. *Green bars* on the right-hand side of the chromosomes show frequencies of copy number gains of the indicated chromosomal regions, while *red bars* on the left present loss of copy number changes in the corresponding regions. The *green asterisk* indicates the upregulated miRNA while the *arrowhead* shows the target gene(s) regulated by this miRNA. The *red asterisk*, respectively, shows the downregulated miRNA and the *arrowhead* the target gene(s) (Modified from Lindholm et al. [8] and Baudis et al. [143])

pressed or had severely reduced expression levels [42]. The target genes for these miRNAs include *CDKN2A*, *NF2*, *JUN* (jun proto-oncogene), *HGF* (hepatocyte growth factor), and *PDGFA* (platelet-derived growth factor alpha) which are some of the most frequently affected genes in MM (Table 19.3). Several miRNAs were located in those chromosomal areas known to be deleted or gained in MM, such as 8q24, 1p36, and 14q32 (Fig. 19.4). Specific miRNAs for each histopathological subtype of MM were also identified. With regard to the smoking status and asbestos exposure, significantly differentially expressed miRNAs were identified in relation to smoking status but not to asbestos exposure status [42]. This may have been due to the method of assessment of asbestos exposure, since asbestos is the main contributor to the development of MM.

Subsequently some of our results have been confirmed by other authors [47], and the power of miRNA profiling to discriminate MM from lung adenocarcinoma [45] and different subtypes of MM [43] or the prognostic value of miRNAs [43, 49] has been reported. Serum levels of miR-126 in association with another MM serum marker soluble mesothelin-related peptide (see later) has been proposed as being a good candidate bioindicator for early detection marker of MM [48] though this speculation will need to be evaluated with larger material.

Histone Modification and DNA Methylation

Histone Modification

Acetylation and methylation are the two main histone modifications that have been associated with pathological epigenetic dysregulations in cancers. Figure 19.5 illustrates the ways by which histone acetylation and methylation together with DNA methylation can activate oncogenes and inactivate tumor suppressor genes. Changes in global histone modification and its prognostic significance have been demonstrated in many common cancers. In MM, a distinct subset of genes silenced by histone H3 lysine 27 trimethylation (H3K27me3) and which can be restored by histone deacetylase (HDAC) inhibitor treatment have been identified [50]. Numerous studies for many cancers, mesothelioma included, are evaluating the therapeutic effectiveness of deacetylases on tumorous cells. The encouraging results obtained in preclinical in vitro studies are the foundation for several early-phase clinical trials now being

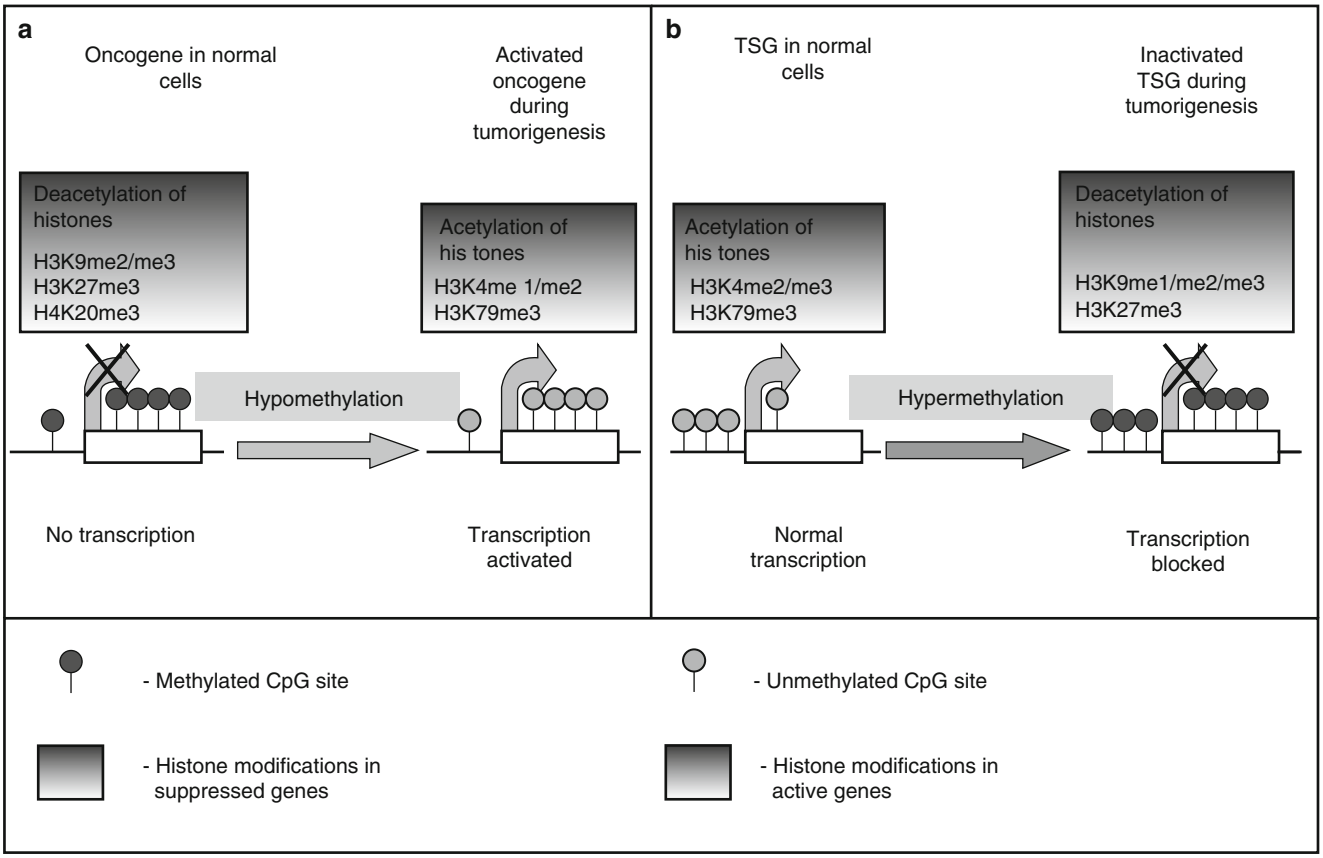


Fig. 19.5 Epigenetic deregulation of (**a**) cancer-associated oncogenes and (**b**) tumor suppressor genes (TSG) (Adapted from Sebova and Fridrichova [144], with permission from Wolters Kluwer Health)

performed on MM patients; the future will show whether the good *in vitro* results can be maintained in the clinic [51, 52].

Methylation

DNA methylation profiles vary extensively according to tissue, with even the normal lung and pleura having distinct basal methylation profiles [53]. It has to be noted also that hypermethylation induced by age or environment is CpG island context dependent and frequently encountered in the noncancerous lung [54, 55]. Nevertheless, DNA hypermethylation is a stable form controlling cell functions and, as such, is a useful target in the search for a MM biomarker (studies listed in Table 19.4) [50, 53–65]. Indeed, samples can be classified based on the CpG methylation profiles. Methylation classes accurately discriminated MM from the normal pleura and nonmalignant pulmonary tissues as well as from lung adenocarcinoma [50, 53, 55, 62]. Several studies have shown that the amount of methylation of *APC* (adenomatous polyposis coli) was significantly elevated in lung adenocarcinoma in comparison to MM, whereas MM displayed higher methylation of *CDH1* (E-cadherin) (Fig. 19.6) [57, 65]. Moreover, methylation of *RASSF1* (Ras association [RalGDS/AF-6] domain family member 1) was associated with SV40 (simian virus 40)-positive MM (Table 19.4). Pathways involved in calcium signaling and Fc Epsilon RI signaling were significantly enriched for methylation in MM in comparison to lung adenocarcinoma. Methylation status or profiles of different genes have been shown to associate with different clinical correlates (Table 19.4). For instance, if one wishes to predict the prognosis in a patient, it has been proposed that a combination of methylation status of several genes such as *RASSF1*, *RARB* (retinoic acid receptor beta), and *DAPK* (death-associated protein kinase 1) in serum of MM patients would be used rather than that of a single gene [64] (Table 19.4).

An increased asbestos fiber burden was associated with an increase in a number of methylated cell cycle tumor suppressor genes, indicating that methylation may be one possible, though not a major, mechanism of action of asbestos in MM (Fig. 19.7) [50, 60].

Gene Expression Profiling

In MM, different microarray approaches have revealed specific gene expression profiles in comparison with lung cancer or with different reference samples, such as when compared

Table 19.4 Methylation studies performed on malignant mesothelioma

Study	Material	No. of subjects[a]	Studied genes[b]	Methylation frequencies in MM/ results[c]	Observed associations
[65] Toyooka S et al. (2001) Cancer Res	Cell lines, tissue	6 MM cell lines 4 nonmalignant mesothelial primary cell cultures 66 MM tumors (of which 32 were SV40 positive) 40 ADCA tumors	*RASSF1*, *GSTP1*, *CDKN2A*, *RARB*, *APC*, *CDH13*, *MGMT*	Lower in MM than ADCA; *APC* promoter 1A methylation in 52 % of ADCA but completely absent in MM; methylation index higher in epithelioid MM than in sarcomatoid/biphasic MM	Methylation of *RASSF1* significantly higher in SV40-positive MM than in negative samples (a trend shown with relationship of low methylation frequency/lack of SV40 sequences and longer survival)
[56] Wong L et al. (2002) Lung Cancer	Cell lines, tissue	10 MM cell lines 2 lung tumor cell lines 11 MM tumors	*CDKN2A*	In 10 % of MM cell lines and in 27 % of MM tumors	
[57] Tsou JA et al. (2005) Lung Cancer	Cell lines, tissue	10 MM cell lines 8 ADCA cell lines 6 MM tumors 7 ADCA tumors Non-tumor lung tissue	14 loci such as *APC*, *CDH1*, *RASSF1*, *PTGR1*, *ESR1*	Shown in Fig. 19.6	*CDH1* showed high methylation in MM versus ADCA ($P<0.002$) and *APC* showed low methylation in MM versus ADCA ($P<0.0001$)
[58] Suzuki M et al. (2005) Oncogene	Cell lines, tissue	6 MM cell lines 4 nonmalignant mesothelial primary cell cultures SV40-infected human mesothelial cells 63 MM tumors	*NAE1*, *CDKN2A*, *RASSF5*, *PRDM2*, *TNFRSF10C*, *PYCARD*, *RBP1*, *HIC1*, *CCND2*, *RRAD*, *GREM1*	Varies between 33 % and 83 % in MM cell lines and between 3 % and 65 % in MM tumors; methylation completely absent in primary mesothelial cell cultures	Methylation of *PYCARD* and *HIC1* with shortened survival; methylation frequencies of *NAE1*, *RASSF1*, *CCND2*, and *RRAD* were significantly higher in SV40-positive MM than in negative samples
[59] Destro A et al. (2007) Lung Cancer	Tissue	79 MM tumors	*CDKN2B*, *CDKN2A*, *RASSF1*, *RASSF5*	*CDKN2B* 19 %; *CDKN2A* 11 %; *RASSF1* 20 %; *RASSF5* 5 % in MM	Methylation with an increased proliferation index (a trend shown with relationship of low methylation frequency and longer survival)
[55] Tsou JA et al. (2007) Lung Cancer	Tissue	52 MM tumors (of which 39 had self-reported asbestos exposure) 38 non-tumor lung tissue from patients with lung cancer	28 marker loci	*ESR1* 71 %, *SLC6A20* 46 %, and *SYK* 67 % showed significantly increased methylation in MM versus non-tumor lung tissue	Methylation status of *MT1A* and *MT2A* with gender, histology, asbestos exposure, and lymph node involvement; methylation status of *LZTS1* and *SLC6A20* with survival
[60] Christensen BC et al. (2008) Carcinogenesis	Tissue	70 MM tumors with quantitative asbestos burden data	*APC*, *RASSF1*, *CCND2*, *CDKN2A*, *CDKN2B*, *NAE1*	*RASSF1* in 33 %, *NAE1* 20 %, *CDKN2A* 13 %, *APC* 9 %, *CCND2* 9 %, *CDKN2B* 4 % of MM	Methylation of any of these genes, particularly *RASSF1*, with higher asbestos body burden; methylation status of *RASSF1* and *CCND2* with age
[61] Kohno H et al. (2010) Oncol Rep	Cell lines, tissue	8 MM cell lines 46 MM tumors	*WIF1 SFRP1*, *SFRP2*, *SFRP4*	*WIF1* in 74 %, *SFRP1* 57 %, *SFRP2* 62 %, *SFRP4* 47 % of MM (not specific for MM)	
[53] Christensen BC et al. (2009) Cancer Res 69(15) [63] Christensen BC et al. (2010) Cancer Res 70(14) [62] Christensen BC et al. (2009) Cancer Res 69(1)	Tissue	158 MM tumors with quantitative asbestos burden data 57 ADCA tumors 18 parietal pleura with asbestos exposure data 48 non-tumor lung tissue from patients with lung cancer 4 non-tumor lung from non-cancer patients	1413/1505 CpG loci 773/803 cancer-related genes integrated analysis of methylation and copy number analysis by SNP array	DNA methylation profiles highly differed between MM, ADCA, and nonmalignant pulmonary tissue; among MM, Fc Epsilon RI and calcium-signaling pathways were enriched for methylation ($P<0.05$)	Asbestos exposure with the degree of methylation; shown in Fig. 19.7; profiles of gene methylation with clinical outcome; methylation of *CDKN2* and *RASSF1* with asbestos body count; a global correlation between epigenetic and genetic alterations in MM

Table 19.4 (continued)

Study	Material	No. of subjects[a]	Studied genes[b]	Methylation frequencies in MM/ results[c]	Observed associations
[50] Goto Y et al. (2009) Cancer Res	Tissue	50 MM tumors 56 ADCA tumors	6157 CpG islands integrated analysis of methylation, aCGH and ChIP arrays (H3K27me3 targets)	6.3 % ($n=387$) genes were hypermethylated in MM; *TMEM30B*, *KAZALD1*, and *MAPK13* specifically methylated in MM; only 11 % of heterozygously deleted genes affected by DNA methylation and/or H3K27me3	Low levels of methylation in a subset of MM ($n=4$, 20 %) with substantially longer survival
[54] Christensen BC et al. (2009) PLoS Genetics	Tissue	217 non-pathological human tissues from 10 anatomic sites	1413 CpG loci 773 genes	Exposures were not strongly associated with array-wide methylation profiles but locus-specific methylation	Among pleural tissues methylation of 24 CpG loci with asbestos exposure
[64] Fischer JR et al. (2006) Lung Cancer	Serum	43 MM patients	*CDH1*, *FHIT*, *APC1A*, *APC1B*, *RASSF1*, *DAPK1*, *CDKN2A/p16*, *CDKN2A/p14*, *RARB*	*CDH1* in 71 %, *FHIT* 78 %, *RARB* 56 %, *p14* 44 %, *APC1B* 33 %, *p16* 28 %, *DAPK1* 20 %, *RASSF1* 20 %, *APC1A* 14 % of MM	Combinations of methylated genes *RARB+DAPK* ($P=0.025$), *RARB+RASSF1* ($P=0.04$), and *RARB+DAPK1+RASSF1* ($P=0.028$) with shorter survival

[a]*MM* malignant mesothelioma, *ADCA* adenocarcinoma of the lung
[b]*APC* adenomatous polyposis coli, *CCND2* cyclin D2, *CDH1* E-cadherin, *CDH13* H-cadherin, *CDKN2B* cyclin-dependent kinase inhibitor 2B, p15, *CDKN2A* cyclin-dependent kinase inhibitor 2A, p16, p14, *DAPK1* death-associated protein kinase 1, *ESR1* estrogen receptor 1, *GREM1* Gremlin 1, DRM, *GSTP1* glutathione s-transferase pi1, *HIC1* hypermethylated in cancer, *KAZALD1* Kazal-type serine peptidase inhibitor domain 1, *LZTS1* leucine zipper tumor suppressor 1, *MAPK13* mitogen-activated protein kinase 13, *MGMT* O-6-methylguanine-DNA methyltransferase, *MT* metallothionein, *NAE1* APPBP1, HPP1, NEDD8 activating enzyme E1 subunit 1, *PTGR1* PGR1 prostaglandin reductase 1, *PYCARD* TMS1, PYD and CARD domain containing, *PRDM2* RIZ1, PR domain containing 2, with ZNF domain, *RARB* retinoic acid receptor beta, *RASSF* Ras association (RalGDS/AF-6) domain family member, *RASSF5* NORE1A, *RBP1* CRBP1, retinol binding protein 1, *RRAD* Ras-related associated with diabetes, *SFRP* secreted frizzled-related protein, *SLC6A20* solute carrier family 6 member 20, *SYK* spleen tyrosine kinase, *TMEM30B* transmembrane protein 30B, *TNFRSF10C* TcR1, tumor necrosis factor receptor superfamily, member 10c, decoy without an intracellular domain, *WIF1* WNT inhibitory factor 1
[c]The methylation frequency percentages were rounded to the nearest whole number
Full names of gene symbols and their synonyms can be found at http://www.genenames.org

with benign mesothelial cells or mesothelial cell lines. However, the large-scale use of gene expression profiles as differential diagnostic markers may be partly limited by the unstable nature of mRNA. Array-based experiments on MM have been reviewed in Gray et al. 2009 and Ombretta et al. 2011 [66, 67].

Arrays can be used to assess biological functions which are enriched among the modulated transcript sets; e.g., in MM, cellular assembly, cellular organization, DNA replication, DNA recombination, and DNA repair as well as cellular movement, cell adhesion, cell cycle, and glucose metabolism were all enriched [68–72]. Serial analysis of gene expression (SAGE) has also been used to reveal novel players in MM, with intelectin being one of the genes identified. Intelectin has also been shown to be induced in human primary mesothelial cells by exposure to crocidolite asbestos and SV40 infection [73].

In particular, if one is intending to devise diagnostic or prognostic tests, then several studies have identified either single genes or gene sets the expression ratios of which are claimed distinguish tumor entities such as MM and lung adenocarcinoma or may have some prognostic value in MM (an example is shown in Table 19.5) (Fig. 19.8) [74, 75]. Molecular diagnostic tests have also been developed to be performed on cells from pleural effusions [75]. Certain gene pair ratios or gene expression levels for use in prognostications of MM patients have been postulated [68, 76–80]. However, prognostic classifiers, presented in the literature so far, have only a few overlapping genes [78]. In epithelioid MM, many genes have been implicated as being upregulated, e.g., those encoding matriptase, ITGB4 (integrin beta 4), and P-cadherin [72, 76, 81]. In contrast, specifically in sarcomatoid MM, only a few genes have been identified as being upregulated; these include those encoding MMP9 (matrix metallopeptidase 9), tissue-type plasminogen activator, and some growth factors or receptors (basic fibroblast growth factor [FGF], platelet-derived growth factor receptor beta [PDGFR-β], FGF receptor 1 [FGFR-1], transforming growth factor beta [TGF-β], and insulin-like growth factor-binding protein [IGFBP] 6 and 7). Some of the genes such as Aurora kinase A (*AURKA*) were also classified as unfavorable genes in the prognosis of the patient [72, 78, 81, 82].

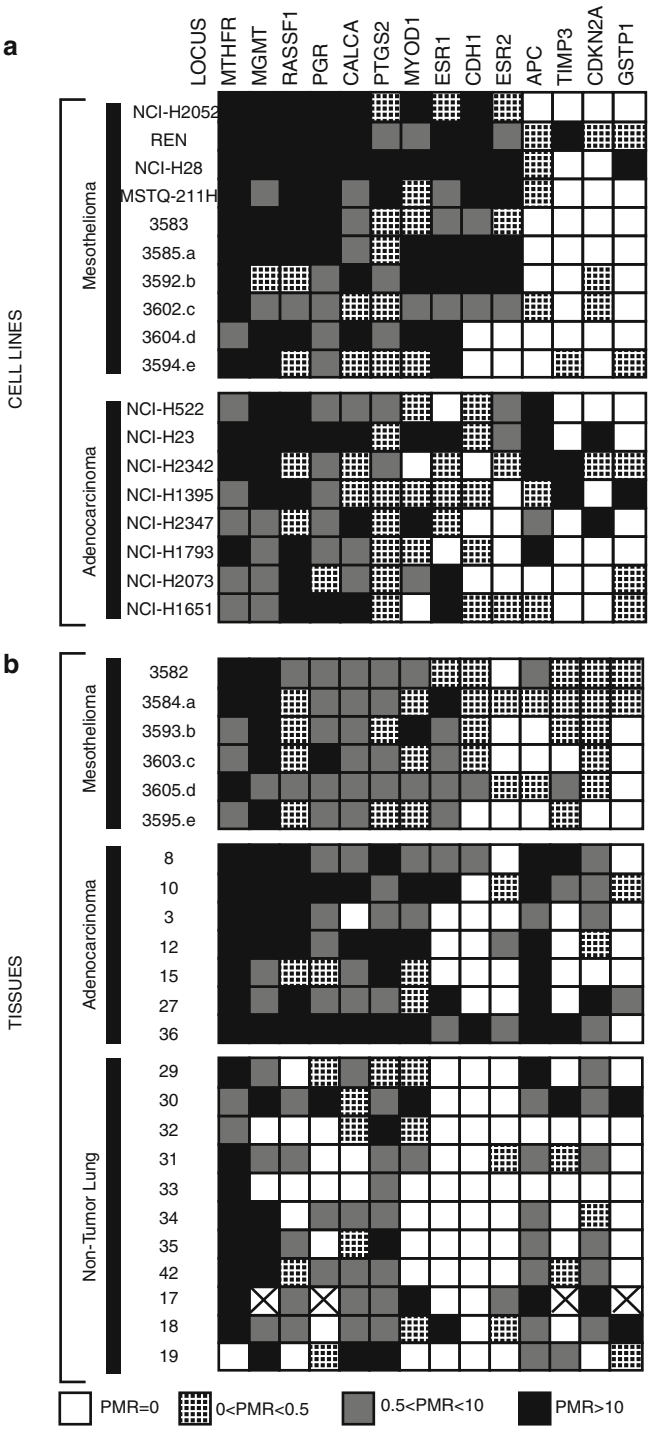


Fig. 19.6 Graphic representation of percentage methylated reference (*PMR*) values obtained for 14 loci in MM and adenocarcinoma cell lines and tumors and non-tumor lung. PMR value is a relative measure comparing methylation in the sample to methylation in enzymatically methylated DNA and values have been categorized as *colored boxes* denoting no detectable methylation (*white*), low methylation 0< PMR ≤0.5 (*light gray*), intermediate methylation 0.5< PMR ≤10 (*dark gray*), and high methylation PMR >10 (*black*). (**a**) Representation of PMR values obtained for ten MM and eight lung adenocarcinoma cell lines. (**b**) Representation of PMR values for tumor and non-tumor tissues. *Lowercase letters* following the numbers indicate the link between tumors and their derived cell lines. Samples for which no PMR value was obtained because of failure of one or both references are indicated by a *crossed box* (Adapted from Tsou et al. [57], with permission from Elsevier, Copyright 2005)

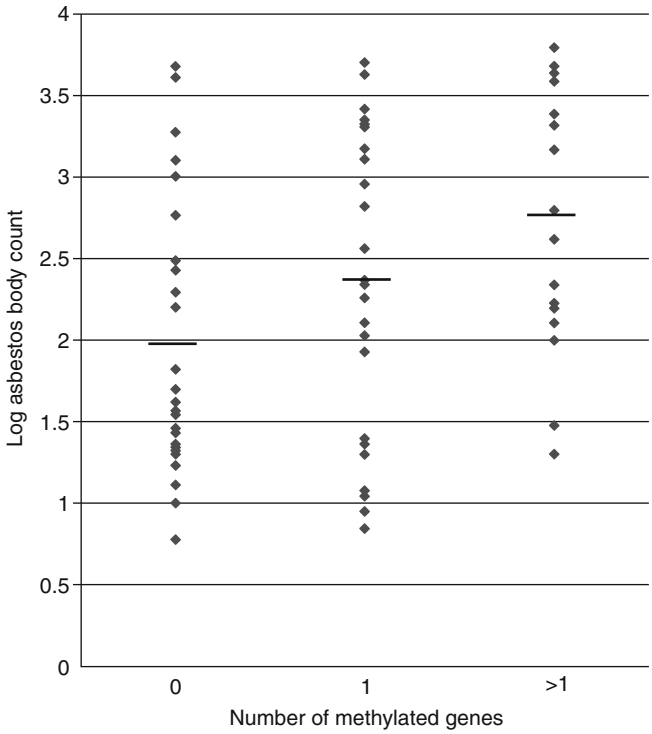


Fig. 19.7 Asbestos body count versus cell cycle gene methylation. Log-transformed asbestos body count (*y*-axis) is plotted versus the number of methylated cell cycle control genes (*APC*, *RASSF1*, *CCND2*, *CDKN2A*, *CDKN2B*, *NAE1*) (*x*-axis). Using simple linear regression, there is a significant association between increasing asbestos burden and increasing number of methylated cell cycle control genes ($P<0.005$, $R^2=0.12$) (Adapted from Christensen et al. [60], by permission of Oxford University Press)

Table 19.5 Accuracy of ratio combinations in predicting tumor diagnosis in a test set of 15 malignant mesotheliomas (MM) and 134 adenocarcinomas of the lung

	Claudin-7	*TACSTD1*	*TITF-1*
Calretinin	97 % (145/149)	98 % (146/149)	91 % (136/149)
VAC-beta	97 % (144/149)	97 % (145/149)	94 % (140/149)
MRC OX-2	97 % (145/149)	97 % (145/149)	95 % (142/149)
KIAA097	97 % (145/149)	95 % (142/149)	94 % (140/149)
PTGIS	97 % (145/149)	97 % (144/149)	96 % (143/149)

Adapted and reprinted by permission from the *American Association for Cancer Research*: Gordon et al. [74]

A total of 15 possible expression ratios (column/row intersection) were calculated from the eight candidate diagnostic genes identified in which both genes used to form the ratio possessed inversely correlated expression levels in MM and adenocarcinoma of the lung. Predictions are stated as the fraction diagnosed correctly

VAC-beta vascular anticoagulant-beta, *MRC OX-2* antigen CD200 molecule, *KIAA097* COBL-like 1, *PTGIS* prostaglandin I2 (prostacyclin) synthase, *Claudin-7* CLDN7, *TACSTD1* EPCAM, epithelial cell adhesion molecule, *TITF-1* NKX2-1, NK2 homeobox 1

Full names of gene symbols and their synonyms can be found at http://www.genenames.org

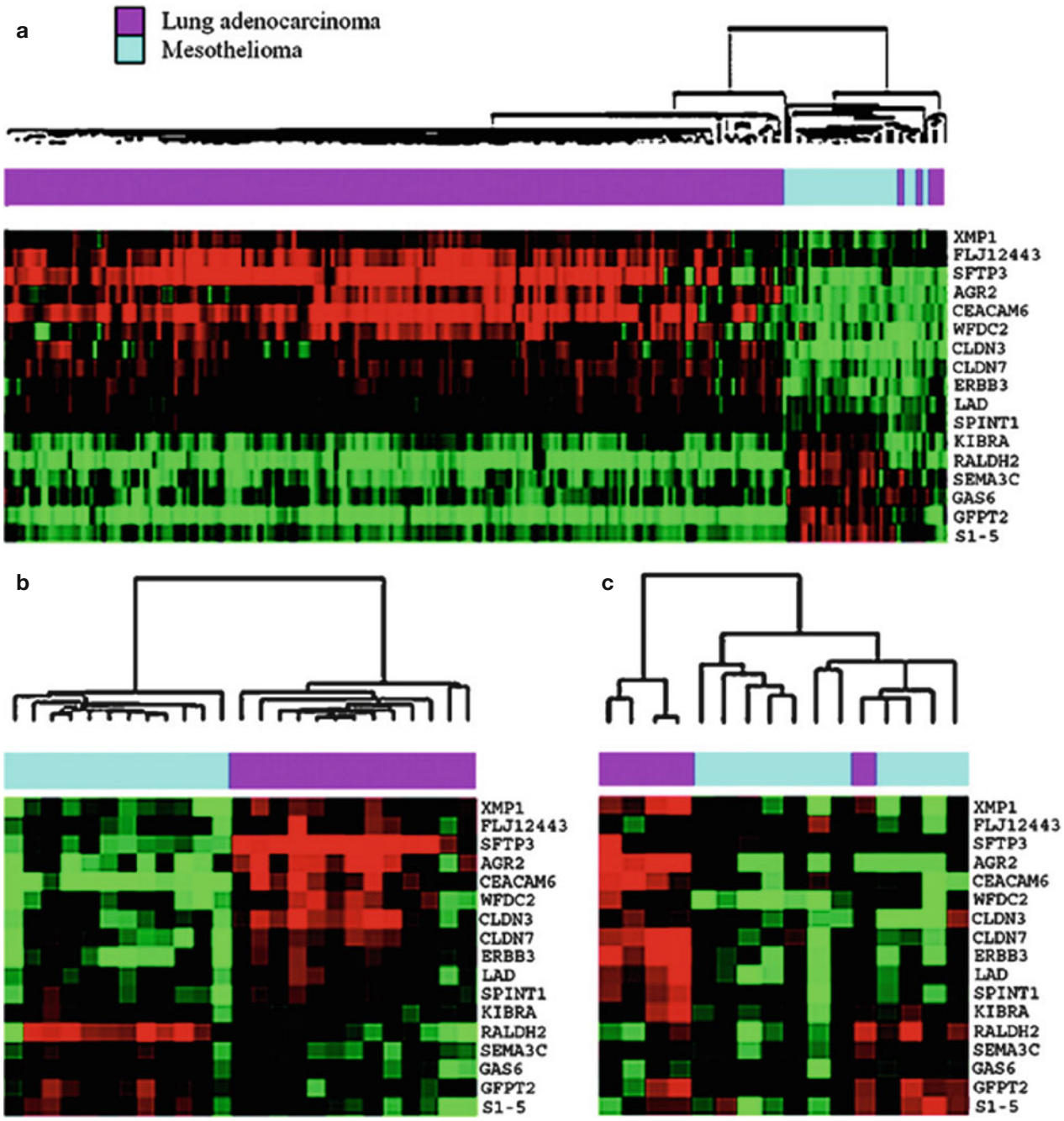


Fig. 19.8 Differential gene expression in MM and adenocarcinoma of the lung. (**a**) Hierarchical cluster analysis of U95A Affymetrix gene expression data set using 17 genes selected with differential expression between MM and lung adenocarcinoma. (**b**) Cluster analysis of quantitative RT-PCR data obtained from fresh-frozen MM and lung adenocarcinoma samples for the same genes as shown in (**a**). (**c**) Cluster analysis of quantitative RT-PCR analysis of fresh-frozen samples of malignant pleural effusions taken from patients with biopsy-proven MM or lung adenocarcinoma. All data are normalized to GAPDH expression (Adapted and reprinted by permission from the *American Association for Cancer Research*: Holloway et al. [75])

Gene expression arrays and subsequent data mining procedures may be relevant in the search for potential therapeutic molecular targets. In a recent data-driven approach, *SIM2s* was revealed as a novel MM-associated gene [10]. *CHEK1* (checkpoint kinase 1), *RAD21* (RAD21 homolog [*S. pombe*]), *FANCD2* (Fanconi anemia, complementation group D2), and *RAN* (member RAS oncogene family) have been proposed as new co-targets in MM [69]. When *CHEK1* siRNA was transfected into MM cell lines, the cells displayed enhanced apoptotic processes [83]. Furthermore, *UBE1L* (ubiquitin-like modifier activating enzyme 7) that is part of the ubiquitin-proteasome pathway showed differential expression in MM cells compared to normal cells [83]. The ubiquitin-proteasome pathway is known to be implicated

in peritoneal MM [84] as well as in asbestos-related lung tumors [85], which may mean that potential future markers relevant in MM may be found in its genes.

Protein/Peptide Markers

Immunohistochemistry (IHC) is probably the most common method using molecular markers for verification and differential diagnostics of MM. IHC is based on the immunohistochemical detection of epithelial and mesothelial marker proteins. There are other techniques utilizing the detection and identification of protein and peptide markers, e.g., enzyme-linked immunosorbent assay (ELISA) and mass spectrometry (MS) [86, 87]. A systematic review has recently been published on markers which have been tested for the noninvasive diagnosis of mesothelioma [88]. After strict exclusion criteria, 82 studies published before the end of 2009 were reviewed. Forty-one of the studies used IHC markers applied on effusion cytological specimens, and in 36 reports serum/effusion markers had been evaluated. Five of the reviewed studies described genetic or several types of markers [88].

Immunohistochemical Markers

In their review, van der Bij et al. noted that there was substantial heterogeneity among the studies reporting a total of 54 different IHC markers tested in cytological analysis of effusions. Carcinoembryonic antigen (CEA or CEACAM5), Ber-EP4, and calretinin performed best in differentiating MM from other malignancies. Epithelial membrane antigen (EMA), in addition to the serum marker soluble mesothelin-related peptide (SMRP), was the most valuable in distinguishing MM from nonmalignant pleural condition (Fig. 19.9) [88]. With respect to calretinin, it is a calcium-binding protein of the EF-hand family, expressed essentially by all epithelioid and mixed-type MM and only in 10 % of lung adenocarcinoma. Nonetheless, it is still unknown whether the transformation process in MM is linked to calretinin expression or not [89]. In contrast to lung adenocarcinoma, MM stains negatively for CEA and Ber-EP4, a monoclonal antibody that recognizes cell surface glycopolypeptides on human epithelial cells.

In addition to the abovementioned IHC markers, keratin 5/6, WT1 (Wilms tumor 1) protein, thrombomodulin, and podoplanin (M2A antigen/D2-40) have been proposed as useful positive MM markers in tissue in diagnosing epithelioid MM, whereas useful positive carcinoma markers in differential diagnosis of MM may be MOC-31, B72.3, BG-8, Leu-M1 (CD15), and CA19-9 (reviewed in Ordonez NG 2007 [90]). Only a minority of sarcomatoid and desmoplastic MM exhibit positive mesothelial markers and 31 % are calretinin positive. Sarcomatoid MM is keratin positive in 93 % of cases [91]. However, also reactive mesothelial cells and reactive submesothelial fibroblasts are keratin positive [91]. The suitable marker choice, thus, depends on the sample under evaluation. The case-specific diagnostics for MM with heterologous elements have been reviewed in detail by Klebe et al. [92].

More recent immunocytological and IHC studies on serous effusions from patients with lung adenocarcinoma, MM, or reactive mesothelial cells (RM) have indicated that expression differences of E-cadherin, CEA, MOC-31, Ber-EP4, calretinin, and thrombomodulin may be able to distinguish lung adenocarcinoma and MM/RM, whereas EMA and desmin (Des) reactivity could discriminate MM and RM [93, 94]. Several of the markers studied by IHC have inconsistent knowledge about their usefulness, e.g., mesothelioma antibody HBME-1 [90, 95]. Tenascin-X protein has been proposed as a potential novel marker for differentiating MM from ovarian/peritoneal serous carcinoma [96].

Though there is still no consensus on the panel selection for IHC markers, the International Mesothelioma Interest Group (IMIG) has agreed on the recommendation guidelines for pathological diagnosis of MM [97]. The exact content of the IHC marker panel is dependent on the context of the differential diagnosis, but it has been recommended by IMIG that the panel should display either sensitivity or specificity greater than 80 % [97].

Serum/Plasma and Effusion Biomarkers

Soluble Mesothelin-Related Peptide (SMRP)

Mesothelin, also called ERC/mesothelin, can be considered as a reference serum biomarker for MM [98]. While C-terminal fragment C-ERC/mesothelin is a membrane-bound protein, soluble megakaryocyte potentiating factor (MPF) or N-ERC/mesothelin is cleaved from the same precursor, and it was first isolated from the culture supernatant of the pancreatic cancer cells (HPC-Y5) [99]. Furthermore, a splicing isoform called soluble mesothelin-related peptide (SMRP), which lacks a GPI-anchoring signal, has been discovered [100]. There is an assay with two antibodies recognizing different epitopes of this protein family which detects members that are referred to different studies as MPF, soluble mesothelin (SM), or SMRP [101, 102]. Several tests have been designed to detect proteins of mesothelin family to increase the potential utility of mesothelin as a biomarker for MM [100, 103–105]. Increased levels of SMRP have been shown in MM serum and pleural effusions in comparison to other non-mesothelial malignancies and asbestos-exposed individuals with a nonmalignant disorder. In pleural disease, fluid concentrations of SMRP are higher than in serum or plasma which displays similar levels of SMRP [106]. The diagnostic performance of SM and MPF has been shown to be equivalent [107].

Importantly, in an attempt to reveal the reference levels and their relevance as a MM biomarker, SM and MPF

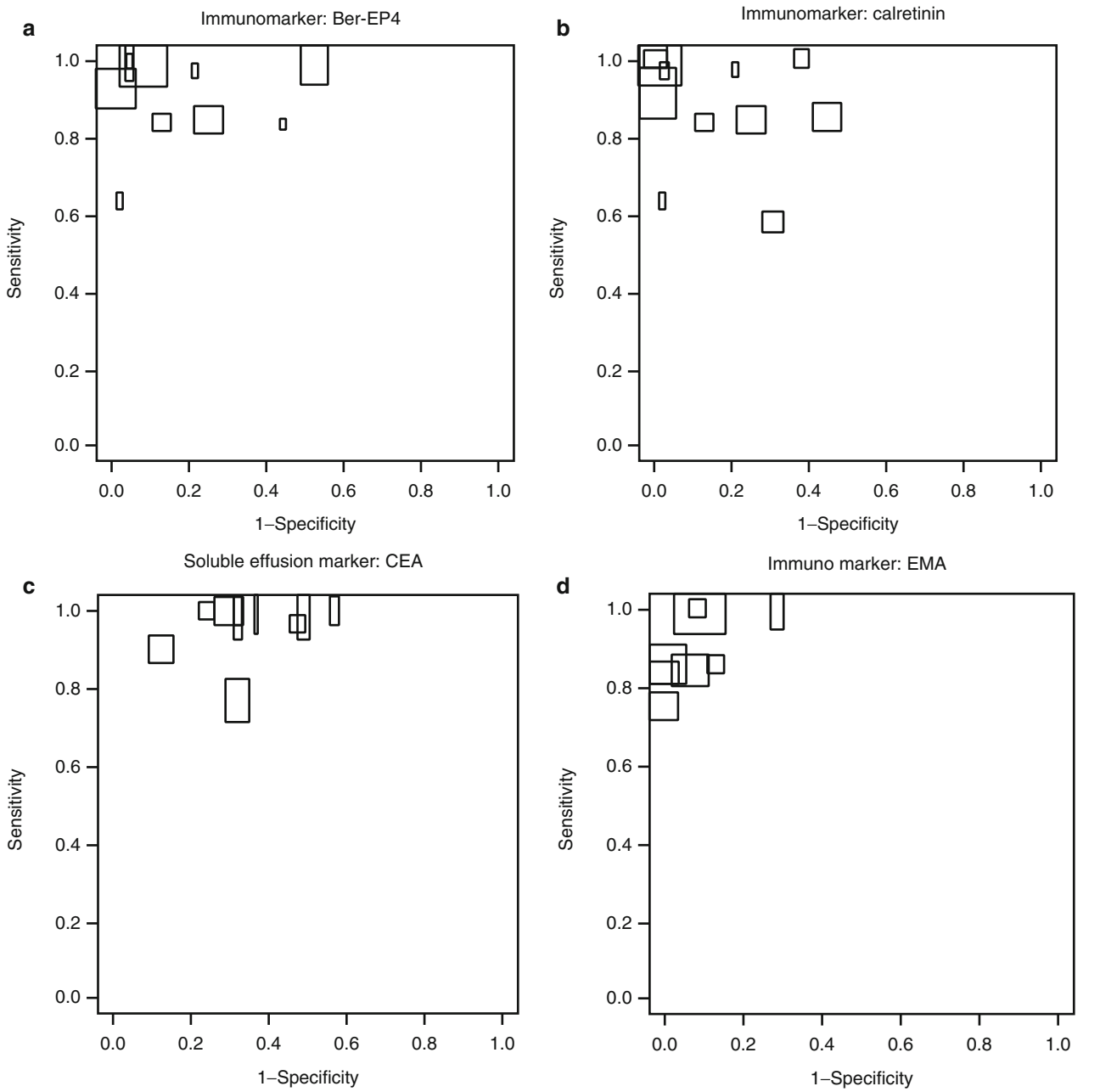


Fig. 19.9 Sensitivity against 1-specificity in receiver operating characteristic (*ROC*) space to discriminate best MM from other malignant diseases using (**a**) Ber-EP4, (**b**) calretinin, and (**c**) CEA and to discriminate best MM from nonmalignancy using (**d**) EMA, all applied to effusion cytology. The height of the blocks is proportional to the reciprocal of the number of MM patients (MM yes subjects), and the width of the blocks is proportional to the reciprocal of the number of patients with other malignant diseases (from **a** to **c**) or nonmalignant patients (**d**) (MM no subjects) (Adapted by permission from Macmillan Publishers Ltd: van der Bij et al. [88], Copyright 2011)

concentrations have been evaluated in a prospective longitudinal cohort study focused on asbestos-exposed individuals without malignant disease (range from 137 to 215 individuals). It was concluded that the minimum requirements of possible screening approach could be serial measurements with screening rules individually adjusted for age and glomerular filtration rate [108, 109]. Previously, the use of SMRP has been suggested as not being practical for screening MM [110]. A positive association has been shown between age and the increase in SMRP values ($P=0.0014$) as well as between serum creatinine concentration and the increase in SMRP values ($P<0.0001$). Furthermore, more than 40 years' asbestos exposure of an individual associated with increase in SMRP levels ($P=0.0265$) [111]. Sample

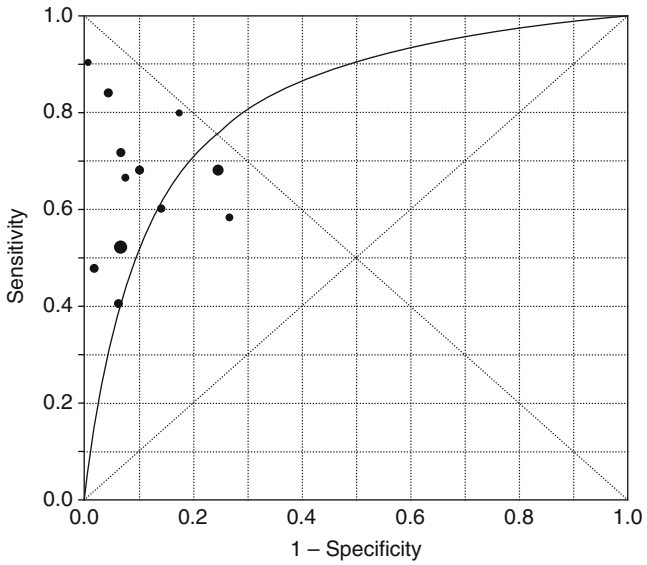


Fig. 19.10 Summary receiver operating characteristic (*ROC*) curves for mesothelin assays. Each *solid circle* represents each study in the meta-analysis. The size of each study is indicated by the size of the *solid circle*. The regression summary ROC curves summarize the overall diagnostic accuracy (Adapted from Luo et al. [113], with permission from Elsevier, Copyright 2010)

handling and storage only slightly influenced the serum SMRP concentration, and it was concluded that frozen serum samples would be suitable for analysis of SMRP in retrospective experiments [111].

SM/SMRP assays have displayed relatively high specificity, but the sensitivity ranges from 50 % at diagnosis to 84 % for advanced disease [112]. A recent meta-analysis covers serum SMRP studies consisting of 717 patients with MM and 2,851 control individuals that had no MM. The summary from these studies estimated 0.64 (95 % confidence interval 0.61–0.68) for sensitivity and 0.89 (95 % CI 0.88–0.90) for specificity. The authors presented a global summary of test performance of the SMRP assays (Fig. 19.10), the area under curve (AUC) being 0.82, indicating that the overall accuracy was less than expected [113]. When the MM (or lung tumor) predicting value of SMRP, CA125, and Cyfra 21-1 was evaluated in a cohort of asbestos-exposed workers, the specificity of SMRP as a tumor marker was relatively high, even when combined with CA125 and Cyfra 21-1, but its sensitivity was low [114]. On the contrary, SMRP levels and their changes did show potential for prognostication and for following up the treatment response in MM [115–119].

Osteopontin

The glycoprotein osteopontin (OPN) was identified in a gene expression study as a potential marker for pleural mesothelioma [120]. Since the overexpression has been detected in several cancer types, too, the increase in OPN level is not specific to MM, but rather, it has been suggested to distinguish asbestos-exposed MM patients from exposed patients without MM [120]. Asbestos-induced overexpression of OPN was investigated in a murine model, and potential target genes, such as those involved in cell signaling, immune defense, extracellular matrix remodeling, and cell cycle regulation, were identified [121]. On the other hand, in a screening study of 525 asymptomatic asbestos-exposed men, OPN levels were increased in those individuals with asbestos-related disorders in comparison to healthy exposed individuals, suggesting that OPN levels may be changed by nonmalignant processes as well [122]. Some discrepancy exists among the factors that have been reported to influence OPN levels although some differences may also exist between the available assays [123–125].

Osteopontin is cleaved by thrombin and, thus, for measurements, plasma is preferred over serum [106, 123]. In the diagnosis of epithelioid MM, OPN has been suggested to be a useful marker, supporting the traditional radiological methods [123]. When the diagnostic accuracy of different serum markers on MM at a level of specificity of 95 % was compared, the sensitivity of mesothelin was superior (73 %), whereas OPN had higher (47 %) sensitivity than MPF (34 %) [115, 126]. OPN may have a potential value as prognostic marker but not as a marker of response [115, 117, 127].

Other Markers

Tissue polypeptide antigen (TPA), hyaluronan, CA 125, and Cyfra 21-1 have been evaluated as serum markers in MM patients. It has been shown that cytokeratin fragments TPA and Cyfra 21-1 (but not hyaluronan or CA 125) may have some value in predicting survival [128, 129]. High levels of hyaluronan have been measured in serum or pleural fluid of MM patients indicating that the diagnostic performance of hyaluronan in pleura was similar to that of soluble mesothelin, while in serum, mesothelin exhibited higher sensitivity than hyaluronan [130, 131]. It is also worth remembering that the CA 125 levels have been demonstrated to increase when serum samples were stored in the freezer for longer periods [111].

Measurements of vascular endothelial growth factor (VEGF), by ELISA, have been shown to increase the diagnostic performance of cytological examination of pleural fluid for MM even by 24 % [132]. Hence, it may serve as an adjunct to diagnostics in MM and also benefit in patient prognosis estimation. However, the specificity of VEGF at recognizing individuals at high cancer risk was not optimal [133, 134]. Serum levels of VEGF β (beta) as well as other angiogenic mediators such as bFGF and HGF were assessed in asbestos-exposed workers; a significant association was detected between the increase in serum level and the increase in asbestos exposure [134].

PDGFR immunopositivity did not differentiate malignant mesothelial cells from reactive mesothelial cells, whereas

those MM patients with a shorter survival had higher levels of PDGF measured from serum, although no significant association was observed [135–137].

Novel potential markers for MM include the C-C motif chemokine 2 (CCL2; also known as monocyte chemoattractant protein 1, MCP-1). In pleural effusions from MM patients, the use of ELISA showed significantly higher level of CCL2 compared with the benign pleural effusions or effusion from lung adenocarcinoma [138]. In an earlier study on rat pleural mesothelial cells, asbestos has been shown to induce increased CCL2 secretion [139].

Exhaled Breath Biomarkers

In order to improve the selection of noninvasive diagnostic methods, the so-called breathprints, i.e., composite biomarker profiles, and the mean values of volatile organic compounds were recently studied in exhaled breath of the patients suffering from MM and in individuals with occupational asbestos exposure [140]. As a result, cyclohexane was claimed to be a possible marker distinguishing MM patients from asbestos-exposed patients without MM and from nonexposed healthy controls, while cyclopentane could distinguish asbestos-exposed individuals from the healthy controls and from the patients with MM [141]. In addition, exhaled nitric oxide and different compounds in exhaled breath condensate have been measured in nontumorous asbestos-related disorders (reviewed in Chapman et al. [142]).

Conclusion

Basic histology and immunohistochemistry using specific antibodies are the cornerstones when one considers the diagnosis of MM. Some cytogenetic changes (e.g., 9p deletions), microRNAs (e.g., miR-17-5p, miR-30c, and miR-29c*), and methylation patterns (e.g., *RARB* + *DAPK1* + *RASSF1*) have shown prognostic value. Furthermore, profiling of DNA copy numbers, gene expression, methylation, and miRNAs as well as potentially assaying the levels of some serum markers (e.g., CCL2) may help in differential diagnosis. The rapidly developing next generation of sequencing technology has already revealed new fusion genes in MM, and it is more than likely that this technology with the rapid innovations in bioinformatics, in the near future, will reveal not only novel prognostic and predictive markers but also therapeutic targets for new drug development and personalized patient treatment. There are also very encouraging preliminary results from the use of serum, plasma, or pleural effusions for early diagnosis of MM. Our understanding about molecular mechanisms by which asbestos causes cancer is increasing, and, for the first time, there are potential biomarkers (copy number changes and miRNAs for lung carcinoma and methylation for mesothelioma) that can be used to determine whether the tumor is or is not asbestos-related.

Acknowledgments We are grateful to Tarja Nieminen for helping with the figures and editing as well as to MD, PhD Ewen MacDonald for the correction of grammar and style. Financial support from the Finnish Work Environment Fund (grants 110405 and 111100) and from the Sigrid Jusélius Foundation is gratefully acknowledged.

References

1. Tiainen M, Tammilehto L, Mattson K, Knuutila S. Nonrandom chromosomal abnormalities in malignant pleural mesothelioma. Cancer Genet Cytogenet. 1988;33:251–74.
2. Hagemeijer A, Versnel MA, Van Drunen E, et al. Cytogenetic analysis of mesothelioma. Cancer Genet Cytogenet. 1990;47:1–28.
3. Factor RE, Dal Cin P, Fletcher JA, Cibas ES. Cytogenetics and fluorescence in situ hybridization as adjuncts to cytology in the diagnosis of malignant mesothelioma. Cancer. 2009;117:247–53.
4. Chiosea S, Krasinskas A, Cagle PT, et al. Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas. Mod Pathol. 2008;21:742–7.
5. Kettunen E, Salmenkivi K, Vuopala K, et al. Copy number gains on 5p15, 6p11-q11, 7p12, and 8q24 are rare in sputum cells of individuals at high risk of lung cancer. Lung Cancer. 2006;54:169–76.
6. Björkqvist AM, Wolf M, Nordling S, et al. Deletions at 14q in malignant mesothelioma detected by microsatellite marker analysis. Br J Cancer. 1999;81:1111–5.
7. Pylkkänen L, Sainio M, Ollikainen T, et al. Concurrent LOH at multiple loci in human malignant mesothelioma with preferential loss of NF2 gene region. Oncol Rep. 2002;9:955–9.
8. Lindholm P, Salmenkivi K, Vauhkonen H, et al. Gene copy number analysis in malignant pleural mesothelioma using oligonucleotide array CGH. Cytogenet Genome Res. 2007;119:46–52.
9. Borze I, Guled M, Musse S, et al. MicroRNA microarrays on archive bone marrow core biopsies of leukemias–method validation. Leuk Res. 2011;35:188–95.
10. Caldas J, Gehlenborg N, Kettunen E, et al. Data-driven information retrieval in heterogeneous collections of transcriptomics data links SIM2s to malignant pleural mesothelioma. Bioinformatics. 2012;28(2):246–53.
11. Ribotta M, Roseo F, Salvio M, et al. Recurrent chromosome 6 abnormalities in malignant mesothelioma. Monaldi Arch Chest Dis. 1998;53:228–35.
12. Mitelman F, Johansson B, Mertens F, editors. Mitelman database of chromosome aberrations in cancer. http://cgap.nci.nih.gov/Chromosomes/Mitelman; 2007.
13. Nymark P, Kettunen E, Knuutila S. Tumors of the lung. In: Heim S, Mitelman F, editors. Cancer cytogenetics. 3rd ed. Hoboken: Wiley; 2009. p. 415–28.
14. Björkqvist A-M, Tammilehto L, Nordling S, et al. Comparison of DNA copy number changes in malignant mesothelioma, adenocarcinoma and large-cell anaplastic carcinoma of the lung. Br J Cancer. 1998;77:260–9.
15. Simon F, Johnen G, Krismann M, Muller K-M. Chromosomal alterations in early stages of malignant mesotheliomas. Virchows Arch. 2005;447:762–7.

16. Pei J, Kruger WD, Testa JR. High-resolution analysis of 9p loss in human cancer cells using single nucleotide polymorphism-based mapping arrays. Cancer Genet Cytogenet. 2006;170:65–8.
17. Illei PB, Rusch VW, Zakowski MF, Ladanyi M. Homozygous deletion of CDKN2A and codeletion of the methylthioadenosine phosphorylase gene in the majority of pleural mesotheliomas. Clin Cancer Res. 2003;9:2108–13.
18. Xio S, Li D, Vijg J, et al. Codeletion of p15 and p16 in primary malignant mesothelioma. Oncogene. 1995;11:511–5.
19. Prins JB, Williamson KA, Kamp MM, et al. The gene for the cyclin-dependent-kinase-4 inhibitor, CDKN2A, is preferentially deleted in malignant mesothelioma. Int J Cancer. 1998;75: 649–53.
20. Cheng JQ, Jhanwar SC, Klein WM, et al. *p16* alterations and deletion mapping of 9p21-p22 in malignant mesothelioma. Cancer Res. 1994;54:5547–51.
21. Krasinskas AM, Bartlett DL, Cieply K, Dacic S. CDKN2A and MTAP deletions in peritoneal mesotheliomas are correlated with loss of p16 protein expression and poor survival. Mod Pathol. 2010;23:531–8.
22. Dacic S, Kothmaier H, Land S, et al. Prognostic significance of p16/cdkn2a loss in pleural malignant mesotheliomas. Virchows Arch. 2008;453:627–35.
23. Reid A, de Klerk N, Ambrosini G, et al. The additional risk of malignant mesothelioma in former workers and residents of Wittenoom with benign pleural disease or asbestosis. Occup Environ Med. 2005;62:665–9.
24. Ascoli V, Aalto Y, Carnovale-Scalzo C, et al. DNA copy number changes in familial malignant mesothelioma. Cancer Genet Cytogenet. 2001;127:80–2.
25. Musti M, Cavone D, Aalto Y, et al. A cluster of familial malignant mesothelioma with del(9p) as the sole chromosomal anomaly. Cancer Genet Cytogenet. 2002;138:73–6.
26. Pylkkänen L, Wolff H, Stjernvall T, et al. Reduced Fhit protein expression in human malignant mesothelioma. Virchows Arch. 2004;444:43–8.
27. Tammilehto L, Tuomi T, Tiainen M, et al. Malignant mesothelioma: clinical characteristics, asbestos mineralogy and chromosomal abnormalities of 41 patients. Eur J Cancer. 1992;28A:1373–9.
28. Jean D, Thomas E, Manie E, et al. Syntenic relationships between genomic profiles of fiber-induced murine and human malignant mesothelioma. Am J Pathol. 2011;178:881–94.
29. Krismann M, Müller K, Jaworska M, Johnen G. Molecular cytogenetic differences between histological subtypes of malignant mesotheliomas: DNA cytometry and comparative genomic hybridization of 90 cases. J Pathol. 2002;197:363–71.
30. Sugarbaker DJ, Richards WG, Gordon GJ, et al. Transcriptome sequencing of malignant pleural mesothelioma tumors. Proc Natl Acad Sci U S A. 2008;105:3521–6.
31. Bueno R, De Rienzo A, Dong L, et al. Second generation sequencing of the mesothelioma tumor genome. PLoS ONE. 2010;5:e10612.
32. Sekido Y. Genomic abnormalities and signal transduction dysregulation in malignant mesothelioma cells. Cancer Sci. 2010;101:1–6.
33. Murthy SS, Testa JR. Asbestos, chromosomal deletions, and tumor suppressor gene alterations in human malignant mesothelioma. J Cell Physiol. 1999;180:150–7.
34. Cortese JF, Gowda AL, Wali A, et al. Common EGFR mutations conferring sensitivity to gefitinib in lung adenocarcinoma are not prevalent in human malignant mesothelioma. Int J Cancer. 2006;118:521–2.
35. Onofre FB, Onofre AS, Pomjanski N, et al. 9p21 Deletion in the diagnosis of malignant mesothelioma in serous effusions additional to immunocytochemistry, DNA-ICM, and AgNOR analysis. Cancer. 2008;114:204–15.
36. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116:281–97.
37. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005;120:15–20.
38. Ambros V. The functions of animal microRNAs. Nature. 2004;431:350–5.
39. Hwang HW, Mendell JT. MicroRNAs in cell proliferation, cell death, and tumorigenesis. Br J Cancer. 2006;94:776–80.
40. Fabbri M, Croce CM, Calin GA. MicroRNAs. Cancer J. 2008;14:1–6.
41. Calin GA, Sevignani C, Dumitru CD, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A. 2004;101:2999–3004.
42. Guled M, Lahti L, Lindholm PM, et al. CDKN2A, NF2, and JUN are dysregulated among other genes by miRNAs in malignant mesothelioma -A miRNA microarray analysis. Genes Chromosomes Cancer. 2009;48:615–23.
43. Busacca S, Germano S, De Cecco L, et al. MicroRNA signature of malignant mesothelioma with potential diagnostic and prognostic implications. Am J Respir Cell Mol Biol. 2010;42:312–9.
44. Gee GV, Koestler DC, Christensen BC, et al. Downregulated microRNAs in the differential diagnosis of malignant pleural mesothelioma. Int J Cancer. 2010;127:2859–69.
45. Benjamin H, Lebanony D, Rosenwald S, et al. A diagnostic assay based on microRNA expression accurately identifies malignant pleural mesothelioma. J Mol Diagn. 2010;12:771–9.
46. Ivanov SV, Goparaju CM, Lopez P, et al. Pro-tumorigenic effects of miR-31 loss in mesothelioma. J Biol Chem. 2010;285:22809–17.
47. Balatti V, Maniero S, Ferracin M, et al. MicroRNAs dysregulation in human malignant pleural mesothelioma. J Thorac Oncol. 2011;6:844–51.
48. Santarelli L, Strafella E, Staffolani S, et al. Association of miR-126 with soluble mesothelin-related peptides, a marker for malignant mesothelioma. PLoS ONE. 2011;6:e18232.
49. Pass HI, Goparaju C, Ivanov S, et al. hsa-miR-29c* is linked to the prognosis of malignant pleural mesothelioma. Cancer Res. 2010;70:1916–24.
50. Goto Y, Shinjo K, Kondo Y, et al. Epigenetic profiles distinguish malignant pleural mesothelioma from lung adenocarcinoma. Cancer Res. 2009;69:9073–82.
51. Paik PK, Krug LM. Histone deacetylase inhibitors in malignant pleural mesothelioma: preclinical rationale and clinical trials. J Thorac Oncol. 2010;5:275–9.
52. Symanowski J, Vogelzang N, Zawel L, et al. A histone deacetylase inhibitor LBH589 downregulates XIAP in mesothelioma cell lines which is likely responsible for increased apoptosis with TRAIL. J Thorac Oncol. 2009;4:149–60.
53. Christensen BC, Marsit CJ, Houseman EA, et al. Differentiation of lung adenocarcinoma, pleural mesothelioma, and nonmalignant pulmonary tissues using DNA methylation profiles. Cancer Res. 2009;69:6315–21.
54. Christensen BC, Houseman EA, Marsit CJ, et al. Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. PLoS Genet. 2009;5:e1000602.
55. Tsou JA, Galler JS, Wali A, et al. DNA methylation profile of 28 potential marker loci in malignant mesothelioma. Lung Cancer. 2007;58:220–30.
56. Wong L, Zhou J, Anderson D, Kratzke R. Inactivation of p16INK4a expression in malignant mesothelioma by methylation. Lung Cancer. 2002;38:131–6.
57. Tsou JA, Shen LY, Siegmund KD, et al. Distinct DNA methylation profiles in malignant mesothelioma, lung adenocarcinoma, and non-tumor lung. Lung Cancer. 2005;47:193–204.
58. Suzuki M, Toyooka S, Shivapurkar N, et al. Aberrant methylation profile of human malignant mesotheliomas and its relationship to SV40 infection. Oncogene. 2005;24:1302–8.

59. Destro A, Ceresoli GL, Baryshnikova E, et al. Gene methylation in pleural mesothelioma: correlations with clinico-pathological features and patient's follow-up. Lung Cancer. 2008;59:369–76.
60. Christensen BC, Godleski JJ, Marsit CJ, et al. Asbestos exposure predicts cell cycle control gene promoter methylation in pleural mesothelioma. Carcinogenesis. 2008;29:1555–9.
61. Kohno H, Amatya VJ, Takeshima Y, et al. Aberrant promoter methylation of WIF-1 and SFRP1, 2, 4 genes in mesothelioma. Oncol Rep. 2010;24:423–31.
62. Christensen B, Houseman E, Godleski J, et al. Epigenetic profiles distinguish pleural mesothelioma from normal pleura and predict lung asbestos burden and clinical outcome. Cancer Res. 2009;69:227–34.
63. Christensen B, Houseman E, Poage G, et al. Integrated profiling reveals a global correlation between epigenetic and genetic alterations in mesothelioma. Cancer Res. 2010;70:5686–94.
64. Fischer JR, Ohnmacht U, Rieger N, et al. Promoter methylation of RASSF1A, RARbeta and DAPK predict poor prognosis of patients with malignant mesothelioma. Lung Cancer. 2006;54:109–16.
65. Toyooka S, Pass HI, Shivapurkar N, et al. Aberrant methylation and Simian virus 40 Tag sequences in malignant mesothelioma. Cancer Res. 2001;61:5727–30.
66. Gray SG, Fennell DA, Mutti L, O'Byrne KJ. In arrayed ranks: array technology in the study of mesothelioma. J Thorac Oncol. 2009;4:411–25.
67. Ombretta M, Alfonso C, Erika M, et al. A review of transcriptome studies combined with data mining reveals novel potential markers of malignant pleural mesothelioma. Mutat Res. 2011;750: 132–40.
68. Crispi S, Calogero RA, Santini M, et al. Global gene expression profiling of human pleural mesotheliomas: identification of matrix metalloproteinase 14 (MMP-14) as potential tumour target. PLoS ONE. 2009;4:e7016.
69. Roe OD, Anderssen E, Sandeck H, et al. Malignant pleural mesothelioma: genome-wide expression patterns reflecting general resistance mechanisms and a proposal of novel targets. Lung Cancer. 2010;67:57–68.
70. Singhal S, Wiewrodt R, Malden LD, et al. Gene expression profiling of malignant mesothelioma. Clin Cancer Res. 2003;9:3080–97.
71. Kettunen E, Nissén AM, Ollikainen T, et al. Gene expression profiling of malignant mesothelioma cell lines: cDNA array study. Int J Cancer. 2001;91:492–6.
72. Kettunen E, Nicholson AG, Nagy B, et al. L1CAM, INP10, P-cadherin, tPA and ITGB4 over-expression in malignant pleural mesotheliomas revealed by combined use of cDNA and tissue microarray. Carcinogenesis. 2005;26:17–25.
73. Wali A, Morin PJ, Hough CD, et al. Identification of intelectin overexpression in malignant pleural mesothelioma by serial analysis of gene expression (SAGE). Lung Cancer. 2005;48:19–29.
74. Gordon G, Jensen R, Hsiao L, et al. Translation of microarray data into clinically relevant cancer diagnostic tests using gene expression ratios in lung cancer and mesothelioma. Cancer Res. 2002;62:4963–7.
75. Holloway AJ, Diyagama DS, Opeskin K, et al. A molecular diagnostic test for distinguishing lung adenocarcinoma from malignant mesothelioma using cells collected from pleural effusions. Clin Cancer Res. 2006;12:5129–35.
76. Gordon GJ, Rockwell GN, Godfrey PA, et al. Validation of genomics-based prognostic tests in malignant pleural mesothelioma. Clin Cancer Res. 2005;11:4406–14.
77. Gordon GJ, Dong L, Yeap BY, et al. Four-gene expression ratio test for survival in patients undergoing surgery for mesothelioma. J Natl Cancer Inst. 2009;101:678–86.
78. Lopez-Rios F, Chuai S, Flores R, et al. Global gene expression profiling of pleural mesotheliomas: overexpression of Aurora kinases and P16/CDKN2A deletion as prognostic factors and critical evaluation of microarray-based prognostic prediction. Cancer Res. 2006;66:2970–9.
79. Pass HI, Liu Z, Wali A, et al. Gene expression profiles predict survival and progression of pleural mesothelioma. Clin Cancer Res. 2004;10:849–59.
80. Mohr S, Keith G, Galateau-Salle F, Icard P, Rihn B. Cell protection, resistance and invasiveness of two malignant mesotheliomas as assessed by 10 K-microarray. Biochim Biophys Acta. 2004;1688:43–60.
81. Hoang C, D'Cunha J, Kratzke M, et al. Gene expression profiling identifies matriptase overexpression in malignant mesothelioma. Chest. 2004;125:1843–52.
82. Sun X, Wei L, Liden J, et al. Molecular characterization of tumour heterogeneity and malignant mesothelioma cell differentiation by gene profiling. J Pathol. 2005;207:91–101.
83. Romagnoli S, Fasoli E, Vaira V, et al. Identification of potential therapeutic targets in malignant mesothelioma using cell-cycle gene expression analysis. Am J Pathol. 2009;174:762–70.
84. Borczuk A, Cappellini G, Kim H, et al. Molecular profiling of malignant peritoneal mesothelioma identifies the ubiquitin-proteasome pathway as a therapeutic target in poor prognosis tumors. Oncogene. 2007;26:610–7.
85. Ruosaari S, Hienonen-Kempas T, Puustinen A, et al. Pathways affected by asbestos exposure in normal and tumour tissue of lung cancer patients. BMC Med Genet. 2008;1:55.
86. Hegmans JP, Veltman JD, Fung ET, et al. Protein profiling of pleural effusions to identify malignant pleural mesothelioma using SELDI-TOF MS. Technol Cancer Res Treat. 2009;8:323–32.
87. Ou WB, Corson JM, Flynn DL, et al. AXL regulates mesothelioma proliferation and invasiveness. Oncogene. 2011;30: 1643–52.
88. van der Bij S, Schaake E, Koffijberg H, et al. Markers for the non-invasive diagnosis of mesothelioma: a systematic review. Br J Cancer. 2011;104:1325–33.
89. Henzi T, Blum WV, Pfefferli M, et al. SV40-induced expression of calretinin protects mesothelial cells from asbestos cytotoxicity and may be a key factor contributing to mesothelioma pathogenesis. Am J Pathol. 2009;174:2324–36.
90. Ordonez NG. What are the current best immunohistochemical markers for the diagnosis of epithelioid mesothelioma? A review and update. Hum Pathol. 2007;38:1–16.
91. Travis WD. Sarcomatoid neoplasms of the lung and pleura. Arch Pathol Lab Med. 2010;134:1645–58.
92. Klebe S, Mahar A, Henderson DW, Roggli VL. Malignant mesothelioma with heterologous elements: clinicopathological correlation of 27 cases and literature review. Mod Pathol. 2008;21:1084–94.
93. Su XY, Li GD, Liu WP, Xie B, Jiang YH. Cytological differential diagnosis among adenocarcinoma, epithelial mesothelioma, and reactive mesothelial cells in serous effusions by immunocytochemistry. Diagn Cytopathol. 2011;39:900–8.
94. Hasteh F, Lin GY, Weidner N, Michael CW. The use of immunohistochemistry to distinguish reactive mesothelial cells from malignant mesothelioma in cytologic effusions. Cancer Cytopathol. 2010;118:90–6.
95. Marchevsky AM. Application of immunohistochemistry to the diagnosis of malignant mesothelioma. Arch Pathol Lab Med. 2008;132:397–401.
96. Yuan Y, Nymoen DA, Stavnes HT, et al. Tenascin-X is a novel diagnostic marker of malignant mesothelioma. Am J Surg Pathol. 2009;33:1673–82.
97. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2009;133:1317–31.

98. Maeda M, Hino O. Molecular tumor markers for asbestos-related mesothelioma: serum diagnostic markers. Pathol Int. 2006;56: 649–54.
99. Yamaguchi N, Hattori K, Oh-eda M, et al. A novel cytokine exhibiting megakaryocyte potentiating activity from a human pancreatic tumor cell line HPC-Y5. J Biol Chem. 1994;269:805–8.
100. Scholler N, Fu N, Yang Y, et al. Soluble member(s) of the mesothelin/megakaryocyte potentiating factor family are detectable in sera from patients with ovarian carcinoma. Proc Natl Acad Sci U S A. 1999;96:11531–6.
101. Robinson BW, Creaney J, Lake R, et al. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet. 2003;362:1612–6.
102. Shiomi K, Miyamoto H, Segawa T, et al. Novel ELISA system for detection of N-ERC/mesothelin in the sera of mesothelioma patients. Cancer Sci. 2006;97:928–32.
103. Segawa T, Hagiwara Y, Ishikawa K, et al. MESOMARK kit detects C-ERC/mesothelin, but not SMRP with C-terminus. Biochem Biophys Res Commun. 2008;369:915–8.
104. Shiomi K, Hagiwara Y, Sonoue K, et al. Sensitive and specific new enzyme-linked immunosorbent assay for N-ERC/mesothelin increases its potential as a useful serum tumor marker for mesothelioma. Clin Cancer Res. 2008;14:1431–7.
105. Hassan R, Remaley AT, Sampson ML, et al. Detection and quantitation of serum mesothelin, a tumor marker for patients with mesothelioma and ovarian cancer. Clin Cancer Res. 2006;12:447–53.
106. Creaney J, Yeoman D, Musk AW, et al. Plasma versus serum levels of osteopontin and mesothelin in patients with malignant mesothelioma-which is best? Lung Cancer. 2011;74:55–60.
107. Hollevoet K, Nackaerts K, Thimpont J, et al. Diagnostic performance of soluble mesothelin and megakaryocyte potentiating factor in mesothelioma. Am J Respir Crit Care Med. 2010;181:620–5.
108. Hollevoet K, Van Cleemput J, Thimpont J, et al. Serial measurements of mesothelioma serum biomarkers in asbestos-exposed individuals: a prospective longitudinal cohort study. J Thorac Oncol. 2011;6:889–95.
109. Boudville N, Paul R, Robinson BW, Creaney J. Mesothelin and kidney function-analysis of relationship and implications for mesothelioma screening. Lung Cancer. 2011;73:320–4.
110. Park EK, Sandrini A, Yates DH, et al. Soluble mesothelin-related protein in an asbestos-exposed population: the dust diseases board cohort study. Am J Respir Crit Care Med. 2008;178:832–7.
111. Weber DG, Johnen G, Taeger D, et al. Assessment of confounding factors affecting the tumor markers SMRP, CA125, and CYFRA21-1 in serum. Biomark Insights. 2010;5:1–8.
112. Creaney J, Robinson BW. Serum and pleural fluid biomarkers for mesothelioma. Curr Opin Pulm Med. 2009;15:366–70.
113. Luo L, Shi H-Z, Liang Q-L, et al. Diagnostic value of soluble mesothelin-related peptides for malignant mesothelioma: a meta-analysis. Respir Med. 2010;104:149–56.
114. Gube M, Taeger D, Weber DG, et al. Performance of biomarkers SMRP, CA125, and CYFRA 21-1 as potential tumor markers for malignant mesothelioma and lung cancer in a cohort of workers formerly exposed to asbestos. Arch Toxicol. 2011;85:185–92.
115. Grigoriu BD, Scherpereel A, Devos P, et al. Utility of osteopontin and serum mesothelin in malignant pleural mesothelioma diagnosis and prognosis assessment. Clin Cancer Res. 2007;13:2928–35.
116. Creaney J, Francis RJ, Dick IM, et al. Serum soluble mesothelin concentrations in malignant pleural mesothelioma: relationship to tumor volume, clinical stage and changes in tumor burden. Clin Cancer Res. 2011;17:1181–9.
117. Wheatley-Price P, Yang B, Patsios D, et al. Soluble mesothelin-related peptide and osteopontin as markers of response in malignant mesothelioma. J Clin Oncol. 2010;28:3316–22.
118. Tajima K, Hirama M, Shiomi K, et al. ERC/mesothelin as a marker for chemotherapeutic response in patients with mesothelioma. Anticancer Res. 2008;28:3933–6.
119. Dipalma N, Luisi V, Di Serio F, et al. Biomarkers in malignant mesothelioma: diagnostic and prognostic role of soluble mesothelin-related peptide. Int J Biol Markers. 2011;26:160–5.
120. Pass HI, Lott D, Lonardo F, et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. N Engl J Med. 2005;353:1564–73.
121. Sabo-Attwood T, Ramos-Nino ME, Eugenia-Ariza M, et al. Osteopontin modulates inflammation, mucin production, and gene expression signatures after inhalation of asbestos in a murine model of fibrosis. Am J Pathol. 2011;178:1975–85.
122. Park EK, Thomas PS, Johnson AR, Yates DH. Osteopontin levels in an asbestos-exposed population. Clin Cancer Res. 2009; 15:1362–6.
123. Cristaudo A, Foddis R, Bonotti A, et al. Comparison between plasma and serum osteopontin levels: usefulness in diagnosis of epithelial malignant pleural mesothelioma. Int J Biol Markers. 2010;25:164–70.
124. Mastrangelo G, Marangi G, Ballarin MN, et al. Osteopontin, asbestos exposure and pleural plaques: a cross-sectional study. BMC Public Health. 2011;11:220.
125. Constantinescu D, Vornicu M, Grigoriu C, Cozmei C, Grigoriu BD. Assaying for circulating osteopontin in practice: a technical note. Eur Respir J. 2010;35:1187–8.
126. Creaney J, Yeoman D, Demelker Y, et al. Comparison of osteopontin, megakaryocyte potentiating factor, and mesothelin proteins as markers in the serum of patients with malignant mesothelioma. J Thorac Oncol. 2008;3:851–7.
127. Cappia S, Righi L, Mirabelli D, et al. Prognostic role of osteopontin expression in malignant pleural mesothelioma. Am J Clin Pathol. 2008;130:58–64.
128. Hedman M, Arnberg H, Wernlund J, Riska H, Brodin O. Tissue polypeptide antigen (TPA), hyaluronan and CA 125 as serum markers in malignant mesothelioma. Anticancer Res. 2003; 23:531–6.
129. Schouwink H, Korse CM, Bonfrer JM, Hart AA, Baas P. Prognostic value of the serum tumour markers Cyfra 21-1 and tissue polypeptide antigen in malignant mesothelioma. Lung Cancer. 1999;25:25–32.
130. Martensson G, Thylen A, Lindquist U, Hjerpe A. The sensitivity of hyaluronan analysis of pleural fluid from patients with malignant mesothelioma and a comparison of different methods. Cancer. 1994;73:1406–10.
131. Grigoriu B, Chahine B, Zerimech F, et al. Serum mesothelin has a higher diagnostic utility than hyaluronic acid in malignant mesothelioma. Clin Biochem. 2009;42:1046–50.
132. Fiorelli A, Vicidomini G, Di Domenico M, et al. Vascular endothelial growth factor in pleural fluid for differential diagnosis of benign and malignant origin and its clinical applications. Interact Cardiovasc Thorac Surg. 2011;12:420–4.
133. Hirayama N, Tabata C, Tabata R, et al. Pleural effusion VEGF levels as a prognostic factor of malignant pleural mesothelioma. Respir Med. 2011;105:137–42.
134. Amati M, Tomasetti M, Mariotti L, et al. Assessment of biomarkers in asbestos-exposed workers as indicators of cancer risk. Mut Res/Genet Toxicol Environ Mutag. 2008;655:52–8.
135. Attanoos RL, Griffin A, Gibbs AR. The use of immunohistochemistry in distinguishing reactive from neoplastic mesothelium. A novel use for desmin and comparative evaluation with epithelial membrane antigen, p53, platelet-derived growth factor-receptor, P-glycoprotein and Bcl-2. Histopathology. 2003;43:231–8.

136. Ascoli V, Scalzo CC, Facciolo F, Nardi F. Platelet-derived growth factor receptor immunoreactivity in mesothelioma and nonneoplastic mesothelial cells in serous effusions. Acta Cytol. 1995;39: 613–22.
137. Filiberti R, Marroni P, Neri M, et al. Serum PDGF-AB in pleural mesothelioma. Tumour Biol. 2005;26:221–6.
138. Gueugnon F, Leclercq S, Blanquart C, et al. Identification of novel markers for the diagnosis of malignant pleural mesothelioma. Am J Pathol. 2011;178:1033–42.
139. Tanaka S, Choe N, Iwagaki A, Hemenway DR, Kagan E. Asbestos exposure induces MCP-1 secretion by pleural mesothelial cells. Exp Lung Res. 2000;26:241–55.
140. Dragonieri S, van der Schee MP, Massaro T, et al. An electronic nose distinguishes exhaled breath of patients with malignant pleural mesothelioma from controls. Lung Cancer. 2012;75:326–31.
141. de Gennaro G, Dragonieri S, Longobardi F, et al. Chemical characterization of exhaled breath to differentiate between patients with malignant pleural mesothelioma from subjects with similar professional asbestos exposure. Anal Bioanal Chem. 2010;398: 3043–50.
142. Chapman EA, Thomas PS, Yates DH. Breath analysis in asbestos-related disorders: a review of the literature and potential future applications. J Breath Res. 2010;4:034001.
143. Baudis M, et al. Progenetix.net: an online repository for molecular cytogenetic aberration data. Bioinformatics. 2001;17(12): 1228–9.
144. Sebova K, Fridrichova I. Epigenetic tools in potential anticancer therapy. Anticancer Drugs. 2010;21:565–77.
145. Carbone M, Yang H, Pass HI, et al. BAP1 and Cancer. Nat Rev Cancer. 2013;13:(3):153–59.

Neoplasm of Soft Tissues

20

Franco Merletti, Emanuela Ciliberto, and Dario Mirabelli

Keywords
Soft tissue sarcoma • Dioxin • Epidemiology

Epidemiology and General, Nonoccupational Risk Factors

According to the 2005–2009 statistics, soft tissue sarcomas (STS) accounted for 33.9 % of all sarcoma cases registered in 18 US areas of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Parenchimatous and retroperitoneal/pleural sarcomas represent, respectively, 50.2 and 15.0 % (SEER Cancer Statistics Review, last accessed on 21/08/2012 at: http://seer.cancer.gov/csr/1975_2009_pops09/index.html). The age-adjusted (2000 US standard population) incidence rates for STS, including heart sarcomas, were provided by the US National Program of Cancer Registries. Rates per 100,000 persons per year for the period 2004–2008 are shown in Table 20.1, by gender, race, and ethnicity (United States Cancer Statistics, last accessed on 21/08/2012 at: http://apps.nccd.cdc.gov/uscs/index.aspx). Since 1999–2008 incidence increased slightly in both genders, with annual percent change (APC) equaling 1 %.

The Nordic Countries Registries estimated the standardized (world standard population) STS incidence in 2005–2009 to be 2.5 cases per 100,000 persons per year in males and 2.0 in females (the difference with the US data is most likely apparent, due to the use of a different standard population: US and world population have rather different age structures). The APC was 2.3 % in men and 1.5 % in women in the last 10 years of observation.

Age-specific incidence rates start to increase in the 45–49 age class in both genders, to subsequently grow according to a power of attained age, a trend common to many adult solid cancers.

Mortality is considerably lower than incidence, mortality rates being equal to about one-third of the corresponding age and time-specific rates in the US populations served by SEER registries and in the Nordic Countries.

The relationship between STS and obesity has been addressed by several researchers. A cohort of 28,129 patients admitted to hospitals with a diagnosis of obesity between 1965 and 1993 was set up in Sweden and followed up for mortality and cancer incidence; 18 cases of connective tissue neoplasms were observed with almost doubled incidence [152]. Samanic and colleagues studied a cohort of 4,500,700 male US veterans (3,668,486 whites; 832,214 blacks) admitted at Veterans Affairs hospitals between 1969 and 1996; obese individuals were identified on the basis a of diagnosis of obesity in discharge records; compared to nonobese veterans, the rate ratio of connective tissue neoplasm was 1.3 (statistically significant, based on 185 cases) among obese whites and 1.1 (nonstatistically significant, based on 20 cases) among obese blacks [122]. Among 362,552 workers (men) from the Swedish Foundation for Occupational Safety and Health of the Construction Industry health examination database, enrolled between 1971 and 1992 and followed up to 1999 for mortality and cancer incidence, the rate ratio for STS among obese workers was 1.6 and marginally significant, based on 20 cases [123].

Occupational Risk Factors for Soft Tissue Sarcomas

STSs raised interest in the scientific and public health communities in the early 1980s, following the appreciation of the potential for widespread population exposure to phenoxy

F. Merletti, MD (✉) • E. Ciliberto, DVM, PhD • D. Mirabelli, MD
Unit of Cancer Epidemiology – Department of Medical Sciences, University of Turin, Via Santena, 7, Turin 10126, Italy
e-mail: franco.merletti@unito.it

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_20,

Table 20.1 Age-adjusted (2000 US standard population) incidence rates per 100,000 persons provided by the US National Program of Cancer Registries for the period 2004–2008, by gender, race, and ethnicity

White	Black	Asian-Pacific	American Indian-Alaskan	Hispanic	All
Men					
3.8 (3.7–3.8)	3.4 (3.3–3.6)	2.5 (2.4–2.8)	2.3 (1.9–2.8)	3.1 (3.0–3.3)	3.8 (3.7–3.8)
Women					
2.7 (2.6–2.7)	3.1 (3.0–3.2)	2.0 (1.9–2.2)	1.7 (1.4–2.1)	2.7 (2.6–2.8)	2.7 (2.6–2.8)

From US Cancer Statistics (http://apps.nccd.cdc.gov/uscs/index.aspx)

herbicides, contaminated toxic agent, 2,4,5,7-tetrachlorodibenzo-p-dioxin (TCDD), and an early report of an increased risk of STS among individuals exposed to phenoxy acids and chlorophenols in agriculture, forestry, and horticulture in Sweden [44].

Since then, a large number of industry- and community-based studies have been carried out. Other agents sharing with TCDD certain toxicological properties (dioxin-like compounds, including TCDD congeners as well as polychlorinated dibenzofurans and polychlorinated biphenyls) have been found, and mechanisms of carcinogenicity for TCDD and dioxin-like compounds have been identified. An overview of cohort studies is shown in Table 20.2, whereas Table 20.3 offers a synthesis of case-control studies. Reflecting these advancements, the International Agency for Research on Cancer (IARC) periodically reviewed the evidence of carcinogenicity for TCDD, dioxin-like compounds, and agents potentially contaminated by TCDD and dioxin-like compounds (see Table 20.4).

Usually, the interpretation of epidemiological evidence in terms of a causal relationship with exposure to specific chemicals, or at least with groups of chemicals, is considered to be relatively easier in cohort studies. However, even in occupational cohort studies, i.e., the vast majority of those included in Table 20.2, exposures could often be defined only in crude terms, such as being employed in particular industrial processes, and when more in-depth knowledge of involved chemicals was available, multiple agents were usually present so that uncertainty exists whether to which ascribe effects, when any was observed. Furthermore cohort studies have been limited in power by the rarity of STSs (even in large occupational cohorts, only a handful of STS cases/deaths was observed) and by the relatively short time elapsed in most cases from exposure start to the end of follow-up (phenoxy herbicides came into production and use in the 1950s).

Case-control studies have the advantage of gathering comparatively large sets of cases and of allowing researchers to restrict their analysis to those satisfying certain diagnostic criteria, thus limiting potential misclassification of diagnosis, but at the expense of greater difficulties in retrospective exposure assessment. It is not surprising, therefore, that controversies repeatedly arose in the interpretation of the epidemiological evidence.

The first (and largest) group of studies focused on chlorophenoxy herbicides or certain fungicides (chlorophenols), their contaminants (polychlorinated dibenzodioxins and furans), and associated occupations, industries, or other exposures (like living in areas contaminated by pollution from industrial sources). They are shown under a common heading in Table 20.2, but no such grouping is possible for case-control studies in Table 20.3.

Industries and occupations associated with increased mortality from or incidence of STSs were production of phenoxy herbicides and chlorophenols, forestry (use of phenoxy acids as herbicides), logging and sawmills (use of chlorophenols as fungicides), agriculture (rice-weeding when phenoxy acids started being used as herbicides), gardening, abattoir workers and pelt treatment in meat works, leather workers, railroad track maintenance, and the general population living in proximity to industrial waste incinerators in Northern Italy (but not in France around a municipal waste incinerator). The largest body of evidence came from population-based case-control studies conducted in Sweden in the late 1970s and 1980s, from the IARC and NIOSH international cohorts and the case-control study nested in the IARC cohort.

Liver hemangiosarcomas were specifically investigated in relation to exposure to vinyl chloride monomer (VCM) in employees of petrochemical plants synthesizing VCM or producing polyvinylchloride. Given the extreme rarity of both disease and exposure, two large, multicentric international studies have been conducted, prompted by case reports and results of experimental work [59]. As mortality from other cancers was also reported, in this chapter we will consider results on deaths from STS, whereas liver hemangiosarcomas will be discussed in Chap. 6.

High-dose ionizing radiation, such as in radiotherapy, has been associated with remarkable increases in STS incidence among patients surviving various types of cancer in a series of studies, as shown in Table 20.2 (studies on survivors of childhood cancer are grouped separately). No excess STS mortality or incidence has been reported in cohorts of individuals occupationally exposed to ionizing radiation or in atomic bombing survivors. Cancer patients may have also undergone chemotherapy, and the association of radio- and chemotherapy increases STS risk more than each taken separately.

Table 20.2 Cohort studies on incidence or mortality from soft tissue sarcomas in groups with occupational, environmental, and other exposures

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Dioxins, phenoxy acids, chlorophenols							
Ruder and Yiin [119], cohort of PCP manufacturers (part of NIOSH industrial cohort), USA	Cohort of 2,122 workers employed at four US plants manufacturing PCP, out of the 12 contributing to the NIOSH cohort, engaged in production of PCP, TCP, or both; mortality follow-up to 2005; vital status 99 %; causes of death ascertainment not stated	Type of chlorophenol produced and potential dioxin contamination	Full cohort	2	1.5 (0.2–5.5)		Extended follow-up study of some US cohorts included also in the IARC [70] and NIOSH [134] cohorts
			PCP and TCP	1	2.3 (0.1–12.6)		Limited power
			PCP (no TCP)	1	1.1 (0.0–6.4)		
Bueno de Mesquita et al. [12], Boers et al. [6], Dutch cohort of phenoxy acids workers, the Netherlands	Cohort of 1,167 workers employed during 1955–1985 in factory A (including 85 cleanup workers, after the 1963 accident) and 1,143 employed during 1965–1986 in factory B. Study restricted to 2,106 men; mortality follow-up from 1955 (or 1965) to 2006; vital status 95 %; cause of death 98 %	(A) Exposure after working in production or contaminated departments, (B) exposure due to the 1963 accident, (C) exposure by proximity	Full cohort	0			Extended follow-up study of the Dutch industrial cohort (factory A) included also in the IARC cohort, Kogevinas et al. [70]
Rylander and Hagmar [121], Svensson et al. [137], Mikoczy and Rylander [95], cohort of fishermen and wives, Sweden	Cohort of fishermen from the East (2,932) and West (8,600) Coast, with membership from the 1930s to 1988. Cohort of women married to cohort members from the East (2,171) or West (7,158) Coast; mortality and cancer incidence follow-up during 1965–2002; vital status and causes of death ascertainment not stated	Fatty fish from the Baltic Sea (East Coast) higher content of persistent organochlorine pollutants	Fishermen				Previously partly (factory A) studied also by Hooiveld et al. [52]
			East Coast	3	1.0 (0.2–2.8)		
			West Coast	8	0.7 (0.3–1.3)		
			Wives				
			East Coast	1	0.5 (0.0–2.8)		
			West Coast	3	0.4 (0.1–1.1)		
Collins et al. [20], industrial cohort Midland, Michigan (USA)	Cohort of 1,615 workers in a Dow Chemical Company plant producing 2,4,5-T from 1948 to 1982 and TCP from 1942 to 1979; mortality follow-up 1942–2003; vital status 99 %; cause of death 99 %	Quantitative internal exposure levels estimated by modeling blood-level data from a subgroup (17 % sample, 280 workers)	Full cohort	4	4.1 (1.1–10.5)		Three malignant fibrous histiocytoma, one angiosarcoma of the scalp. In previous studies, 1 was reported to be a clear cell renal carcinoma
			Unit risk for 1 ppb/year increase in cumulative exposure		1.06 (1.02–1.11)		
Ramlow et al. [111], Collins et al. [21], industrial cohort Midland, Michigan (USA)	Cohort of 773 workers in a Dow Chemical Company plant producing PCP from 1937 to 1980 (157 of whom developed chloracne); mortality follow-up started in 1940, end not stated; vital status 100 %; cause of death 100 %	Quantitative internal exposure levels estimated by modeling blood-level data from a subgroup (128 workers)	Full cohort	1	2.2 (0.0–12–1)		The STS death occurred in one of the 196 workers who had also TCP exposure

(continued)

Table 20.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
McBride et al. [82], New Plymouth cohort of phenoxy acids producers and sprayers, New Zealand	Cohort of 1,559 workers in production of phenoxy herbicides >1 day from 1969 to 1988; mortality follow-up 1969–2004; vital status 79 %; causes of death 100 %	Quantitative internal exposure levels estimated by modeling blood-level data from a subgroup (346 workers)	TCDD exposure				Extension and expansion (to workers with any length of employment and employed up to 1988) of part of the New Plymouth cohort, reported by 't Mannetje et al. [78] and included in the IARC cohort
			Ever	1	3.4 (0.1–19.5)		
			Never	0	0.0 (0.0–34.9)		
			0–68.3 ppt-mo	0	0.0 (0.0–44.8)		
			68.4–475.0 ppt-mo	0	0.0 (0.0–43.2)		
			475.1–2085.7 ppt-mo	1	15.5 (0.4–86.5)		
			2,085–8 + ppt-mo	0	0.0 (0.0–61.0)		
Pesatori et al. [104, 105], Seveso area residents (Italy)	Individuals residing at the time of the Seveso accident (1976) in three zones with decreasing TCDD soil levels (zone A, very high, 723; zone B, high, 4,821; zone R, low, 31,643) and in a surrounding non-contaminated reference territory, 181,574; cancer incidence 1977–1996; vital status 99 %	Model of deposition for the cloud released by the accident. Measurement of TCDD concentration in soils and blood samples	Zone A	0	–		Population not covered by a cancer registry. Cancer incidence estimated through the regional hospital admission records. Among zone A + B residents 1.2 STS cases expected. Results by elapsed time since the 1976 accident not given for STS cases
			Zone B	0	–		
			Zone R	9	1.3 (0.6–2.7)		
Consonni et al. [24], Seveso area residents (Italy)	Individuals residing at the time of the Seveso accident (1976), or immigrating/born 10 years thereafter, in three zones with decreasing TCDD soil levels (zone A, very high, 804; zone B, high, 5,941; zone R, low, 38,623) and in a surrounding non-contaminated reference territory, 232,740; mortality follow-up 1976–2011; vital status 99 %; cause of death 99 %	Model of deposition for the cloud released by the accident. Measurement of TCDD concentration in soils and blood samples	Zone A	0	–		Results by elapsed time since the 1976 accident not given for STS deaths. Among 182 individuals who developed chloracne after the accident 2 deaths observed overall
			Zone B	0	–		
			Zone R	4	0.8 (0.3–2.1)		
Hansen et al. [43], Danish occupational cohort, Denmark	Cohort of 3,156 gardeners (men) listed in the gardeners' section of the Danish Union of General Workers 1973 file and alive in 1975; cancer incidence follow-up 1975–2001; vital status ascertainment not stated	According to year of birth, 3 subcohorts: early (high exposure), intermediate (medium exposure), late (low exposure)	Full cohort	4	2.0 (0.5–5.0)		
			Early	3	5.9 (1.9–18.2)		
			Intermediate	0	0.0 (0.0–3.8)		
			Late	1	1.8 (0.2–12.9)		

McLean et al. [87], IARC cohort of pulp and paper workers, international	Cohort of 60,468 workers employed >1 year in the pulp and paper industry between 1920 and 1996 in 11 countries; mortality follow-up started between 1943 and 1980, ended between 1991 and 1996; vital status 98 %; causes of death ascertainment not stated	Experts developed an exposure matrix assigning exposure to 27 agents by plant, department and period, based on company questionnaires and about 31,000 exposure measurements	Exposure to volatile organochlorine compounds Never Ever High Exposure to nonvolatile organochlorine compounds Never Ever	 2 12 4 8 4	 0.9 (0.1–3.2) 1.1 (0.6–2.0) 1.8 (0.5–4.5) 1.2 (0.5–2.4) 0.8 (0.2–2.0)		
Demers et al. [27], BC sawmill workers cohort, British Columbia, Canada	Cohort of 27,464 workers (men) employed >1 year in any of 14 sawmills between 1950 and 1995; mortality follow-up 1950–1995, cancer incidence follow-up 1969–1995; vital status 96 %; causes of death ascertainment not stated	Plant records and interviews with senior employees. Dermal exposure to chlorophenols (PCP and TeCP, used 1950–1990), according to plant, job, and fungicide formulations, as exposure hours per year and full-time equivalent years	Full cohort Mortality Incidence Incidence, by exposure-years to chlorophenols <1 1–2 2–5 5+	 7 13 2 5 4 2	 1.1 (0.4–2.3) 0.8 (0.5–1.4) 1 (ref) 0.9 (0.3–2.4) 0.6 (0.2–1.8) 0.3 (0.1–1.2)	Age, calendar period, race Smoking, 2-naphtylamine exposure	Incidence by exposure-years to specific agents (PCP and TeCP) and lag (10 or 20 years) showed the same pattern
Mikoczy et al. [93], Mikoczy and Hagmar [96], cohort of tannery workers, Sweden	Cohort of 20,231 workers (482 women) employed in three tanneries at least 1 year 1900–1989; cancer incidence follow-up 1958–1999; vital status ascertainment >99 %	Cohort membership	Full cohort, no lag Full cohort, 20-year lag	6 6	2.6 (0.96–5.7) 3.3 (1.2–7.3)		Chlorophenols used from 1950s to 1980s A nested case-control study [94] based on 4 of STS cases found no dose-response relationship with an index of cumulative exposure to chlorophenols
‘t Mannetje et al. [78], New Plymouth cohort of phenoxy acids producers and sprayers, New Zealand	Cohort of workers, in phenoxy herbicides (2,4,5-T) and TCP production for >1 month between 1969 and 1984 (1,025, 813 exposed) or spraying between 1973 and 1984 (703, 699 exposed); mortality follow-up from 1969 (producers) or 1973 (sprayers) to 2000; vital status 78 % (producers), 91 % (sprayers); causes of death ascertainment not stated	Job history of herbicides producers. Based on company questionnaires, assessment of exposure by job Exposure history questionnaires for sprayers	Production Spraying	0 1	0.0 (0.0–19.3) 4.3 (0.1–23.8)		Extended follow-up study of a cohort included in the IARC cohort Producers subcohort expanded and extended by McBride et al. [82] Low power (0.05 STS cases expected among producers, 0.23 among sprayers)
Swaen et al. [138], Swaen et al. [139], licensed herbicide applicators, the Netherlands	Cohort of 1,341 workers who in 1980 had been licensed for herbicide application work for government agencies; mortality follow-up 1980–2001; vital status 99 %; causes of death 99 %	After a 1980 survey, a list of agents was compiled. Phenoxy acids <10 % of active agent by weight	Full cohort	0	0.0 (0.0–7.4)		Low power (0.5 cases of connective tissue neoplasms expected)

(continued)

Table 20.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Costani et al. [25], Comba et al. [23], residents in certain boroughs of Mantua, Italy	General population residing 1984–1996 in three boroughs of Mantua, at increasing distance from a petrochemical plant and the annexed industrial waste incinerator; cancer incidence follow-up 1984–1996	Three residential zones: (A) from 2 to 4 km, (B) from 3 to 4 km, (C) from 3 to 4 km	Overall (A) (B) (C)	20 13 2 5	2.3 (1.3–3.5) 3.3 (1.7–5.6) 1.9 (0.2–6.9) 3.1 (1.0–7.2)		Ecological (spatial clustering) study. Reference incidence rates from the Varese province cancer registry
Bodner et al. [5], various plants, Dow Chemical industrial cohort, USA	Cohort of 2,187 workers (men) in Dow Chemical Company plants producing 2,4,5-T; mortality follow-up 1940–1994; vital status 100 %; cause of death 100 %	TCDD exposure score assigned by applying a job-exposure matrix	Full cohort	2	2.4 (0.3–8.6)		Extended follow-up study of the Dow Chemical cohort, included in the NIOSH and IARC cohorts
			Chloracne subcohort	1	10.9 (0.3–61.9)		Part of this cohort further updated by Collins et al. [20]
Stern [135], tannery workers in Red Wing, Minnesota, and Milwaukee, Wisconsin (USA)	Cohort of 9,352 workers employed in two leather tanneries 1940–1979 and 1940–1980, respectively; mortality follow-up 1940–1993; vital status 96 %; cause of death ascertainment not stated	Work area (beamhouse, tanyard, retan-color-fat liquor, finishing, others) and duration	Full cohort Beamhouse Tanyard Retan-color-fat liquor Finishing Others	4 1 0 2 1 0	1.3 (0.4–3.4) Not reported 3.0 (0.4–10.7) Not reported		Limited power. No trend by duration of employment in tannery
Rodvall et al. [117], children of licensed pesticide applicators, Sweden	Cohort of 27,329 children born 1958–1994 to Swedish licensed pesticide applicators; mortality and cancer incidence follow-up 1958–1994; vital status ascertainment not stated	Cohort membership	Full cohort	1	0.4 (0.0–2.1)		Inadequate length of follow-up for part of the cohort. Very limited power (overall 51 cancer cases observed, 73 expected)
Iaia et al. [58], tannery workers of Valdarno Inferiore, Italy	Cohort of 4,874 workers (4,150 men, 724 women) employed in any of 92 leather tanneries active in Valdarno Inferiore from 1970 to 1996; mortality follow-up 1998; vital status 100 %; causes of death 100 %	Job	Full cohort	0			Limited power. Likely major heterogeneity of exposure across the different small tanneries where the cohort was enrolled
Viel et al. [146], residents in Doubs department, France	General population residing 1980–1995 in the Doubs department, broken down by electoral ward, at increasing distance from an urban solid waste incinerator located in Besançon; cancer incidence 1980–1995	Residence by electoral ward, space- and time-clustering	Besançon and Audeux electoral wards (closest to the incinerator)	45	1.4 ($P=0.004$)		Ecological (spatial clustering) study. Formal case-control study by Floret et al. [35]

Fingerhut et al. [31], Steenland et al. [134], various plants, NIOSH industrial cohort, USA	Cohort of 5,132 workers (men) in 12 plants, producing herbicides and chemicals contaminated by TCDD; subcohort of 3,538 workers with estimated TCDD exposure; subcohort of 608 workers with chloracne; mortality follow-up 1948–1993; vital status 99 %; cause of death 98 %	Company questionnaires and TCDD contamination, individual occupational history; chloracne 608 workers; job-exposure matrix applied to 3,538 workers; serum TCDD measured for 177 workers	Full cohort Chloracne subcohort	4 3	2.3 (0.6–5.9) 11.3 (2.3–33)	Extended follow-up study of the US NIOSH cohort, included also in the IARC cohort, Kogevinas et al. [70] Partly extended and expanded by Ruder and Yudin [119]
Fleming et al. [32], cohort of Florida licensed pesticide applicators, USA	Cohort of 33,658 licensed pesticide applicators aged ≥20 years from the 1975–1993 state list; mortality follow-up 1975–1993; vital status and cause of death ascertainment not stated, but 92 % of all licensees had complete information for personal identification	Private, commercial or public type of license	Men Women	0 0	(0.0–1.7) (0.0–16.3)	Inadequate length of follow-up
Lynge [75–77], Danish industrial cohort, Denmark	Cohort of 2,119 workers (men and women), employed between 1947 (or 1951) and 1981 at two plants manufacturing phenoxy acids (mainly MCPA); cancer incidence follow-up 1947–1993; vital status 99 %	Employment in phenoxy acids production or packaging and maintenance	Full cohort	4	2.2 (0.6–5.6)	Included also in the IARC cohort, Kogevinas et al. [70]
Flesch-Janys et al. [33], industrial cohort, Germany	Cohort of 1,189 workers (men) employed in one plant on 1 Jan 1952 or later (until 1984) for at least 3 months; mortality follow-up 1952–1992; vital status and cause of death ascertainment not stated	Quantitative internal exposure levels estimated by modeling blood-level data from a subgroup of workers	Quartiles of TCDD/TEQ concentration	0	–	Expected number of STS deaths, 0.3 Included also in the IARC cohort, Kogevinas et al. [70]
Hooiveld et al. [52], The Netherlands, industrial cohort	Cohort of 1,167 workers (men) employed in a plant where phenoxy herbicides were synthesized and formulated; mortality follow-up 1955–1991; vital status 95 %; cause of death ascertainment not stated	Company questionnaires and individual occupational history. Exposed 549, unexposed 482 men. TCDD blood level modeled from measurements in 47 workers	Full cohort	0	–	Included also in the IARC cohort, Kogevinas et al. [70] Updated by Boers et al. [6]
Rix and Lynge [115], Rix et al. [116], Danish pulp and paper workers, industrial cohort, Denmark	Cohort of 14,362 workers (11,335 men and 3,454 women) in three pulp and paper industries between 1943 and 1990; mortality and cancer incidence follow-up 1943–1993; vital status 97 %; causes of death ascertainment not stated	Job	Full cohort, men Full cohort, women Sorting/packing, women	12 11 8	1.2 (0.6–2.0) 2.6 (1.3–4.7) 4.0 (1.7–7.8)	Men had little direct manual contact with paper
Kogevinas et al. [70], international (12 countries), IARC industrial cohort	Cohort of 21,863 exposed workers (20,851 men, 1,012 women) and 4,160 unexposed workers engaged in production or spraying of TCDD-/PCDD-contaminated phenoxy herbicides or chlorophenols in 36 plants; mortality follow-up, varying according to cohort, 1939–1992; vital status 95.6 %; cause of death ascertainment not stated	Company questionnaires and individual occupational history. Workers classified according to longest-held job as exposed or not exposed to 2,3,7,8-TCDD or higher chlorinated PCDDs	Exposed to phenoxy herbicides/chlorophenols Exposed to 2,3,7,8-TCDD or higher PCDDs Exposed to lower or no PCDD	9 6 2	2.0 (0.9–3.8) 2.0 (0.8–4.4) 1.4 (0.2–4.9)	

(continued)

Table 20.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Gambini et al. [37], rice growers in Novara province, Italy, occupational cohort	Cohort of 1,493 rice growers (men) from the pension fund 1988 file, dating back to 1957; mortality follow-up 1957–1992; vital status 99 %; cause of death 99 %	Calendar period/agent matrix	Full cohort	1	4.0 (0.1–22.3)		2,4-D used in the 1960s, 2,4,5-T in the 1960s and 1970s, MCPA and MCPP until the 1990s
Zober et al. [156], Ott and Zober [100], BASF Ag Ludwigshafen, Germany, industrial cohort	Cohort of 247 workers (243 men, 4 women) participating in cleanup after the 1953 accident, in maintenance or in demolition (1968–1969) of a trichlorophenol plant; mortality follow-up 1953–1992; cancer incidence follow-up 1993; vital status 100 %; cause of death 99 %	Estimate of TCDD dose by modeling work activities and data on TCDD blood level among 138 employees. Subcohort of workers with chloracne in 1954 (69, 68 men)	Full cohort	0	–		Very limited power
Becher et al. [3], Germany, industrial cohort	Cohort of workers (men) employed in four plants: (I) Boehringer Ingelheim Hamburg, 1,144 workers; (II) Bayer Uerdingen, 135 workers; (III) Bayer Dormagen, 520 workers; (IV) BASF Ludwigshafen, 680 workers. Mortality follow-up ended 1989 (1992 for cohort II); cause of death ascertainment not stated	Historical process reconstruction with measurements of TCDD concentration in products	Plant I	0	–		Cohort I included, with updated follow-up, in the IARC cohort and reported by Flesch-Janys et al. [33]
			Plant II	0	–		
			Plant III	0	–		Expected number of STS and bone sarcoma deaths among workers in plants II, III and IV: 0.5
			Plant IV	0	–		
Riihimaki et al. [114], Asp et al. [2], Finnish cohort of phenoxy herbicide applicators, Finland	Cohort of 1,909 workers (men) employed in spraying phenoxy herbicides 1955–1971; mortality and cancer incidence follow-up 1972–1989; vital status 100 %; causes of death ascertainment not stated	Cohort membership. Mailed questionnaire in 1988 (to next of kin, for decedents), on full job history and herbicide exposure after 1972	Full cohort	0			Expected number of STS deaths, allowing for 15 year latency: 0.25. Limited power, and short period of follow-up for part of the cohort
Collins et al. [19], Nitro, West Virginia (USA), industrial cohort	Cohort of 754 workers employed in the Monsanto plant for 2,4,5-trichlorophenol production between 8 March (accident) and 22 November 1949 (end of cleanup); mortality follow-up 1949–1987; vital status 97 %; causes of death 99 %	Identification of workers with (a) chloracne from the accident, 122; (b) potential exposure to TCDD and/or chloracne, 214; (c) potential 4-aminobiphenyl exposure, 196	Full cohort	3	6.7 (1.4–19.4)	Exposure to 4-aminobiphenyl	The STS diagnosis in Group 2 was not confirmed after tissue review
			No chloracne from accident and no 4-aminobiphenyl exposure, 461	0	(0.0–13.1)		Part of the cohort included in the NIOSH cohort and in the IARC cohort
			No chloracne from accident but 4-aminobiphenyl exposure, 171	1	11.1 (0.1–61.8)		The worker with no chloracne from accident but 4-aminobiphenyl exposure actually had chloracne
			Chloracne from accident and 4-aminobiphenyl exposure, 25	2	142 (16.0–516)		
			Chloracne from accident and no 4-aminobiphenyl exposure, 97	0	(0.0–55.6)		

Blair et al. [4], USA, farmers	Deaths in 23 states, 1984–1988, proportional mortality study	Occupation and industry codes on death certificates	White, northeast White, south White, central White, west Non-white, northeast Non-white, south Non-white, central Non-white, west	1 30 55 12 0 10 0 0	0.37 (ns) 0.86 (ns) 0.96 (ns) 1.38 (ns) – 2.08 (ns) – –	
Coggon et al. [18], the British cohort of phenoxy acids workers, Great Britain	Cohort of 2,239 workers (men) employed in four British plants 1963–1985 producing phenoxy herbicides; mortality follow-up 1963–1987; vital status 98 %; causes of death 100 %	Cohort membership	Full cohort	0		Relatively short follow-up after enrollment. Overall 152 decedents (7 % of cohort members) Included in the IARC cohort
Green [38], industrial cohort, forestry workers in Ontario (Canada)	Cohort of 1,222 forestry workers (men) spraying herbicides, including phenoxy acids from 1950 to 1982; mortality follow-up 1950–1982; vital status 96 %; causes of death ascertainment not stated	Cohort membership	Full cohort	0		Relatively short follow-up after enrollment. Overall 80 decedents (7 % of cohort members)
Seniori Costantini et al. [127], cohort of leather tannery workers in Santa Croce sull'Arno, Italy	Cohort of 2,916 workers (men) employed at least 6 months as leather tanners from the records of the municipal employment office; mortality follow-up 1950–1983; vital status 99 %; causes of death ascertainment not stated	Cohort membership	Full cohort	2	21.8 (2.5–80.2)	
Coggon et al. [17], industrial cohort, UK	Cohort of 5,784 workers (men) employed 1947–1975 by a company producing MCPA, and formulating and spraying phenoxy herbicides; mortality and cancer incidence follow-up 1947–1983; vital status 98 %; cause of death	Grades High: process, laboratories and application Low: stores, maintenance, transports Background	Full cohort High exposure	1 1	1.1 (0.1–5.9) 2.8 (0.1–15.6)	
Pippard and Acheson [107], boot and shoemakers, UK	Cohort of 5,017 workers (men) employed in the boot and shoe manufacturing industry in three towns in Great Britain in 1939; mortality follow-up 1939–1982; vital status 98 %; causes of death ascertainment not stated	Job, as from population registers of the three municipalities	Full cohort	0		Expected deaths from STS 1.6 (based on England and Wales death rates) Occupation in 1939
Vinyl chloride						
Boffetta et al. [7], meta-analysis of industrial cohorts	Two international multicenter studies on workers exposed to vinyl chloride (IARC and North American cohorts) and six smaller industrial cohorts		Meta-analytic estimate, all cohorts Meta analytic estimate, two multicenter cohorts	22 18	2.5 (1.6–4.1) 2.4 (1.5–4.0)	

(continued)

Table 20.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Bosetti et al. [9], combined analysis of the IARC and North American cohorts	Two international multicenter studies on workers exposed to vinyl chloride (IARC and North American cohorts)		Meta-analytic estimate	10	1.3 (0.6–2.4)		Only deaths with confirmed STS diagnosis were considered for the combined analysis (reference rates are based on all deaths)
Ward et al. [149], the European vinyl chloride cohort, international	Cohort of 12,700 workers employed in any of 19 factories in Italy, Norway, Sweden, and the UK producing vinyl chloride or PVC (one processing PVC); mortality and cancer incidence follow-up from 1955 to 1993–1997 (varying by country; cancer incidence data available from Norway, Sweden, and the UK); vital status 99 %; causes of death ascertainment not stated	Full job histories, vinyl chloride exposure job-exposure matrix, quantitative estimates for 9,775 members (82 %) of the cohort, ranked level index on the basis of maximum exposure level at any job	Full cohort	6	1.9 (0.7–4.1)		OR estimates by cumulative exposure from an internal reference analysis conducted on 37 liver angiosarcoma cases identified according to best evidence among 71 liver neoplasm cases
Mundt et al. [97], the North American vinyl chloride cohort, international	Cohort of 10,109 workers (men) employed 1942–1972 for at least 1 year in a job with exposure to vinyl chloride in any of 37 factories producing the monomer or PVC; mortality follow-up 1942–1995; vital status 97 %; causes of death 99 %	Cohort membership	Full cohort	12	2.7 (1.4–4.7)		Mortality from liver tumors: SMR 3.6 (95 %CI 2.8–4.5); out of 80 deaths from liver cancer, 48 were due to angiosarcoma of the liver
Ionizing radiation							
Mery et al. [90], cohort of breast cancer survivors, USA	Cohort of 563,155 women with primary breast cancer from SEER cancer registries 1973–2003; cancer incidence follow-up 1973–2003; vital status ascertainment not stated	Type of treatment	Radiotherapy	366	1.5 (1.3–1.8)		Risk highest for in-field STS, peaking about 10 years after diagnosis
			No radiotherapy	582	(ref)		
Schaapvel et al. [125], cohort of breast cancer survivors, the Netherlands	Cohort of 58,068 women with breast cancer 1989–2003 from the Groningen, Amsterdam, and Eindhoven region cancer registries; mortality follow-up 2005; vital status ascertainment not stated	Type of treatment	Full cohort	38	1.9 (1.4–2.7)		Full cohort: SIR (external reference)
			Radiotherapy		2.8 (0.3–23.2)		
			Chemotherapy		3.6 (0.7–18.5)		
Boice et al. [8], Montrose County residents, Colorado (USA)	Individuals living in Montrose County, near uranium and vanadium mines and mills (24,423 persons); mortality rates 1950–2000 compared with those of residents in five referent counties (159,318 persons)		Residents vs nonresidents	12	1.3 (0.7–2.4)		Radio- and chemotherapy: HR (internal comparison)
			Residents vs nonresidents living in the two most similar counties	12	2.1 (0.9–4.9)		
Virtanen et al. [148], Finnish survivors of cancer, Finland	Cohort of 332,163 patients with malignancies of breast, cervix uteri, corpus uteri, lung, ovary, prostate, or rectum and lymphoma diagnosed 1953–2003, from the Finnish Cancer Registry; cancer incidence follow-up 1953–2003; vital status ascertainment not stated	Type of primary malignancy and treatment	Full cohort	19	5.0 (3.0–7.8)		Only trunk angiosarcoma cases
			Lag 10 years:				
			Full cohort	8	5.8 (2.5–11.0)		
			Radiotherapy	3	4.1 (0.8–12.0)		
			Radio- and chemo-therapy	1	100 (2.5–560)		

Mellemkjaer et al. [88], cohort of breast cancer survivors, international	Cohort of 525,527 women with primary breast cancer from 13 population-based cancer registries in Europe, Canada, Australia, and Singapore, 1947–2000; cancer incidence follow-up 1947–2000; vital status ascertainment not stated	Type of primary cancer and treatment	Primary breast cancer			
			Premenopausal	30	13.7 (9.2–19.7)	
			Perimenopausal	26	6.3 (4.1–9.2)	
			Postmenopausal	58	4.6 (3.5–5.9)	
			Radiotherapy:			
			Premenopausal	17	17.7 (10.3–28.4)	
			Perimenopausal	16	9.3 (5.3–15.1)	
			Postmenopausal	25	9.2 (5.9–13.6)	
Dores et al. [28], cohort of Hodgkin lymphoma survivors	Cohort of 32,591 patients diagnosed 1935–1994 from 16 cancer registries in Europe and North America; cancer incidence follow-up ending from 1992 to 1995, according to registry; vital status ascertainment not stated	Type of treatment	Full cohort	32	5.1 (3.5–7.2)	Incidence by treatment not reported for STS alone
Huang and Mackillop [57], invasive breast cancer patients cohort, USA	Cohort of 194,798 women with invasive, non-metastatic breast cancer, 1973–1995 registered in SEER cancer registries, surviving >2 years; mortality and cancer incidence follow-up 1973–1995; vital status ascertainment not stated	Two subcohorts, with (RT) and without (non-RT) radiotherapy	RT			
			Angiosarcomas	20	26.2 (16.5–41.4)	
			Other STS	34	2.5 (1.8–3.5)	
			Non-RT			
			Angiosarcomas	7	2.1 (1.0–4.4)	
			Other STSs	14	1.3 (1.0–1.7)	
Childhood cancer						
Maule et al. [81], survivors of childhood non-central nervous system solid tumors, Europe, Singapore, Australia, and Canada	Cohort of 10,988 children (5,271 males, 5,369 females) surviving a non-central nervous system solid tumor (>1 day) 1943–2000, from 13 population-based cancer registries; incidence follow-up 1943–2000; vital status ascertainment not stated	Type of primary tumor	Full cohort	10	14.1 (6.7–25.8)	
			Time since diagnosis (years)			
			<5	1	5.6 (0.1–31.4)	
			5–9	1	8.4 (0.2–46.9)	
			≥10	8	19.3 (8.3–38.0)	
O'Brien et al. [99], Stanford survivors of childhood Hodgkin disease, USA	Cohort of 112 children surviving Hodgkin lymphoma treated at Stanford University 1970–1990; vital status and cancer incidence follow-up 2007; vital status ascertainment not stated	Type of chemotherapy and radiotherapy	Full cohort	4	88.9 (24.2–227)	
Maule et al. [80], survivors of childhood central nervous system tumors, Europe, Singapore, Australia, and Canada	Cohort of 8,431 children (4,572 males, 3,859 females) surviving a central nervous system tumor (>1 day) 1943–2000, from 13 population-based cancer registries; incidence follow-up 1943–2000; vital status ascertainment not stated	Type of primary tumor	Full cohort	4	7.7 (2.1–20)	
Maule et al. [79], survivors of childhood leukemia and lymphoma, Europe, Singapore, Australia, and Canada	Cohort of 16,540 children surviving leukemia or lymphoma (>1 day) 1943–2000, from 13 population-based cancer registries; incidence follow-up 1943–2000; vital status ascertainment not stated	Type of primary tumor	Leukemia	2	4.1 (0.5–14.9)	
			Non-Hodgkin lymphoma	0	0.0 (0.0–26.1)	
			Hodgkin lymphoma	2	17.8 (2.2–64.4)	

(continued)

Table 20.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Inskip and Curtis [63], survivors of childhood cancer, USA	Cohort of 25,965 survivors (>2 months), first diagnosed 1973–2002 registered in SEER cancer registries; mortality and cancer incidence follow-up 1973–2002; vital status 89 %	Type of primary cancer, radiotherapy, and/or chemotherapy	Full cohort Any radiation No radiation	41 18 6	18.6 ($P<0.05$) 26.4 ($P<0.05$) 7.1 ($P<0.05$)		
Jenkinson et al. [64], survivors of childhood cancer, Great Britain	Cohort of 16,541 survivors (>3 years), first diagnosed 1962–1988 in the National Registry of Childhood Tumours; mortality and cancer incidence follow-up 1962–1990; vital status 89 %	Type of primary cancer, radiotherapy, and/or chemotherapy	Full cohort Chemotherapy Radiotherapy Both	39 1 6 8	16.1 (9.4–25.8) 16.9 (0.4–94.1) 17.6 (6.5–38.3) 34.5 (14.9–68.0)		
Kleinerman et al. [68], cohort of hereditary neuroblastoma survivors, USA	Cohort of 1,601 survivors (>1 year) of neuroblastoma, 963 of the hereditary form, in two medical centers in New York and one in Boston; mortality and cancer incidence follow-up 2000; vital status ascertainment not stated	Type of treatment	Full cohort Radiotherapy Yes No Chemotherapy Yes No	69 66 3 32 33	184 (143–233) 212 (164–270) 47 (9.4–137) 236 (161–333) 193 (133–271)		
Menu-Branthomme et al. [89], French-British cohort	Cohort of 4,400 survivors (>3 years) of childhood cancers from a series of clinical centers 1942–1985; mortality and cancer incidence follow-up 1942–1992; vital status 88 %	Type of primary cancer, radiotherapy, and/or chemotherapy	Full cohort Radiotherapy Chemotherapy Radio- and chemotherapy	16 2 1 13	54 (34–89) 19 (3–60) 28 (2–125) 113 (62–185)		
Neglia et al. [98], Childhood Cancer Survivor Study	Cohort of 20,245 children surviving cancer (>5 years) from 25 US and Canadian institutions, 1970–1986; cancer incidence follow-up 1970–2000; vital status 13,581, 67 % (2,901 lost to follow-up, 3,104 refused to participate, 659 pending consent)	Type of primary cancer, radiotherapy, and/or chemotherapy	Full cohort	32	6.3 (4.3–8.9)		Significant positive trend in SMR with increasing exposure to anthracyclines
Metayer et al. [91], childhood Hodgkin lymphoma survivors, international	Cohort of 5,925 patients surviving (>1 year) from the US (SEER) and European cancer registries diagnosed from 1935 to 1994; cancer incidence follow-up varying according to cancer registry, ending from 1992 to 1995	Radiotherapy vs no radiotherapy	Full cohort	9	15.1 (6.9–28.7)		SIR after radiotherapy estimated for all sarcomas
Other exposures							
Kjaer and Hansen [67], male nurses, Denmark	Cohort of 3,369 nurses (men), from the files of the Danish Nurses Association; mortality and cancer incidence follow-up 1980–2003; vital status ascertainment not stated	None	Full cohort	4	5.4 (1.5–13.9)		
Samanic et al. [123], cohort of Swedish construction workers, Sweden	Cohort of 362,552 workers (men) from the Swedish Foundation for Occupational Safety and Health of the Construction Industry health examination database; mortality and cancer incidence follow-up 1999; vital status ascertainment not stated	Body mass index	Normal weight Overweight Obese	105 82 20	1 (ref) 1.1 (0.8–1.4) 1.6 (1.0–2.7)		Internal comparison, cancer mortality in obese and overweight vs nonobese workers

Samanic et al. [122], cohort of male US veterans, USA	Cohort of 4,500,700 male US veterans (3,668,486 whites; 832,214 blacks) from discharge records at Veterans Affairs hospitals between 1969 and 1996, race known; vital status and causes of death ascertainment not stated	Obese vs nonobese	Obese subjects White Black	 185 20	 1.3 (1.1–1,5) 1.1 (0.7–1.8)	Internal comparison, cancer mortality in obese vs nonobese veterans
Sulem and Rafnsson [136], deck officers, Iceland	Cohort of 3,874 deck officers (men) graduated to the Navigation School 1900–1991 and alive as of 1966; cancer incidence follow-up 1966 (or graduation, if later)–1998; vital status ascertainment not stated	Since the end of World War II, steep increase in electronic instrumentation	Full cohort Born <1921 Born >1921	9 3 6	2.7 (1.2–5.1) 2.8 (0.6–8.1) 2.7 (1.0–5.8)	
Wolk et al. [152], cohort of obese patients, Sweden	Cohort of 28,129 patients with hospital admissions for obesity 1965–1993; mortality and cancer incidence follow-up 1965–1993; vital status ascertainment not stated	Cohort membership	Full cohort	18	1.9 (1.1–3.0)	
Wilczynska et al. (2001), cohort of rubber workers, Poland	Cohort of 17,747 workers (11,660 men, 6,087 women) employed >6 months from 1950 to 1995 in a Polish tire production plant; mortality follow-up 1950–1995; vital status 94 %; causes of death 94 %	Job histories. Classification according to the longest-held job as follows: preparation of materials, production of tires and tubes, maintenance, storage, and others	Men Overall Less than 5 years duration 5 years or more Preparation Production Maintenance Storage Others	 3 1 2 0 1 2 0 0	 3.0 (0.6–8.7) 2.2 3.6 (0.4–13.1) 2.6 6.0 (0.7–21.7)	The most recent update of mortality among Polish rubber workers does not report on STSs [26]

*p-value if no confidence interval indicated

Table 20.3 Case-control studies on the association between soft tissue sarcoma occurrence and occupational or environmental exposures

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Pahwa et al. [101–103], population-based case-control study in six provinces, Canada	STS incident cases (357), men, 1991–1994, from cancer registries (Saskatchewan, Alberta, British Columbia, Manitoba, Ontario) and from hospitals (Quebec); 61 % respondents	Randomly selected population controls (1,506), frequency matched by age and province; 48 % respondents	Lifetime occupational history and reported exposure from postal questionnaire; supplemental telephone questionnaire on pesticides	Use of the following: *Phenoxy acids* 2,4-D *Mecoprop* *MCPA* *Diclofop-methyl* *Aldrin* *Diazinon*	 1.1 (0.8–1.5) 1.0 (0.7–1.4) 1.3 (0.8–2.2) 1.1 (0.6–2.2) 1.2 (0.4–2.9 3.7 (1.0–13.8) 3.3 (1.8–6.2)	Age, province of residence, medical history items	Self-reported occupational or nonoccupational exposure to a list of agents, mailed to persons reporting >10 h per year of pesticide use, plus a 15 % sample of the others
Hossain et al. [55], population-based case-control study in six provinces, Canada	STS incident cases (357), men, 1991–1994, from cancer registries (Saskatchewan, Alberta, British Columbia, Manitoba, Ontario) and from hospitals (Quebec)	Randomly selected population controls (1,474), frequency matched by age and province	Lifetime occupational history and reported exposure from postal questionnaire	*Radium* Longest-held job Farmer Machinist Short-term jobs Ground maintenance at apartment complex	2.8 (1.8–7.3) 1.0 (0.7–1.6) 2.4 (1.2–4.8) 2.2 (1.1–4.2)	Age and province of residence	Short-term jobs, <1 year at a time
Zambon et al. [155], population-based case-control study, Venice province, Italy	Sarcoma incident cases 1990–1996 from the Veneto cancer registry; included 186 cases (81 STS) >14 years old, out of 205	Randomly selected population controls (558), frequency matched by age and sex	Residential history since 1960 from population registries Identification of incinerators and dioxin-emitting industries. Modeling of emission fallout, cumulative exposure	Average exposure *I-TEQ (PCDD/PCDFs*, fg/m^3) <4 4–6 >6	 1 (ref) 1.4 (0.7–2.5) 3.3 (1.4–7.9)	Age and sex	Results pertaining STS
Floret et al. [35], population-based case-control study, Doubs, France	STS incident cases (37) 1980–1995 in resident in the city of Besançon, from the Doubs cancer registry	Randomly selected 10 population controls per case, age- and sex-matched to cases	Residential distance from the local municipal waste incinerator. Spatial modeling of dioxin fallout, defining areas of relative air concentration	*I-TEQ (PCDD/PCDFs)* exposure Very low Low Intermediate High	 1 (ref) 1.2 (0.4–3.4) 1.4 (0.5–4.1) 0.9 (0.2–5.1)	Age and sex	

Tuomisto et al. [143, 144], hospital-based case-control study, Helsinki, Kuopio, Turku, and Tampere, Finland	STS cases referred to the four participating hospitals for surgery June 1997–December 1999, >15 years old. Out of 148 cases, 110 could be matched to at least one control	All patients >15 years old operated due to appendicitis in 16 hospitals located in the catchment areas of the four hospitals where cases were recruited. Out of 806 patients, 227 were age- and area-matched to cases (at most 3 controls per case)	Concentration of 17 toxic polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/ Fs) plus 3 PCB congeners in subcutaneous fat samples Questionnaire on socioeconomic and lifestyle factors and chemical exposures	Quintiles of *WHO TEQ (PCDD/PCDFs)* First Second Third Fourth Fifth	 1 (ref) 0.4 (0.2–1.1) 0.7 (0.3–1.8) 0.4 (0.1–1.1) 0.5 (0.2–1.5)	Sex, age, education, body mass index, chemical exposure, fish consumption, smoking, and alcohol	Enrolled cases were 70 %, 9 %, 17 %, and 26 % of all incident STS cases in Helsinki, Turku, Tampere, and Kuopio, respectively. At most one-fourth of appendicitis cases participated, with large differences across hospitals
Briggs et al. [11], population-based multisite case-control study in areas served by cancer registry, USA	STS incident cases (335, diagnoses reviewed by 3 pathologists), African-American and white men aged 32–60 years	Age- and regionfrequency- matched controls (matched to lymphoma cases)	Full occupational history and specific questions on exposure to selected carcinogens	*African-Americans* Wood dust Sawmill Wood preservatives Pesticides *Whites* Wood dust Sawmill Wood preservatives Pesticides	 3.7 (1.6–8.7) 2.9 (0.9–9.1) 1.3 (0.4–4.2) 2.7 (0.8–9.0) 1.1 (0.8–1.5) 1.1 (0.6–2.0) 1.0 (0.6–1.6) 0.8 (0.5–1.4)	Age and cancer registry	Self-reported exposure
Comba et al. [22], population-based case-control study, Mantua, Italy	STS incident cases (37, histological confirmation) 1989–1998 in the population resident in Mantua and in the three neighboring municipalities	Age- and sex-matched controls from population registers (171)	Distance (in 1 km bands) of the longest-held residence discarding the last 10 years	<2 km 2–3 km 3–4 km 4–5 km >5 km	31.4 (5.6–176) 0.7 (0.2–3.1) 1.2 (0.4–3.4) 1.6 (0.6–4.5) 1.0 (ref)	Age and sex	Only 1 case was included in the original ecological study (Costani et al. [25], Comba et al. [23])
Hoppin et al. [54], population-based case-control study (Selected Cancers Study), USA	Sarcoma 1984–1988 incident cases (48 DFSP, 67 LeS, 53 LiS, 32 MFH, 51 SkS cases) in men born 1929–1953 (eligible for service in Vietnam), from eight cancer registries, confirmed by a panel of three pathologists, alive at the time of interview	Age- and areafrequency-matched population controls (1910)	Full occupational history, military service and use of phenoxy herbicides; telephone interview. Expert-based assessment of exposure to chlorophenols	*Chlorophenols, high intensity* DFSP LeS LiS MFH SkS *Herbicide use on a farm* DFSP LeS LiS MFH SkS	 2.1 (0.2–8.9) 2.8 (0.8–7.6) 2.1 (0.4–7.1) 3.6 (0.9–11.2) 1.5 (0.2–6.2) 1.9 (0.8–4.4) 1.8 (0.8–3.6) 1.1 (0.4–2.6) 2.9 (1.1–7.3) 0.5 (0.1–1.6)		Dermatofibrosarcoma protuberans (DFSP), leiomyosarcoma (LeS), liposarcoma (LiS), malignant fibrohistiocytic sarcoma (MFH), skeletal sarcoma (SkS)

(continued)

Table 20.3 (continued)

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Hoppin et al. [53], population-based case-control study (Selected Cancers Study), USA	STS incident cases (295) in men born 1929–1953 (eligible for service in Vietnam), from eight cancer registries, confirmed by a panel of three pathologists, alive at the time of interview	Age- and areafrequency-matched population controls (1910)	Full occupational history, military service, and use of phenoxy herbicides; telephone interview. Expert-based assessment of exposure to chlorophenols	*Chlorophenols* *Chlorophenols* (high confidence in exposure assessment) Low, medium or high level Medium or high level High level	1.1 (0.8–1.4) 1.7 (1.1–2.7) 1.7 (1.1–2.9) 2.1 (1.2–3.7)		For substantial and moderate/substantial exposures to chlorophenols, a positive trend in ORs with increasing duration was present. The frequency of phenoxy herbicide use did not differ between cases and controls
Mikoczy et al. [94], multisite nested case-control study within the cohort of tannery workers, Sweden	STS incident cases (4), men and women	Incidence-density sample of 178 healthy controls, matched by age, sex, and plant	Expert assessment Intensity (ordinal scale), frequency, and duration of exposure to various agents, including chlorophenols. Exposed individuals assigned an index of cumulative exposure = duration × frequency	*Chlorophenols*, index of cumulative exposure 0 ≥0.5	 1 (ref) 0	Gender, age, plant	Cohort reported by Mikoczy et al. [93] and Mikoczy and Hagmar [96] All STS incident cases occurred among workers not considered exposed to chlorophenols
Kogevinas et al. [69], nested case-control study within the IARC cohort, international	Decedents from STS or STS incident cases (11), men and women	Incidence-density sample of 55 healthy controls, matched by age, sex, and country of residence	Expert assessment of exposure to major phenoxy herbicides, PCDDs, raw materials, and other process chemicals	*Any phenoxy herbicide* *Any PCDD or PCDF* *2,3,7,8-TCDD* *TCDD* Unexposed Low Medium High	10.3(1.2–90.6) 5.6(1.1–27.7) 5.2(0.9–31.9) 1.0 2.8 (0.05–54.8) 6.6 (0.08–540) 10.6(0.6–671)		Test for trend $P=0.04$
Hardell [46], Hardell et al. [47], combined analysis of four population-based case-control studies, Sweden	STS incident cases (434)	Population controls (948)	Full job histories and supplementary information for those working in agriculture, forestry, or horticulture. Self-administered questionnaire and telephone interview to study subjects or proxies	*All dioxins* <1 year ≥1 year *TCDD* <1 year ≥1 year *Other dioxins* <1 year ≥1 year	 2.4 (1.7–3.4) 6.4 (3.5–12) 3.0 (2.0–4.5) 7.2 (2.6–20) 1.7 (1.0–2.9) 6.2 (2.9–13)	Gender, age, county (or municipality) of residence	Combined analysis of previously reported studies: Hardell and Sandstrom [44], Eriksson et al. [29], Hardell and Eriksson [45], Eriksson et al. [30]

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Smith and Christophers [131], population-based multisite case control study, Victoria, Australia	STS incident cases, men, aged ≥30 years, admitted to six Melbourne hospitals, alive at enrollment, 1982–1988 (30 respondents)	One cancer control per case (excluding leukemias and lymphomas) and one population control, age and gender matched	Full job histories and supplementary information for occupations likely to involve the chemicals of interest. Interview-administered questionnaire	*Phenoxy acids or chlorophenols* >1 day >30 days	 1.0 (0.3–3.1) 2.0 (0.5–8.0)		Among enrolled patients, 101 did not satisfy the eligibility criteria, 55 had died, 14 moved home, 18 were sent an incorrect letter. Out of 301 patients correctly contacted, 164 were interviewed
Franceschi and Serraino [36], Serraino et al. [128], hospital-based case control study, Italy	STS newly diagnosed cases (93, 53 men and 40 women) admitted 1985–1991 to the Aviano Cancer Center or to the general hospital in the study area, aged 16–79	Patients admitted for a wide spectrum of diseases (721, 371 men, 350 women)	Face-to-face interview, data on selected occupations and exposure	*Use of herbicides/ pesticides* <10 years >10 years	 0.7 (0.2–2.5) 0.4 (0.1–1.2)		Small study (low power) and crude exposure data
Wingren et al. [150], population-base case-control study in the Linkoping region, Sweden	STS incident cases (96, 32 of whom dead), men, aged 25–80, from the regional cancer registry 1975–1982	Living controls, 200 randomly selected men frequency matched by age Dead controls, 250 randomly selected men frequency matched by age Cancer controls, 200 individuals with cancers other than STS	Mailed questionnaire with specific questions on occupation and use of chemicals Jobs plus groups of jobs likely to entail exposure to phenoxy acids or chlorophenols	*Gardeners* *Phenoxy acids or chlorophenols* (potential) *Farmers, forestry* *Railroad workers*	4.4 (1.0–18) 4.2 (0.4–41) 1.5 (0.7–3.0) 4.8 (0.8–24)		Ninety percent confidence intervals given. Results with population referents are reported
Eriksson et al. [30], population-based case-control study, Uppsala region, Sweden	STS incident cases (237, 150 dead) 1978–1986 among residents	One gender-, age-, and county-matched control from the National Population registry (living cases) or from the National Registry of Causes of Death (dead cases). Overall 237 controls	Full job histories and supplementary information for those working in agriculture, forestry, or horticulture. Self-administered questionnaire and telephone interview	*Phenoxy acids or chlorophenols* *Non-2,4,5-T phenoxy acids* Ever In the 1950s *2,4,5-T* Ever In the 1950s *Chlorophenols* (high grade) *Only Ph or Ch with dioxin*	1.8 (1.0–3.2) 0.6 (0.2–2.1) 2.4 (1.0–5.4) 1.8 (0.9–3.9) 2.9 (1.1–8.0) 5.3 (1.7–16.3) 2.4 (1.3–4.5)	Gender, age, county of residence	
Reif et al. [112], registry-based case-control study, New Zealand	STS incident cases (171) in adult males 1980–1984 from the New Zealand Cancer Registry	All other incident cancer cases (24,762)	Recorded occupation (current or most recent job)	*Abattoir workers*	1.9 (0.9–4.0)		2,4,6-TCP used for treatment of pelts

(continued)

Table 20.3 (continued)

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Reif et al. [113], registry-based case-control study, New Zealand	STS incident cases (142) in adult males 1980–1984 from the New Zealand Cancer Registry with a registered occupation	All other incident cancer cases (19,904)	Recorded occupation (current or most recent job)	*Forestry workers* *Forestry workers* aged 20–59	3.2 (1.2–8.9) 4.9 (1.8–13.3)		No increase was observed among sawmill workers. All cases in forestry workers were among men aged 20–59
Hardell and Eriksson [45], population-based case-control study, Umea region, Sweden	STS incident cases (55, 37 dead) 1978–1983 among male residents aged from 25 to 80	Four age- and county-matched controls (220) from the National Population registry and two dead controls (110) Cancer controls (190) drawn at random from the regional cancer registry	Full job histories and supplementary information for those working in agriculture, forestry, or horticulture. Self-administered questionnaire and telephone interview to study subjects or proxies	Exposure to *phenoxy acids*	3.3 (1.4–8.1)	Age, county of residence	Results pertaining comparison between the whole set of cases and living controls are shown
Hoar et al. [50], population-based multisite casecontrol study, Kansas, USA	STS incident cases (139) 1976–1982, men aged ≥21 years, from the Kansas cancer registry, with histological confirmation	Age-matched population controls (1,005)	Telephone interview on agricultural work: crops, pesticide use, application methods, and protective equipment. Survey of products at suppliers	Use of *any herbicide* Use of *insecticides on animals* Use of *insecticides on crops*	0.9 (0.5–1.6) 1.6 (0.9–2.5) 0.8 (0.4–1.6)		No pattern in risk was observed with duration or frequency of herbicide use
Woods et al. [153], population-based case-control study, western Washington State, USA	STS incident cases (128) 1981–1984, men aged 20–79, from the local cancer registry	Living controls (622) aged 20–64 by random digit dialing, aged 65–79 Health Care Financing Administration files. Deceased controls (288) from noncancer death certificates	Face-to-face interview, questionnaire on principal occupations or activities involving exposure to phenoxy acids or chlorophenols	*Phenoxy acids* None Low Medium High *Chlorophenols* None Low Medium High	 1 (ref) 0.6 (0.3–1.1) 1.0 (0.6–1.7) 0.9 (0.4–1.9) 1 (ref) 0.9 (0.5–1.6) 0.9 (0.6–1.5) 0.9 (0.5–1.8)		
Vineis et al. [147], population-based case-control study, Novara, Vercelli and Alessandria provinces, Italy	STS incident cases from 1981 to 1983 living in the ricegrowing provinces of Northern Italy, identified through the pathology services of local, Turin, and Milan hospitals, diagnosis confirmed by a panel of two pathologists; 68 incident and confirmed cases accepted to participate out of 135 candidate cases	Random sample of residents in the study area (living controls), plus two decedents for each of the 37 deaths among the 135 candidate cases	Full job and residential histories and supplementary information for those working in agriculture. Face-to-face interview. Simplified postal questionnaire to nonrespondents. Expert-based exposure assessment	*Living subjects* Men, exposure to *phenoxy acids* Definite Possible Women, exposure to *phenoxy acids* Definite Possible	 0 0.9 (0.2–3.9) 2.7 (0.6–12.4) 2.4 (0.6–10.3)		Ninety percent confidence intervals given Rice-weeding was a typical female job during the 1950s, when herbicide use started

Kang et al. [66], registry-based case-control study, USA	STS cases (279) with pathological revision of diagnosis at AFIP 1975–1980, men born 1940–1955 (draftable in the Vietnam war era)	Randomly selected cancer cases (808) from the files of the referring pathologists, excluding STS, NHL, and HL patients	Occupational history and military service. Telephone interview	*Service in Vietnam* Work with *herbicides* Use *herbicides in farm or ranch* Use *herbicides in yard work*	0.8 (0.6–1.2) 0.6 (0.3–1.2) 0.5 (0.2–1.4) 1.1 (0.7–1.7)	No association was found also with radiotherapy (OR:1.0, 95 %CI: 0.8–1.2)
Kang et al. [65], hospital-based case-control study, USA	STS cases (234) among male US veterans, among 418 with a Veterans Administration hospital admission for connective tissue neoplasm, after review of pathology reports	Randomly selected patients (14,931) from the same Vietnam era veteran patient population	Military personnel records	*Service in Vietnam*	0.8 (0.6–1-1)	Crude exposure assessment
Smith and Pearce [132], registrybased case-control study, New Zealand	STS incident cases (men) 1980–1982 from the National Cancer Registry, notified by public hospitals	Age-matched cancer controls from the National Cancer Registry, already selected for a study on lymphoma and myeloma	Next-of-kin telephone interview on occupations known to entail exposure to phenoxy acids or chlorophenols	*Phenoxy acids* >5 years before diagnosis, probable or definite *Abattoir workers*	0.7 (0.3–1.5) 1.6 (0.9–3.0)	Abattoir workers
Greenwald et al. [39], populationbased case-control study, New York State, USA	STS incident cases (men, 310) from State Cancer Registry 1962–1980, aged 18–29 from 1962 to 1971 (130 died at time of study)	Age- and ZIP code of residence-matched living controls, plus a deceased control for each deceased case	Full military service history and description of jobs with potential exposures of interest	*Military service* *Vietnam service* *Agent Orange, dioxin, or 2,4,5-T* *Manufacture of chemicals*	0.5 (0.4–0.8) 0.5 (0.2–1.3) 0.7 (0.2–2.9) 1.8 (0.8–3.7)	Inadequate time elapsed from possible exposure during service in Vietnam. Limited power (only 10 cases ever served in Vietnam)
Smith et al. [130], registry-based case-control study, New Zealand	STS incident cases (men) 1976–1980 from the National Cancer Registry, notified by public hospitals	One age-matched cancer control from the National Cancer Registry	Next-of-kin telephone interview on occupations known to entail exposure to phenoxy acids or chlorophenols	*Phenoxy acids* >5 years before diagnosis Potential Probable or definite *Chlorophenols* >5 years before diagnosis Potential *Abattoir workers* *Pelt departments* in meat works	 1.3 (0.6–2.5) 1.6 (0.7–3.3) 1.5 (0.5–4.5) 2.8 (1.3–6.3) 4.7 (P=0.15)	Tannery: 3 exposed cases, no exposed control

(continued)

Table 20.3 (continued)

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Eriksson et al. [29], population-base case-control study, Malmohus, Kristianstad, Blekinge, Kronoberg, and Halland, Sweden	STS incident cases (110, 36 dead) 1974–1978 among residents	Two age- and municipality-matched controls from the National Population registry (living cases). Age-, municipality-, and year of death- matched controls from the National Registry of Causes of Death (dead cases), with the exclusion of decedents from cancer or suicide. Overall 220 controls	Full job histories and supplementary information for those working in agriculture, forestry, or horticulture. Self-administered questionnaire and telephone interview to study subjects or proxies	*Exposure to* Phenoxy acids		Age, municipality of residence, and year of death (for dead cases and controls)	
				>30 days	8.5 ($P=0.002$)		
				≤30 days	5.7 ($P=0.006$)		
				None	Ref		
				Non 2,4,5-T phenoxy acids	4.2 ($P=0.01$)		
				2,4,5-T and other phenoxy acids	17.0 ($P=0.0004$)		
				Total phenoxy acids	6.8 (2.6–17.3)		
				Chlorophenols	3.3 (1.3–8.1)		
Hardell and Sandstrom [44], population-based case-control study, Umea, Sweden	STS incident cases (52, 31 dead) 1970–1977 admitted to the Oncology Department of Umea University Hospital	Four gender-, age-, and municipality-matched controls from the National Population registry (living cases). Age-, municipality-, and year of death- matched controls from the National Registry of Causes of Death (dead cases), with the exclusion of decedents from cancer or suicide. Overall 220 controls	Full job histories and supplementary information for those working in agriculture, forestry, or horticulture. Self-administered questionnaire and telephone interview to study subjects or proxies	*Phenoxy acids or chlorophenols*	5.7 (2.9–11.3)	Gender, age, municipality of residence	
				Phenoxy acids only	5.3 (2.4–11.5)		
				Chlorophenols only	6.6 ($P<0.001$)		

*p-value if no confidence interval indicated

Table 20.4 Summary of IARC evaluations for polychlorinated dibenzodioxins and furans, agents known to be potentially contaminated by polychlorinated dibenzodioxins and furans, and for polychlorinated biphenyls

Agent	Evaluation	Volume	Year	Remarks
Chlorophenoxy herbicides	2B	Suppl 7	1987	(1)
	HL	41	1986	
2,4-Dichlorophenoxy acid	AI	15	1977	(1)
2,4,5-Trichlorophenoxy acid	AI	15	1977	(1)
Polychlorophenols	2B	71	1999	
	2B	53	1991	
	2B	Suppl 7	1987	
	HL	41	1986	(1)
2,4,5-Trichlorophenol	AI	20	1979	(1)
2,4,6-Trichlorophenol	AI	20	1979	(1)
Pentachlorophenol	AI	20	1979	(1)
	2B	53	1991	
Polychlorinated-dibenzo-p-dioxins, other than TCDD	3	69	1997	
2,3,7,8-Tetrachloro-dibenzo-p-dioxin (TCDD)	1	100 F	2012	
	1	69	1997	
Polychlorinated biphenyls	2A	Suppl 7	1987	
	HL	18	1978	(1)
	AS	7	1974	(1)
3,3′,4,4′,5-Pentachlorobiphenyl	1	100 F	2012	
Polychlorinated dibenzofurans	3	69	1997	
2,3,4,7,8-Pentachloro-dibenzofuran	1	100 F	2012	
Toxaphene	2B	79	2001	
	2B	Suppl 7	1987	
	AS	20	1979	

(1) IARC current classification for the evidence of carcinogenicity was introduced in the 1987 Supplement 7 to IARC monographs. Previously, animal (A) and human (H) data were separately summarized as showing sufficient (S), limited (L), and inadequate (I) evidence, and it was suggested that carcinogenicity to experimental animals should be considered to predict carcinogenicity to humans

Epidemiological data on the abovementioned risk factors will be examined in detail in the next two paragraphs. Three isolated reports of excess STS occurrence came from a study on men registered with the Danish Nurses Association [67], a cohort of Icelandic deck officers [136], and a cohort of Polish rubber workers [151]. The cohort of Danish nurses was relatively small (3,369 individuals) but could be carefully followed up for cancer incidence through record linkage with the Danish cancer registry from 1980 to 2003; a relatively high number of STS cases (4) were observed, with a significantly increased standardized incidence ratio (SIR) as high as 5.4. Such result may be due to exposures to ionizing radiation or drugs used in cancer chemotherapy. A statistically significant SIR for STS, based on nine cases, was observed among almost 4,000 deck officers in Iceland; no putative causal agent could be identified, but it was noticed that, since the end of World War II, there had been a steep increase in the use of electronic instrumentation. An increase in mortality among Polish rubber workers was suggested in a large cohort (more than 17,000 workers) with follow-up from 1950 to 1995 based on three deaths, but the standardized mortality ratio (SMR) was not statistically different from unity.

Soft Tissue Sarcomas Associated with Specific Agents

Dioxins, Phenoxy Acids, Chlorophenols

In this section we will first revise the early findings on workers using or producing phenoxy acids- or chlorophenols-based herbicides and fungicides, up to the publication of the results from the NIOSH and IARC multicentric cohort studies. We will then examine the most recent literature, following three different threads: updates of NIOSH or IARC subcohorts, studies on workers classified as potential users of herbicides or fungicides and, lastly, studies of subgroups of the general population considered to have high potential exposure to the same agents, including the Seveso cohort. Studies in this last group investigated nonoccupational exposures, but may contribute to our general knowledge of the relationship between the agents of interest and STS.

Four methodologically related population-based case-control studies were conducted in Sweden in the late 1970s and 1980s among residents in the Umea and Uppsala regions and in the counties of Malmohus, Kristianstad, Blekinge, Kronoberg, and Halland [29, 30, 44, 45]. Controls were

selected from population registries, matched to living cases by gender and age, or from death registries, matched to dead cases by gender, age, and year of death. A self-administered questionnaire to study subjects was used to collect lifetime job histories and identify jobs in agriculture, forestry, or horticulture, for which supplementary information was sought. The use of specific products (trade names, period and frequency of use, chemical composition) was investigated by telephone interviews and inquiries at the employers. Exposure to agents (or classes of agents) such as phenoxy acids (in general and containing or not 2,4,5-trichlorophenoxy acid – 2,4,5-T) and chlorophenols could be assessed. The odds ratios (ORs) were increased, particularly for use of phenoxy acids containing 2,4,5-T, phenoxy acids or chlorophenols contaminated by dioxins, phenoxy herbicides in the 1950s, and high-grade chlorophenols. In a combined analysis of the four studies [47], exposure to all dioxins, TCDD, and other dioxins, was assessed: ORs for exposure to all dioxins, TCDD, and other dioxins largely overlapped, and increased with longer (>1 year) duration of use.

The publication of the first study by Hardell and Sandstrom [44] hit the scientific and public health communities at a time when the potential for widespread population exposure to phenoxy herbicides was starting to be appreciated. In 1976 in Seveso, Italy, the accidental release into the environment surrounding a chemical plant of the mass reaction from a vessel where trichlorophenol synthesis was being performed had raised considerable concern, following the outbreak of a chloracne epidemic in the affected population and the appreciation that contamination with TCDD had occurred. At that time, it was becoming common knowledge that a number of similar accidents had happened previously, that herbicides with relatively high TCDD concentrations had been used massively by the US forces during military operations in Vietnam, and that even phenoxy herbicides and chlorophenols commonly used since the 1950s had a potential for TCDD contamination [48].

From Sweden positive findings continued to be reported [29, 30, 45, 150], but they were not replicated, or not clearly replicated, in other countries. In New Zealand smaller and nonsignificant increases in the OR associated with phenoxy acid use were detected, although abattoir workers had an almost doubled, and forestry workers an even higher, risk of STS [112, 113, 130, 132]. In the USA, three investigations were conducted on the association of STS among men with military service in Vietnam, with negative results [39, 65, 66]. Two further US population-based case-control studies reported ORs very close to unity for workers exposed to herbicides [50, 51] and phenoxy acids and chlorophenols [153]. In Australia, a nonsignificantly increased OR for STS was found among workers exposed to phenoxy herbicides or chlorophenols with duration longer than 30 days [131]. In Italy, a markedly but not significantly increased OR for STS was found among female rice-weeders in a small population-based case-control study [147]. Definitely negative was a small, hospital-based case-controls study, in which exposure assessment was rather crude [128]. Also, no STS death was found (0.25 expected) in a Finnish cohort of phenoxy herbicide applicators in forestry, consisting of almost 2,000 men followed from 1972 to 1989 [114, updated by [2].

All of these studies were limited by low to very low power to detect an association; relatively short time elapsed since exposure onset, or cruder exposure assessment, compared with that developed by Swedish researchers.

All individual cohort studies of workers employed in the manufacture and formulation of phenoxy herbicides were particularly limited by lack of power, even more so considering that exposed subcohorts, when identified, were often rather small. Some of these studies did not contribute to the IARC international and multicentric cohort: the study on mortality of two methyl-4 chlorophenoxyacetic acid (MCPA) manufacturers in the UK [17] and that on cleanup and demolition workers after the 1,953 accident at BASF Ludwigshafen [100, 156]. Others were included, or at least partially included: workers of two Danish plants manufacturing phenoxy acids, mainly MCPA [75, 76]; four British plants producing phenoxy herbicides [18]; the NIOSH industrial cohort of herbicide producers [31]; the Monsanto plant for 2,4,5-trichlorophenol production in Nitro, West Virginia [19]; and four German plants, Boehringer Ingelheim Hamburg, Bayer Uerdingen, Bayer Dormagen, BASF Ludwigshafen [3]. Table 20.2 shows that almost all papers reported no or at most one STS death (or case), with the exception of the Danish industrial cohort, the Nitro cohort, and the NIOSH cohort (which included the Nitro cohort). To increase power, in 1978 NIOSH launched a multicentric cohort study including workers employed at 12 US plants manufacturing herbicides, but only four STS deaths were observed [31].

In 1980 IARC established an even larger international cohort study of phenoxy herbicide producers and sprayers that later incorporated the NIOSH cohort. The mortality of almost 22,000 exposed and more than 4,000 unexposed workers could be studied in relation to phenoxy herbicides/chlorophenols and to TCDD or higher polychlorinated dioxins (PCDD). Based on nine (exposure to phenoxy herbicides/chlorophenols) and six (exposure to TCDD or higher PCDDs) STS deaths, SMRs were increased even if confidence intervals included unity [70]. A nested case-control analysis of STS incidence provided evidence of a tenfold increase in the OR associated with exposure to phenoxy herbicides and of a significantly increasing trend according to categories of TCDD exposure, with ORs of 2.8, 6.6, and 10.6, respectively, for low, medium, and high exposure (see also Table 20.3) [69].

Most recent papers regarded either the presentation of results for subcohorts of the IARC cohort, often with updated follow-up or some redefinition of cohort membership, or the analysis of STS mortality/incidence in groups of workers potentially engaged in using, rather than producing, herbicides or wood and pelt preservatives. Some studies were also published on groups with possible nonoccupational exposure.

To the first group belong scientific reports on: the Netherlands cohort ([12], partly updated by [52], updated and expanded by [6]); a subgroup from one plant of the German cohort [33]; the Danish cohort [77]; the New Zealand cohort, also known as the Dow Chemical New Plymouth cohort of 2,4,5-T/TCP producers and sprayers ([78]; updated and expanded by [82]); the NIOSH cohort [134]; the NIOSH subcohort of the US Dow Chemical plants [5, 20, 21]; and the NIOSH subcohort of four plants manufacturing PCP [119].

No further STS deaths were found in the update of the NIOSH cohort; the "chloracne subcohort" had a remarkably and significantly increased SMR [134].

Among workers employed in US Dow Chemical plants, SMRs were generally increased and the increase was statistically significant for 2,4,5-T/TCP producers, with a positive dose-response relationship according to estimates of cumulative dose [20].

Excess STS mortality was also observed in US PCP manufacturers [119], New Plymouth producers and sprayers of 2,4,5-T/TCP [78, 82], and Danish producers of MCPA [77], even if SMRs had wide confidence intervals including unity.

No STS death was reported from the Netherlands [12, 6, 52] and Germany [33].

In summary, even if these investigations continue to suffer from lack of power, they provide some additional evidence to the IARC study findings.

In the group of potential users of phenoxy herbicides or chlorophenols, we may include leather workers [58, 93, 94, 96, 127, 135]; farmers, gardeners, and sawmill and forestry workers [2, 4, 27, 32, 37, 38, 43, 138, 139]; and pulp and paper workers [87, 115, 116]. We also add to this group all case-control studies as, while they potentially recruit subject with any type of exposure with non-null prevalence and may thus include producers of phenoxy acids and chlorophenols, the largest number of exposed jobs corresponds to users of these agents [11, 53–55, 101–103, 143, 144].

Blair and colleagues conducted a proportional mortality study based on occupation and industry reported on death certificates and failed to find any association with STS mortality [4].

The others were formal cohort or case-control studies, but had, once again, low power. Furthermore, the possibility for researchers to identify cohort members with actual exposure to the agents of interest was more limited, compared to studies of phenoxy herbicides/chlorophenols producers, if not completely lacking: in most cases, exposure to chemicals could be assessed only on an "ecological" basis, i.e., knowledge that during particular periods phenoxy acids had been possibly used – sometimes largely used – in trades like forestry, rice-growing, etc. It is not surprising, thus, that no STS risk was reported, with few exceptions. Case-control studies in their turn had low power due to low prevalence of exposure and surprisingly, being recently conducted, relied on cruder exposure assessment (mainly self-reported usage of pesticides) compared with those of the 1980s and early 1990s.

In three cohorts of leather workers – out of four reporting on STS deaths – increased SMRs were found, albeit based on small numbers of observed deaths [96, 127, 135]. An in-depth investigation on possible causes of excess mortality was attempted, conducting a multisite case-control study nested in the Swedish cohort of leather tanners [94]. At the time, four STS incident cases had been identified by linkage with the National Cancer Registry. Exposure to several agents, including chlorophenols, was assessed by experts in terms of intensity (on an ordinal scale), frequency, and duration. For exposed individuals an index of cumulative exposure was developed as the product of frequency and duration, disregarding intensity. All STS cases occurred among individual classified as nonexposed to chlorophenols. As the number of STS cases was limited and some uncertainties on retrospective exposure assessment are unavoidable, this evidence cannot be considered conclusively negative, especially considering the persisting increase in the SMR for STS in the most recent update of this cohort [96].

In a study on more than 27,000 sawmill workers in British Columbia (Canada), particular efforts were dedicated to assess dermal exposure to chlorophenols (pentachlorophenol, PCP, and tetrachlorophenol, TeCP, used from 1950 to 1990) by plant, job, and fungicide formulation; exposure hours per year and full-time equivalent years of exposure were assigned to cohort members. No excess in STS mortality (based on seven deaths) or incidence (based on 13 cases), as well as no increase according to exposure indices [27], was present in the cohort. A population-based case-control study reported a nonsignificant increase in the OR for STS among African-American but not white sawmill workers, based on self-reported exposures [11].

STS risk in pulp and paper workers has been addressed by Rix and coworkers [115, 116], who analyzed mortality and cancer incidence among more than 14,000 workers from three Danish industries, finding an increased SIR among women employed as sorters/packers; the authors noticed that these jobs had the highest contact with paper and potential for dermal exposure, whereas men had little direct manual contact. An even larger (60,000 workers) international cohort study on pulp and paper workers including part of the Danish

cohort was carried out by IARC and reported on STS mortality, with exposure assessment based on careful evaluation of production processes and about 31,000 exposure measurements: chlorophenol exposure was not assessed but a nonsignificantly increased SMR among subjects with high exposure to organochlorine compounds was found [87].

Agricultural and forestry workers were included in a number of cohorts, the largest of which enumerated more than 33,000 Florida (US) pesticide applicators [32]. Unfortunately, mortality follow-up was inadequate, coinciding with cohort recruitment, and no data on exposures of cohort members was available. Two small mortality studies reported an elevated, albeit nonstatistically significant, SMR (one death) among female rice-weeders [37] and an elevated and statistically significant SMR (three deaths) among Danish gardeners supposed to have been at work during the early period of herbicide use, when exposure was highest and no safety measures were enforced [43].

Exposure to chlorophenols entailed a statistically significant increase in the OR in a US population-based case-control study, including 295 STS incident cases in men born 1929–1953 (eligible for service in Vietnam) from eight cancer registries. Assessment of exposure to chlorophenols had been carried out by an expert using questionnaire information about working with wood preservatives, cutting oils, sawmills, leather tanning, or shoe dust [53]. ORs were increased for all main histological subtypes, with the exception of skeletal sarcomas [54].

In another large, population-based multisite case-control study in US areas served by a cancer registry, self-reported exposure to the broad categories of pesticides and wood preservatives was associated with nonsignificant increases in the ORs [11].

The third, large population-based case-control study was conducted in six Canadian provinces, Saskatchewan, Alberta, British Columbia, Manitoba, Ontario, and Quebec; the OR for self-reported exposure to phenoxy acids, 2,4-D, and MCPA was close to unity, whereas it was increased for aldrin and diazinon [103] and for employment in ground maintenance at apartment complexes [55].

In Finland, a hospital-based case-control study aimed to assess STS risk according to the body burden of dioxin-like compounds. Concentrations of 17 toxic polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) plus three PCB congeners were determined in subcutaneous fat samples from STS cases referred to participating hospitals for surgery and control patients operated due to appendicitis. Efforts were spent to avoid bias from differential referral of cases (to specialized hospitals) and controls (to general hospitals), by seeking to recruit controls from all general hospitals in the catchment area of the specialized hospitals. Analysis by quintiles of dioxin-like compounds expressed as WHO toxic equivalents (TEq) showed a decrease in risk for all quintiles from the second to the fifth [143, 144]. Such a paradoxical result suggests that dioxin-like compound concentration after STS diagnosis does not represent the biologically relevant exposure.

In summary, suggestive evidence of an STS risk, possibly associated with use of phenoxy herbicides or chlorophenols, was found in the leather and pulp and paper industries, but not in (Canadian) sawmills. Other cohort studies with negative or nonsignificant results were inconclusive due to their inherent limitations. An elevated risk associated with use of chlorophenols due to several different circumstances was found in a case-control study where expert-based exposure assessment had been carried out. Case-controls studies analyzed according to self-reported exposure found no increase in risk.

Subgroups of the general population with possible nonoccupational high-level exposure included: fishermen and their spouses expected to have high consumption of contaminated fish [121, 137, 95]; the general population living in an area contaminated after the 1976 chemical accident in Seveso, Italy [24, 104, 105]; the general population living in areas contaminated by emissions from industrial [22, 23, 25] and urban waste incinerators [35, 146, 155]; and children of Swedish pesticide applicators [117].

Swedish fishermen and their family members are known to have diets with high fish consumption, and Baltic Sea fish is recognized to have higher content of persistent organochlorine compounds. A series of cohort studies on mortality and cancer incidence was conducted, based on the assumption that this would be a population subgroup with high dietary intake of dioxin-like compounds. STS occurrence was not different from expected among fishermen and their wives in the East (Baltic Sea) or West Coast [121, 137, 95].

In 1976 a runaway reaction caused an explosion in a chemical plant in Italy and the release of a cloud whose fallout contaminated a vast area, divided in three zones with decreasing TCDD concentration in soil: zone A, mostly included in the municipality of Seveso, very high; zone B, high; and zone R, low. Population residing in these areas (723, 4,821, and 31,643, respectively) and in a surrounding non-contaminated reference territory (181,574 persons) was followed up for mortality and cancer incidence. STS mortality and incidence were not increased by comparison with residents in the reference territory, and STS deaths/cases were found among people from zone R, but not from zones A or B. Epidemiological surveillance of this population is of obvious importance, but in interpreting its current negative findings, it must be borne in mind that the high-exposure subgroup (zone A, where the prevalence of chloracne cases in the aftermath of the accident was particularly high) was small and constituted mainly of children (who accounted for 88 % of all chloracne cases) and that follow-up for cancer incidence, ending in 1996, was relatively short.

The observation of an unusual concentration of STS cases among residents in a borough of Mantua (Italy) lead to an investigation of spatial clustering of STS cases according to residential distance from an industrial waste incinerator, suggesting significantly higher incidence in two out of three areas close to the source [23, 25]. A population-based case-control study on histologically confirmed STS incident cases in 1989–1998 was carried out in the population of Mantua and three neighboring municipalities, with a large increase in the OR for residence in a band of less than 2 km distance from the incinerator [22].

A population-based case-control study was conducted in Venice province, Italy, enrolling sarcoma incident cases in 1990–1996 from the Veneto cancer registry >14 years old, among which 81 were STS cases [155]. Incinerators and dioxin-emitting industries were identified, and through spatial modeling average and cumulative residential exposure was assessed. There was a positive trend in the OR for STS according to average exposure.

A time- and space-clustering study was completed in the department of Doubs (France), finding a slightly but significantly increased risk of STS for residence in the electoral wards closest to the Besançon urban waste incinerator. A subsequent population-based case-control study, using a more refined geographical assessment of residential distance from the source and defining areas of relative concentration based on modeling of dioxin emissions, could not find a trend in the OR according to semiquantitative categories of exposure [35].

In a cohort of more than 27,000 children born from 1958 to 1994 to Swedish pesticide applicators and followed up for cancer incidence from 1958 to 1994, 51 cancer cases were observed (out of 73 expected), with one STS case [117]. Cancer incidence was studied in a further cohort of about 20,000 children born from 1952 to 1988 to sawmill workers exposed to chlorophenols in British Columbia at least 1 year between 1950 and 1985 [49]. Forty cancer cases were observed from 1969 to 1993, after linkage with the British Columbia Cancer Registry, but no data on STS occurrence were given.

In summary, studies on nonoccupationally exposed groups were sometimes affected by uncertainties regarding exposure, in particular what subset of the cohorts were exposed and what were its characteristics. This applies especially to the studies on Swedish fishermen and children of Swedish pesticide applicators, which yielded negative results. Further, lack of power due to the small dimension of high-exposure groups and/or insufficient observation time since exposure characterized these and other negative studies, among which was the Seveso cohort. The investigations that could exploit the most favorable setting for a "natural" experiment were the population-based case-control studies on STS incidence among residents around incinerators. The two Italian studies, but not that conducted in the French department of Doubs, provided evidence of an association between residing in proximity to incinerators and STS incidence.

The IARC international, multicentric study on producers of phenoxy acids and chlorophenols provides strong evidence of a causal relationship between exposure to TCDD-contaminated agents and STS, supported by the earlier population-based case-control studies from Sweden (which had thorough retrospective exposure assessment) and by subsequent observations in some of the updated and/or expanded local or national cohorts of herbicide producers. More limited evidence is provided by studies of STS mortality or incidence among industrial workers potentially using phenoxy acids or chlorophenols, or in subgroups of the general population with potential exposure to TCDD, as with few exceptions, exposure was considerably more difficult to characterize. Negative studies almost invariably had low power to detect a possible association, insufficient time since exposure, inadequate identification of exposed subgroups, or some combination of these limitations.

Vinyl Chloride

In the early 1970s, case reports on cases of liver angiosarcoma among workers employed in the manufacture of PVC alerted on the possible carcinogenicity of VCM. Two multicentric cohort studies were initiated.

The North American vinyl chloride cohort includes more than 10,000 workers employed between 1942 and 1972 in 37 US and Canadian plants producing VCM or PVC and was promoted by the Chemical Manufacturers' Association [97]. Twelve deaths from STS were observed, with a significantly increased SMR, in addition to liver angiosarcoma deaths.

The IARC international multicentric cohort included more than 12,000 workers from 19 plants in Italy, Norway, Sweden, and the UK, producing VCM or PVC – one processing PVC [149]. Six deaths from STS were reported, with a nonsignificantly increased OR.

Other smaller studies reported one death from STS, without providing SMR estimates [73] or mortality from bone and soft tissue sarcoma altogether [142, 133].

A meta-analytic estimate of STS mortality was provided by Boffetta et al. [7] by combining results of the two multicenter cohorts, with a meta-SMR of 2.4 and 95 % confidence interval (95 %CI) 1.5–4.0. Also Bosetti et al. [9] conducted a meta-analysis of the two international studies, estimating a meta-SMR of 1.3 (95 %CI 0.6–2.4); in doing so, they considered only decedents whose STS diagnosis could be confirmed, even if reference rates include all deaths certified as due to STS.

In summary, vinyl chloride exposure may cause also STS and not only liver angiosarcomas. Noticing the inconsistency in results between the two main studies, IARC concluded that the evidence of an association between vinyl chloride and STS is contradictory [61, 62].

Ionizing Radiation

Many cohort studies have been carried out on long-term survivors of adult cancers, namely, tumors of the female breast, cervix and corpus uteri, ovary, prostate, lung, large bowel, and lymphomas [10, 16, 28, 57, 88, 90, 125, 148]. Most of these studies take advantage of US (SEER) and European cancer registries, providing large, nationwide lists of incident cancer cases; information on basic and adjuvant treatment; and outcome in terms of survival and incidence of second cancers, and can reach hundreds of thousands of participants. The power to assess incidence of STS is therefore large, and SMRs/SIRs are systematically increased among patients who underwent radio- or chemotherapy and especially among those who received both treatments.

Also survivors of childhood cancer have been subjected to long-term surveillance. The largest studies were the Childhood Cancer Survivor Study [98], the SEER cohort [63], and an international multicentric cohort [79, 80, 81]. Extremely high incidence of STS has been reported by all authors, particularly but not only among patients who received radio- or chemotherapy or both [63, 64, 68, 79, 89, 91, 98, 80,99].

On the other hand, increased STS mortality or incidence has not been reported among populations with exposures at comparatively lower doses of ionizing radiation, such as atomic bombing survivors [106, 108, 110], Colorado residents in proximity to uranium and vanadium mines [8], Three Mile Island residents [42], Mayak workers and Techa river residents [71, 109, 129], uranium miners [72, 126, 145], and uranium processing and nuclear power plant workers [1, 13–15, 40, 41, 56, 74, 83–86, 92, 118, 124, 140, 141, 154]. The absence of evidence for STS risk at low doses of radiation should not be regarded, however, as conclusive, as most studies had limited power to detect a low risk and/or limited time since first exposure.

Clinical and Pathological Features of Occupational Soft Tissue Sarcomas

Sarcomas, as STSs, deriving from mesenchymal tissues different from bone and cartilage may arise practically in every anatomical site, but visceral sarcomas are usually included among all other malignant tumors of the organs in which they develop. They contribute, therefore, to mortality, incidence, and survival statistics for that organ or site, including the retroperitoneum, and among STSs are enumerated only those located in the extremities, trunk, and abdominal wall.

A great variety of histological subtypes are recognized. The WHO classification of soft tissue tumors is summarized in Table 20.5 [34].

The most frequent histological types are high-grade pleomorphic – or malignant fibrous histiocytoma (MFH)-like – sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors, and approximately 75 % are graded as highly malignant. Nevertheless, the 5-year survival rate for STS arising in the limbs is in the order of 65–75 %. The 5-year relative survival estimated by SEER cancer registries is currently 83 % for cases confined to their primary site (55 % of all STS), 62 % for cases with regional lymph node involvement (24 % of all STS), and drop to 17 % for cases with distant metastases at the diagnosis (15 % of all STS). Unstaged cases, representing 7 % of all STS, have relative survival of 52 % (http://seer.cancer.gov/statfacts/html/soft.html#incidence-mortality, last accessed on 21/08/2012).

Occupational STS cases have no specific clinical or pathological features.

Means of Exposure Assessment

The assessment of exposure to dioxins, dioxin-like compounds, phenoxy herbicides, and chlorophenols is complex from many points of view, among which are their partial overlapping, the difficulty in identifying and quantifying contamination by dioxins and congeners, as well as that of identifying referent groups, as none can be considered strictly speaking unexposed. It may be, therefore, of interest to examine the methods used by different authors.

The early population-based case-control studies conducted in Sweden were characterized by similar methods of exposure assessment [29, 44, 45, 30]. As the first step in data collection, a questionnaire was mailed to living cases and controls or to respondents (next of kin) for deceased study subjects (dead controls were used for dead cases). The questionnaire investigated lifetime work history and exposure in the working environment and during leisure time to a list of chemicals and specific products (asking for trade names, periods and frequency of use, chemical composition). As a second step, a telephone interview was carried out, to complete questionnaire data when necessary and to supplement information on exposure for persons ever working in forestry, agriculture, horticulture, carpentry, or sawmills since 1948. Further, as a validation tool, during the first study a questionnaire was sent to employers of all study subjects who reported employment in forestry, sawmills, and pulp and paper mills, to inquire about the use of products

Table 20.5 WHO classification of soft tissue tumors (only non-benign types of adults are shown)

Group	Type
Adipocytic tumors	
	Well-differentiated liposarcoma
	Dedifferentiated liposarcoma
	Myxoid liposarcoma
	Pleomorphic liposarcoma
	Mixed-type liposarcoma
Fibroblastic/myofibroblastic tumors	
	Superficial fibromatoses[a]
	Desmoid-type fibromatoses[a]
	Solitary fibrous tumors[b]
	Hemangiopericytoma[b]
	Inflammatory myofibroblastic tumors[b]
	Low-grade myofibroblastic sarcoma
	Myxoinflammatory fibroblastic sarcoma
	Adult fibrosarcoma
	Myxofibrosarcoma
	Low-grade fibromyxoid sarcoma
	Sclerosing epithelioid fibrosarcoma
So-called fibrohistiocytic tumors	
	Diffuse-type giant cell tumor[a]
	Malignant giant cell tumors of tendon sheath
	Giant cell tumor of soft tissue[b]
	Undifferentiated pleomorphic sarcomas[c]
	Giant cell malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma with giant cells
	Inflammatory malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma with prominent inflammation
Smooth muscle tumors	
	Leiomyosarcoma
Pericytic (perivascular) tumors	
	Malignant glomus tumors (glomangiosarcomas)
Skeletal muscle tumors	
	Pleomorphic rhabdomyosarcoma
Vascular tumors	
	Kaposiform hemangioendothelioma[a]
	Retiform hemangioendothelioma[b]
	Papillary intralymphatic angioendothelioma[b]
	Composite hemangioendothelioma[b]
	Epithelioid hemangioendothelioma
	Angiosarcoma
Chondro-osseous tumors	
	Extraskeletal osteosarcoma
Tumors of uncertain differentiation	
	Ossifying fibromyxoid tumor[b]
	Mixed tumor/myoepithelioma/parachordoma[b]
	Synovial sarcoma
	Epithelioid sarcoma
	Clear cell sarcoma
	Extraskeletal myxoid chondrosarcoma
	Desmoplastic small round cell tumor
	Extrarenal rhabdoid tumors
	Neoplasms with perivascular epithelioid cell differentiation (PEComas)
	Intimal sarcomas

[a]Nonmetastasizing, but locally infiltrating and recurring, neoplasm
[b]Malignant behavior is sometimes exhibited
[c]Including pleomorphic malignant fibrous histiocytoma. The term malignant fibrous histiocytoma may be used as a synonym

containing phenoxy acids or chlorophenols; agreement was considered satisfactory [44, 47]. Self-reported exposure was assessed in terms of ever exposure to phenoxy acids and chlorophenols separately. Product composition was used to assign exposure to phenoxy acids and chlorophenols contaminated with 2,4,5-T. In the combined analysis of the four case-control studies, exposure to dioxin-containing phenoxy acids or chlorophenols (TCDD, other dioxins, and all dioxins) was assessed [47]. Quantitative assessment was based on duration. Exposures lasting 1 day or occurring less than 5 years before diagnosis were ignored.

Compared with this approach, that used in many subsequent population-based studies of work-related risk for STSs was cruder. Exposure was assessed solely or mainly in terms of ever employment in a job or industry [55, 112, 150] or ever use of broad categories of agricultural/industrial chemicals, such as "herbicides" [50, 51, 11, 128]. Exposure to phenoxy acids and chlorophenols could be assessed by some researchers on the basis of employment in a predefined list of occupations [130, 153] or of period and place of military service in Vietnam [39, 65] and [66]. Until recently, only a few studies relied on expert-based exposure assessment [53, 131, 147, 54].

Tuomisto and colleagues measured the concentration of 17 polychlorinated dibenzo-p-dioxins and dibenzofurans plus three polychlorobiphenyl congeners in subcutaneous fat samples from a series of STS cases undergoing surgery and hospital controls operated because of appendicitis. The concentrations were weighted by the relative toxic potency (toxic equivalency factor, TEF) of the different substances and toxic equivalent concentrations (WHO-TEq) were obtained. All measurements were carried out at a laboratory accredited for the analysis of dioxins in human samples, where severe quality-control measures were adopted. WHO-TEq concentrations averaged at around 30 mg/kg in fat were strongly dependent on age and did not differ between cases and controls. This approach, while rather sophisticated, presents some drawbacks. The first is that the concentrations measured at the time of surgery do not reflect those present at the time exposure (if any). Another critical point is that the need to ensure tissue samples for the analysis introduces a strong selection for both cases and controls, with a potential for severe bias. In this study, enrolled cases represented 70 % of incident STS cases occurring in Helsinki during the study period, but only 9 %, 17 %, and 26 % in Turku, Tampere, and Kuopio, respectively. As with controls, at most 25 % of appendicitis cases, with large differences across hospitals, were included in the set from which controls were sampled and matched to cases.

Industry-based studies may in theory allow researchers to conduct more careful exposure assessment. In the IARC international cohort study, industrial hygienists used plant-specific information, gathered by means of company questionnaires, and serum levels of TCDD, when available, to identify periods, work areas, and jobs entailing the exposures of interest. The occupational histories of cohort members were then used to classify workers, according to their longest-held job, as exposed or not exposed to 2,3,7,8-TCDD or higher chlorinated TCDDs [70]. In a nested case-control study, a panel of industrial hygienist semiquantitatively assessed exposure to 21 chemicals or mixtures, including 2,3,7,8-TCDD [69].

In the analysis of the NIOSH cohort, a job-exposure matrix (JEM) was developed taking into account company questionnaires, industrial hygiene surveys of participating plants, development of chloracne among workers, and TCDD serum measurements in a small group of cohort members. The JEM was applied to exposure histories, to assign cumulative exposure scores. As only four deaths were observed, analyses for STS could be conducted only for the whole cohort and for the small chloracne subcohort.

In some studies, internal exposure to TCDD was estimated by collecting serum samples from current and former workers. Lipid-adjusted TCDD serum concentrations and an estimate of TCDD half-life were used to back-calculate corresponding values during the whole work period for all of these workers, giving a pattern of increasing level during exposure and decreasing thereafter. Cumulative exposure was defined as the integral of concentration over time. As measurements were in general available for a limited number of cohort members, groups of workers sharing the same exposure conditions were defined according to process information, to calculate specific (e.g., department-specific) average yearly increases in blood concentration applicable to workers with no measurement [33, 52, 82, 100]. In all of these cohorts, however, either no STS death was observed or there were too few to allow an analysis to be performed according to exposure categories.

In the remaining studies, exposure has been defined by cohort membership, even if in some cases it was possible to identify high-exposure subgroups, like chloracne workers or individuals living in areas with different levels of soil contamination in the aftermath of the Seveso 1976 accident.

Conclusion

Strong evidence supports a causal role of TCDD and TCDD-contaminated agents for STSs. Mechanistic considerations were at the basis of the evaluation of TCDD as a human carcinogen by IARC in 1997 and 2012: even if epidemiological evidence of carcinogenicity had been considered in itself limited, there was sufficient evidence in experimental animals, and mechanisms of carcinogenicity were thought to be identical in animals and human beings [60, 62].

For ionizing radiation at high doses (as in radiotherapy), also consistent results pointing to a causative effect

emerged from the literature. There is suggestive but limited evidence of a causal role of VCM.

TCCD and dioxins were estimated to have caused about 300 cancer cases in 2005 in the UK, approximately 10 % of which was represented by STS [120].

References

1. Akiba S, Mizuno S. The third analysis of cancer mortality among Japanese nuclear workers, 1991–2002: estimation of excess relative risk per radiation dose. J Radiol Prot. 2012;32:73–83.
2. Asp S, Riihimäki V, Hernberg S, Pukkala E. Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators: an 18-year prospective follow-up. Am J Ind Med. 1994;26:243–53.
3. Becher H, Flesch-Janys D, Kauppinen T, Kogevinas M, Steindorf K, Manz A, Wahrendorf J. Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. Cancer Causes Control. 1996;7:312–21.
4. Blair A, Dosemeci M, Heineman HF. Cancer and other causes of death among male and female farmers from twenty-three states. Am J Ind Med. 1993;23:729.
5. Bodner KM, Collins JJ, Bloemen LJ, Carson ML. Cancer risk for chemical workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Occup Environ Med. 2003;60:672–5.
6. Boers D, Portengen L, Bueno-de-Mesquita HB, Heederik D, Vermeulen R. Cause-specific mortality of Dutch chlorophenoxy herbicide manufacturing workers. Occup Environ Med. 2010;67:24–31.
7. Boffetta P, Matisane L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health. 2003;29:220–9.
8. Boice Jr JD, Mumma MT, Blot WJ. Cancer and noncancer mortality in populations living near uranium and vanadium mining and milling operations in Montrose County, Colorado, 1950–2000. Radiat Res. 2007;167:711–26.
9. Bosetti C, La Vecchia C, Lipworth L, McLaughlin JK. Occupational exposure to vinyl chloride and cancer risk: a review of the epidemiologic literature. Eur J Cancer Prev. 2003;12:427–30.
10. Brennan P, Scélo G, Hemminki K, Mellemkjaer L, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Seow A, Pompe-Kirn V, Martos C, Jonasson JG, Colin D, Boffetta P. Second primary cancers among 109 000 cases of non-Hodgkin's lymphoma. Br J Cancer. 2005;93:159–66.
11. Briggs NC, Levine RS, Hall HI, Cosby O, Brann EA, Hennekens CH. Occupational risk factors for selected cancers among African American and White men in the United States. Am J Public Health. 2003;93:1748–52.
12. de Mesquita HB B, Doornbos G, Van der Kuip DA, Kogevinas M, Winkelmann R. Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in The Netherlands. Am J Ind Med. 1993;23:289–300.
13. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn YO, Amoros E, Ashmore P, Auvinen A, Bae JM, Solano JB, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklof M, Engels H, Engholm G, Gulis G, Habib R, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ. 2005;331:77.
14. Carpenter LM, Higgins CD, Douglas AJ, Maconochie NE, Omar RZ, Fraser P, Beral V, Smith PG. Cancer mortality in relation to monitoring for radionuclide exposure in three UK nuclear industry workforces. Br J Cancer. 1998;78:1224–32.
15. Chan C, Hughes TS, Muldoon S, Aldrich T, Rice C, Hornung R, Brion G, Tollerud DJ. Mortality patterns among Paducah Gaseous Diffusion Plant workers. J Occup Environ Med. 2010;52:725–32.
16. Chaturvedi AK, Engels EA, Gilbert ES, Chen BE, Storm H, Lynch CF, Hall P, Langmark F, Pukkala E, Kaijser M, Andersson M, Fosså SD, Joensuu H, Boice JD, Kleinerman RA, Travis LB. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. J Natl Cancer Inst. 2007;99:1634–43.
17. Coggon D, Pannett B, Winter PD, Acheson ED, Bonsall J. Mortality of workers exposed to 2 methyl-4 chlorophenoxyacetic acid. Scand J Work Environ Health. 1986;12:448–54.
18. Coggon D, Pannett B, Winter P. Mortality and incidence of cancer at four factories making phenoxy herbicides. Br J Ind Med. 1991;48:173–8.
19. Collins JJ, Strauss ME, Levinskas GJ, Conner PR. The mortality experience of workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin in a trichlorophenol process accident. Epidemiology. 1993;4:7–13.
20. Collins JJ, Bodner K, Aylward LL, Wilken M, Bodnar CM. Mortality rates among trichlorophenol workers with exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Am J Epidemiol. 2009;170:501–6.
21. Collins JJ, Bodner K, Aylward LL, Wilken M, Swaen G, Budinsky R, Rowlands C, Bodnar CM. Mortality rates among workers exposed to dioxins in the manufacture of pentachlorophenol. J Occup Environ Med. 2009;51:1212–9.
22. Comba P, Ascoli V, Belli S, Benedetti M, Gatti L, Ricci P, Tieghi A. Risk of soft tissue sarcomas and residence in the neighbourhood of an incinerator of industrial wastes. Occup Environ Med. 2003;60:680–3.
23. Comba P, Fazzo L, Berrino F. Soft tissue sarcomas in Mantua: epidemiological evidence and perspectives for environmental remediation. Epidemiol Prev. 2004;28:266–71 [article in Italian].
24. Consonni D, Pesatori AC, Zocchetti C, Sindaco R, D'Oro LC, Rubagotti M, Bertazzi PA. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. Am J Epidemiol. 2008;167:847–58.
25. Costani G, Rabitti P, Mambrini A, Bai E, Berrino F. Soft tissue sarcomas in the general population living near a chemical plant in Northern Italy. Tumori. 2000;86:381.
26. de Vocht F, Sobala W, Wilczynska U, Kromhout H, Szeszenia-Dabrowska N, Peplonska B. Cancer mortality and occupational exposure to aromatic amines and inhalable aerosols in rubber tire manufacturing in Poland. Cancer Epidemiol. 2009;33:94–102.
27. Demers PA, Davies HW, Friesen MC, Hertzman C, Ostry A, Hershler R, Teschke K. Cancer and occupational exposure to pentachlorophenol and tetrachlorophenol (Canada). Cancer Causes Control. 2006;17:749–58.
28. Dores GM, Metayer C, Curtis RE, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, van Leeuwen FE, Holowaty EJ, Andersson M, Wiklund T, Joensuu T, van't Veer MB, Stovall M, Gospodarowicz M, Travis LB. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol. 2002;20:3484–94.
29. Eriksson M, Hardell L, Berg NO, Möller T, Axelson O. Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. Br J Ind Med. 1981;38:27–33.
30. Eriksson M, Hardell L, Adami HO. Exposure to dioxins as a risk factor for soft tissue sarcoma: a population-based case-control study. J Natl Cancer Inst. 1990;82:486–90.
31. Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steenland K, Suruda AJ.

Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. N Engl J Med. 1991;324:212–8.
32. Fleming LE, Bean JA, Rudolph M, Hamilton K. Mortality in a cohort of licensed pesticide applicators in Florida. Occup Environ Med. 1999;56:14–21.
33. Flesch-Janys D, Steindorf K, Gurn P, Becher H. Estimation of the cumulated exposure to polychlorinated dibenzo-p-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. Environ Health Perspect. 1998;106 Suppl 2:655–62.
34. Fletcher CDM, Krishnan Unni K, Mertens F, editors. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC; 2002.
35. Floret N, Mauny F, Challier B, Cahn JY, Tourneux F, Viel JF. Dioxin emissions and soft-tissue sarcoma: results of a population-based case-control study. Rev Epidemiol Sante Publique. 2004;52:213–20 [article in French].
36. Franceschi S, Serraino D. Risk factors for adult soft tissue sarcoma in northern Italy. Ann Oncol. 1992;3 Suppl 2:S85–8.
37. Gambini GF, Mantovani C, Pira E, Piolatto PG, Negri E. Cancer mortality among rice growers in Novara Province, northern Italy. Am J Ind Med. 1997;31:435–41.
38. Green LM. A cohort mortality study of forestry workers exposed to phenoxy acid herbicides. Br J Ind Med. 1991;48:234–8.
39. Greenwald P, Kovasznay B, Collins DN, Therriault G. Sarcomas of soft tissues after Vietnam service. J Natl Cancer Inst. 1984;73:1107–9.
40. Guérin S, Richard G, Biau A, Lebre S, Crescini D, Haddy N, Guldner L, Paoletti C, Hill C, de Vathaire F. Cancer mortality among French nuclear contract workers. Am J Ind Med. 2009;52:916–25.
41. Guseva Canu I, Cardis E, Metz-Flamant C, Caër-Lorho S, Auriol B, Wild P, Laurier D, Tirmarche M. French cohort of the uranium processing workers: mortality pattern after 30-year follow-up. Int Arch Occup Environ Health. 2010;83:301–8.
42. Han YY, Youk AO, Sasser H, Talbott EO. Cancer incidence among residents of the Three Mile Island accident area: 1982–1995. Environ Res. 2011;111:1230–5.
43. Hansen ES, Lander F, Lauritsen JM. Time trends in cancer risk and pesticide exposure, a long-term follow-up of Danish gardeners. Scand J Work Environ Health. 2007;33:465–9.
44. Hardell L, Sandström A. Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer. 1979;39:711–7.
45. Hardell L, Eriksson M. The association between soft tissue sarcomas and exposure to phenoxyacetic acids. A new case-referent study. Cancer. 1988;62:652–6.
46. Hardell L. Phenoxy herbicides, chlorophenols, soft-tissue sarcoma (STS) and malignant lymphoma. Br J Cancer. 1993;67:1154–6.
47. Hardell L, Eriksson M, Degerman A. Metaanalysis of 4 Swedish case-control studies on exposure to pesticides as risk-factor for soft-tissue sarcoma including the relation to tumor-localization and histopathological type. Int J Oncol. 1995;6:847–51.
48. Hardell L. Pesticides, soft-tissue sarcoma and non-Hodgkin lymphoma–historical aspects on the precautionary principle in cancer prevention. Acta Oncol. 2008;47:347–54.
49. Heacock H, Hertzman C, Demers PA, Gallagher R, Hogg RS, Teschke K, Hershler R, Bajdik CD, Dimich-Ward H, Marion SA, Ostry A, Kelly S. Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenate fungicides. Environ Health Perspect. 2000;108:499–503.
50. Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni Jr JF. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA. 1986;256:1141–7.
51. Hoar Zahm S, Blair A, Holmes FF, Boysen CD, Robel RJ. A case-referent study of soft-tissue sarcoma and Hodgkin's disease. Farming and insecticide use. Scand J Work Environ Health. 1988;14:224–30.
52. Hooiveld M, Heederik DJ, Kogevinas M, Boffetta P, Needham LL, Patterson Jr DG, Bueno-de-Mesquita HB. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. Am J Epidemiol. 1998;147:891–901.
53. Hoppin JA, Tolbert PE, Herrick RF, Freedman DS, Ragsdale BD, Horvat KR, Brann EA. Occupational chlorophenol exposure and soft tissue sarcoma risk among men aged 30–60 years. Am J Epidemiol. 1998;148:693–703.
54. Hoppin JA, Tolbert PE, Flanders WD, Zhang RH, Daniels DS, Ragsdale BD, Brann EA. Occupational risk factors for sarcoma subtypes. Epidemiology. 1999;10:300–6.
55. Hossain A, McDuffie HH, Bickis MG, Pahwa P, Cross Canada Study of Pesticides and Health Researchers. Case-control study on occupational risk factors for soft-tissue sarcoma. J Occup Environ Med. 2007;49:1386–93.
56. Howe GR, Zablotska LB, Fix JJ, Egel J, Buchanan J. Analysis of the mortality experience amongst U.S. nuclear power industry workers after chronic low-dose exposure to ionizing radiation. Radiat Res. 2004;162:517–26.
57. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer. 2001;92:172–80.
58. Iaia TE, Bartoli D, Calzoni P, Comba P, De Santis M, Dini F, Ercolanelli M, Farina GA, Pirastu R, Seniori Costantini A, Valiani M. Cohort study of mortality among leather tanners in the Lower Valdarno area. Med Lav. 2002;93:95–107 [article in Italian].
59. IARC. Vinyl chloride. In: Some anti-thyroid and related substances, nitrofurans and industrial chemicals, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 7. Lyon: IARC; 1974.
60. IARC. Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 69. Lyon: IARC; 1997.
61. IARC. Vinyl chloride. In: 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide), IARC monographs on the evaluation of carcinogenic risk to humans, vol. 97. Lyon: IARC; 2008.
62. IARC. Vinyl chloride. In: Chemical agents and related occupations, IARC monographs on the evaluation of carcinogenic risk to humans, vol. 100F. Lyon: IARC; 2012.
63. Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973–2002. Int J Cancer. 2007;121:2233–40.
64. Jenkinson HC, Winter DL, Marsden HB, Stovall MA, Stevens MC, Stiller CA, Hawkins MM. A study of soft tissue sarcomas after childhood cancer in Britain. Br J Cancer. 2007;97:695–9.
65. Kang HK, Weatherbee L, Breslin PP, Lee Y, Shepard BM. Soft tissue sarcomas and military service in Vietnam: a case comparison group analysis of hospital patients. J Occup Med. 1986;28:1215–8.
66. Kang H, Enzinger FM, Breslin P, Feil M, Lee Y, Shepard B. Soft tissue sarcoma and military service in Vietnam: a case-control study. J Natl Cancer Inst. 1987;79:693–9.
67. Kjaer TK, Hansen J. Cancer incidence among male Danish nurses, 1980–2003. Int Nurs Rev. 2010;57:211–6.
68. Kleinerman RA, Tucker MA, Abramson DH, Seddon JM, Tarone RE, Fraumeni Jr JF. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst. 2007;99:24–31.
69. Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, Bueno-de-Mesquita HB, Coggon D, Green L, Johnson E, Littorin M, Lynge E, Marlow DA, Mathews JD, Neuberger M, Benn T, Pannett B, Pearce N, Saracci R. Soft tissue sarcoma and

non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. Epidemiology. 1995;6:396–402.
70. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Saracci R. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epidemiol. 1997;145:1061–75.
71. Krestinina LY, Davis F, Ostroumova E, Epifanova S, Degteva M, Preston D, Akleyev A. Solid cancer incidence and low-dose-rate radiation exposures in the Techa River cohort: 1956 2002. Int J Epidemiol. 2007;36:1038–46.
72. Kreuzer M, Walsh L, Schnelzer M, Tschense A, Grosche B. Radon and risk of extrapulmonary cancers: results of the German uranium miners' cohort study, 1960–2003. Br J Cancer. 2008;99:1946–53.
73. Laplanche A, Clavel-Chapelon F, Contassot JC, Lanouzière C. Exposure to vinyl chloride monomer: results of a cohort study after a seven year follow up. The French VCM Group. Br J Ind Med. 1992;49:134–7.
74. Laurent O, Metz-Flamant C, Rogel A, Hubert D, Riedel A, Garcier Y, Laurier D. Relationship between occupational exposure to ionizing radiation and mortality at the French electricity company, period 1961–2003. Int Arch Occup Environ Health. 2010;83:935–44.
75. Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br J Cancer. 1985;52:259–70.
76. Lynge E. Cancer in phenoxy herbicide manufacturing workers in Denmark, 1947–87 – an update. Cancer Causes Control. 1993;4:261–72.
77. Lynge E. Cancer incidence in Danish phenoxy herbicide workers, 1947–1993. Environ Health Perspect. 1998;106 Suppl 2:683–8.
78. 't Mannetje A, McLean D, Cheng S, Boffetta P, Colin D, Pearce N. Mortality in New Zealand workers exposed to phenoxy herbicides and dioxins. Occup Environ Med. 2005;62:34–40.
79. Maule M, Scélo G, Pastore G, Brennan P, Hemminki K, Tracey E, Sankila R, Weiderpass E, Olsen JH, McBride ML, Brewster DH, Pompe-Kirn V, Kliewer EV, Chia KS, Tonita JM, Martos C, Jonasson JG, Merletti F, Boffetta P. Risk of second malignant neoplasms after childhood leukemia and lymphoma: an international study. J Natl Cancer Inst. 2007;99:790–800.
80. Maule M, Scélo G, Pastore G, Brennan P, Hemminki K, Pukkala E, Weiderpass E, Olsen JH, Tracey E, McBride ML, Brewster DH, Pompe-Kirn V, Tonita JM, Kliewer EV, Chia KS, Jonasson JG, Martos C, Magnani C, Boffetta P. Risk of second malignant neoplasms after childhood central nervous system malignant tumours: an international study. Eur J Cancer. 2008;44:830–9.
81. Maule M, Scélo G, Pastore G, Brennan P, Hemminki K, Olsen JH, Tracey E, Pukkala E, Weiderpass E, Brewster DH, Tamaro S, Chia KS, Pompe-Kirn V, Kliewer EV, Tonita JM, Martos C, Jonasson JG, Merletti F, Boffetta P. Second malignancies after childhood noncentral nervous system solid cancer: results from 13 cancer registries. Int J Cancer. 2011;129:1940–52.
82. McBride DI, Burns CJ, Herbison GP, Humphry NF, Bodner K, Collins JJ. Mortality in employees at a New Zealand agrochemical manufacturing site. Occup Med. 2009;59:255–63.
83. McGeoghegan D, Binks K. The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946–95. J Radiol Prot. 2000;20:111–37.
84. McGeoghegan D, Binks K. The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946–95. J Radiol Prot. 2000;20:381–401.
85. McGeoghegan D, Binks K. The mortality and cancer morbidity experience of employees at the Chapelcross plant of British Nuclear Fuels plc, 1955–95. J Radiol Prot. 2001;21:221–50.
86. McGeoghegan D, Gillies M, Riddell AE, Binks K. Mortality and cancer morbidity experience of female workers at the British Nuclear Fuels Sellafield plant, 1946–1998. Am J Ind Med. 2003;44:653–63.
87. McLean D, Pearce N, Langseth H, Jäppinen P, Szadkowska-Stanczyk I, Persson B, Wild P, Kishi R, Lynge E, Henneberger P, Sala M, Teschke K, Kauppinen T, Colin D, Kogevinas M, Boffetta P. Cancer mortality in workers exposed to organochlorine compounds in the pulp and paper industry: an international collaborative study. Environ Health Perspect. 2006;114:1007–12.
88. Mellemkjaer L, Friis S, Olsen JH, Scélo G, Hemminki K, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Kee-Seng C, Pompe-Kirn V, Martos C, Jonasson JG, Boffetta P, Brennan P. Risk of second cancer among women with breast cancer. Int J Cancer. 2006;118:2285–92.
89. Menu-Branthomme A, Rubino C, Shamsaldin A, Hawkins MM, Grimaud E, Dondon MG, Hardiman C, Vassal G, Campbell S, Panis X, Daly-Schveitzer N, Lagrange JL, Zucker JM, Chavaudra J, Hartman O, de Vathaire F. Radiation dose, chemotherapy and risk of soft tissue sarcoma after solid tumours during childhood. Int J Cancer. 2004;110:87–93.
90. Mery CM, George S, Bertagnolli MM, Raut CP. Secondary sarcomas after radiotherapy for breast cancer: sustained risk and poor survival. Cancer. 2009;115:4055–63.
91. Metayer C, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, Joensuu T, van Leeuwen FE, van't Veer MB, Curtis RE, Holowaty EJ, Andersson M, Wiklund T, Gospodarowicz M, Travis LB. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol. 2000;18:2435–43.
92. Metz-Flamant C, Samson E, Caër-Lorho S, Acker A, Laurier D. Solid cancer mortality associated with chronic external radiation exposure at the French atomic energy commission and nuclear fuel company. Radiat Res. 2011;176:115–27.
93. Mikoczy Z, Schütz A, Hagmar L. Cancer incidence and mortality among Swedish leather tanners. Occup Environ Med. 1994;51:530–5.
94. Mikoczy Z, Schütz A, Strömberg U, Hagmar L. Cancer incidence and specific occupational exposures in the Swedish leather tanning industry: a cohort based case-control study. Occup Environ Med. 1996;53:463–7.
95. Mikoczy Z, Rylander L. Mortality and cancer incidence in cohorts of Swedish fishermen and fishermen's wives: updated findings. Chemosphere. 2009;74:938–43.
96. Mikoczy Z, Hagmar L. Cancer incidence in the Swedish leather tanning industry: updated findings 1958–99. Occup Environ Med. 2005;62:461–4.
97. Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bigelow C. Historical cohort study of 10 109 men in the North American vinyl chloride industry, 1942–72: update of cancer mortality to 31 December 1995. Occup Environ Med. 2000;57:774–81.
98. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst. 2001;93:618–29.
99. O'Brien MM, Donaldson SS, Balise RR, Whittemore AS, Link MP. Second malignant neoplasms in survivors of pediatric Hodgkin's lymphoma treated with low-dose radiation and chemotherapy. J Clin Oncol. 2010;28:1232–9.
100. Ott MG, Zober A. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. Occup Environ Med. 1996;53:606–12.
101. Pahwa P, McDuffie HH, Dosman JA, Robson D, McLaughlin JR, Spinelli JJ, Fincham S. Exposure to animals and selected risk factors among Canadian farm residents with Hodgkin's disease,

multiple myeloma, or soft tissue sarcoma. J Occup Environ Med. 2003;45:857–68.
102. Pahwa P, McDuffie HH, Dosman JA, McLaughlin JR, Spinelli JJ, Robson D, Fincham S. Hodgkin lymphoma, multiple myeloma, soft tissue sarcomas, insect repellents, and phenoxyherbicides. J Occup Environ Med. 2006;48:264–74.
103. Pahwa P, Karunanayake CP, Dosman JA, Spinelli JJ, McLaughlin JR, Cross-Canada Group. Soft-tissue sarcoma and pesticides exposure in men: results of a Canadian case-control study. J Occup Environ Med. 2011;53:1279–86.
104. Pesatori AC, Consonni D, Bachetti S, Zocchetti C, Bonzini M, Baccarelli A, Bertazzi PA. Short- and long-term morbidity and mortality in the population exposed to dioxin after the "Seveso accident". Ind Health. 2003;41:127–38.
105. Pesatori AC, Consonni D, Rubagotti M, Grillo P, Bertazzi PA. Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. Environ Health. 2009;8:39.
106. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, part I. Cancer: 1950–1990. Radiat Res. 2012;178:AV61–87.
107. Pippard EC, Acheson ED. The mortality of boot and shoe makers, with special reference to cancer. Scand J Work Environ Health. 1985;11:249–55.
108. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res. 2007;168:1–64.
109. Preston DL, Krestinina LY, Sokolnikov ME, Ron E, Davis FG, Ostroumova EV, Gilbert ES. How much can we say about site-specific cancer radiation risks? Radiat Res. 2010;174:816–24.
110. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality: 1950–1997. Radiat Res. 2012;178:AV146–72.
111. Ramlow JM, Spadacene NW, Hoag SR, Stafford BA, Cartmill JB, Lerner PJ. Mortality in a cohort of pentachlorophenol manufacturing workers, 1940–1989. Am J Ind Med. 1996;30:180–94.
112. Reif JS, Pearce NE, Fraser J. Cancer risks among New Zealand meat workers. Scand J Work Environ Health. 1989;15:24–9.
113. Reif J, Pearce N, Kawachi I, Fraser J. Soft-tissue sarcoma, non-Hodgkin's lymphoma and other cancers in New Zealand forestry workers. Int J Cancer. 1989;43:49–54.
114. Riihimäki V, Asp S, Hernberg S. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland: first report of an ongoing prospective cohort study. Scand J Work Environ Health. 1994;8:37–42.
115. Rix BA, Lynge E. Soft tissue sarcomas among female paper sorters in Denmark. Cancer Causes Control. 1997;8:259.
116. Rix BA, Villadsen E, Engholm G, Lynge E. Hodgkin's disease, pharyngeal cancer, and soft tissue sarcomas in Danish paper mill workers. J Occup Environ Med. 1998;40:55–62.
117. Rodvall Y, Dich J, Wiklund K. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. Occup Environ Med. 2003;60:798–801.
118. Rogel A, Carré N, Amoros E, Bonnet-Belfais M, Goldberg M, Imbernon E, Calvez T, Hill C. Mortality of workers exposed to ionizing radiation at the French National Electricity Company. Am J Ind Med. 2005;47:72–82.
119. Ruder AM, Yiin JH. Mortality of US pentachlorophenol production workers through 2005. Chemosphere. 2011;83:851–61.
120. Rushton L, Hutchings SJ, Fortunato L, Young C, Evans GS, Brown T, Bevan R, Slack R, Holmes P, Bagga S, Cherrie JW, Van Tongeren M. Occupational cancer burden in Great Britain. Br J Cancer. 2012;107 Suppl 1:S3–7.
121. Rylander L, Hagmar L. Mortality and cancer incidence among women with a high consumption of fatty fish contaminated with persistent organochlorine compounds. Scand J Work Environ Health. 1995;21:419–26.
122. Samanic C, Gridley G, Chow WH, Lubin J, Hoover RN, Fraumeni Jr JF. Obesity and cancer risk among white and black United States veterans. Cancer Causes Control. 2004;15:35–43.
123. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni Jr JF. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes Control. 2006;17:901–9.
124. Samson E, Telle-Lamberton M, Caër-Lorho S, Bard D, Giraud JM, Metz-Flamant C, Neron MO, Quesne B, Acker A, Tirmarche M, Hill C. Cancer mortality among two different populations of French nuclear workers. Int Arch Occup Environ Health. 2011;84:627–34.
125. Schaapveld M, Visser O, Louwman MJ, de Vries EG, Willemse PH, Otter R, van der Graaf WT, Coebergh JW, van Leeuwen FE. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. J Clin Oncol. 2008;26:1239–46.
126. Schubauer-Berigan MK, Daniels RD, Pinkerton LE. Radon exposure and mortality among white and American Indian uranium miners: an update of the Colorado Plateau cohort. Am J Epidemiol. 2009;169:718–30.
127. Seniori Costantini A, Paci E, Miligi L, Buiatti E, Martelli C, Lenzi S. Cancer mortality among workers in the Tuscan tanning industry. Br J Ind Med. 1989;46:384.
128. Serraino D, Franceschi S, La Vecchia C, Carbone A. Occupation and soft-tissue sarcoma in northeastern Italy. Cancer Causes Control. 1992;3:25–30.
129. Shilnikova NS, Preston DL, Ron E, Gilbert ES, Vassilenko EK, Romanov SA, Kuznetsova IS, Sokolnikov ME, Okatenko PV, Kreslov VV, Koshurnikova NA. Cancer mortality risk among workers at the Mayak nuclear complex. Radiat Res. 2003;159:787–98.
130. Smith AH, Pearce NE, Fisher DO, Giles HJ, Teague CA, Howard JK. Soft tissue sarcoma and exposure to phenoxyherbicides and chlorophenols in New Zealand. J Natl Cancer Inst. 1984;73:1111–7.
131. Smith JG, Christophers AJ. Phenoxy herbicides and chlorophenols: a case control study on soft tissue sarcoma and malignant lymphoma. Br J Cancer. 1992;65:442–8.
132. Smith AH, Pearce NE. Update on soft tissue sarcoma and phenoxyherbicides in New Zealand. Chemosphere. 1986;15:1795–8.
133. Smulevich VB, Fedotova IV, Filatova VS. Increasing evidence of the rise of cancer in workers exposed to vinylchloride. Br J Ind Med. 1988;45:93–7.
134. Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Natl Cancer Inst. 1999;91:779–86.
135. Stern FB. Mortality among chrome leather tannery workers: an update. Am J Ind Med. 2003;44:197–206.
136. Sulem P, Rafnsson V. Cancer incidence among Icelandic deck officers in a population-based study. Scand J Work Environ Health. 2003;29:100–5.
137. Svensson BG, Nilsson A, Jonsson E, Schütz A, Akesson B, Hagmar L. Fish consumption and exposure to persistent organochlorine compounds, mercury, selenium and methylamines among Swedish fishermen. Scand J Work Environ Health. 1995;21:96–105.
138. Swaen GM, van Vliet C, Slangen JJ, Sturmans F. Cancer mortality among licensed herbicide applicators. Scand J Work Environ Health. 1992;18:201–4.
139. Swaen GM, van Amelsvoort LG, Slangen JJ, Mohren DC. Cancer mortality in a cohort of licensed herbicide applicators. Int Arch Occup Environ Health. 2004;77:293–5.
140. Telle-Lamberton M, Bergot D, Gagneau M, Samson E, Giraud JM, Néron MO, Hubert P. Cancer mortality among French Atomic Energy Commission workers. Am J Ind Med. 2004;45:34–44.

141. Telle-Lamberton M, Samson E, Caër S, Bergot D, Bard D, Bermann F, Gélas JM, Giraud JM, Hubert P, Metz-Flamant C, Néron MO, Quesne B, Tirmarche M, Hill C. External radiation exposure and mortality in a cohort of French nuclear workers. Occup Environ Med. 2007;64:694–700.
142. Thériault G, Allard P. Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer. J Occup Med. 1981;23:671–6.
143. Tuomisto JT, Pekkanen J, Kiviranta H, Tukiainen E, Vartiainen T, Tuomisto J. Soft-tissue sarcoma and dioxin: a case-control study. Int J Cancer. 2004;108:893–900.
144. Tuomisto J, Pekkanen J, Kiviranta H, Tukiainen E, Vartiainen T, Viluksela M, Tuomisto JT. Dioxin cancer risk – example of hormesis? Dose Response. 2010;3:332–41.
145. Vacquier B, Caer S, Rogel A, Feurprier M, Tirmarche M, Luccioni C, Quesne B, Acker A, Laurier D. Mortality risk in the French cohort of uranium miners: extended follow-up 1946–1999. Occup Environ Med. 2008;65:597–604.
146. Viel JF, Arveux P, Baverel J, Cahn JY. Soft-tissue sarcoma and non-Hodgkin's lymphoma clusters around a municipal solid waste incinerator with high dioxin emission levels. Am J Epidemiol. 2000;152:13–9.
147. Vineis P, Terracini B, Ciccone G, Cignetti A, Colombo E, Donna A, Maffi L, Pisa R, Ricci P, Zanini E, Comba P. Phenoxy herbicides and soft-tissue sarcomas in female rice weeders. A population-based case-referent study. Scand J Work Environ Health. 1987;13:9–17.
148. Virtanen A, Pukkala E, Auvinen A. Angiosarcoma after radiotherapy: a cohort study of 332,163 Finnish cancer patients. Br J Cancer. 2007;97:115–7.
149. Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, De Santis M, Engholm G, Hagmar L, Langard S, Lundberg I, McElvenny D, Pirastu R, Sali D, Simonato L. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. Epidemiology. 2001;12:710–8.
150. Wingren G, Fredrikson M, Brage HN, Nordenskjöld B, Axelson O. Soft tissue sarcoma and occupational exposures. Cancer. 1990;66:806–11.
151. Wilczyńska U, Szadkowska-Stańczyk I, Szeszenia-Dabrowska N, Sobala W, Strzelecka A. Cancer mortality in rubber tire workers in Poland. Int J Occup Med Environ Health. 2001;14:115–25.
152. Wolk A, Gridley G, Svensson M, Nyrén O, McLaughlin JK, Fraumeni JF, Adami HO. A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control. 2001;12:13–21.
153. Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. J Natl Cancer Inst. 1987;78:899–910.
154. Zablotska LB, Ashmore JP, Howe GR. Analysis of mortality among Canadian nuclear power industry workers after chronic low-dose exposure to ionizing radiation. Radiat Res. 2004;161:633–41.
155. Zambon P, Ricci P, Bovo E, Casula A, Gattolin M, Fiore AR, Chiosi F, Guzzinati S. Sarcoma risk and dioxin emissions from incinerators and industrial plants: a population-based case-control study (Italy). Environ Health. 2007;6:19.
156. Zober A, Messerer P, Huber P. Thirty-four-year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. Int Arch Occup Environ Health. 1990;62:139–57.

Malignant Neoplasms of the Skin

21

Malcolm R. Sim, Stephanie S.H. Tan,
and Rosemary L. Nixon

Keywords
Skin cancer • Occupational factors • Basal cell carcinoma • Skin squamous cell carcinoma • Malignant melanoma • UV light • Arsenic • Ionizing radiation • Polyaromatic hydrocarbons • Shift work

Introduction

Malignant neoplasms of the skin comprise a group of cancers often less commonly considered occupational than many other types of cancers related to workplace exposures, such as mesothelioma, lung, or bladder cancer. One reason for this is that skin neoplasms are very common in the community and the main causal exposure, sunlight, is ubiquitous. Therefore, occupational risk factors may not be recognized when a case of skin cancer is diagnosed.

This current low awareness is despite a type of skin cancer being the first occupational cancer to be described in the literature. In 1775, Sir Percival Pott first described a type of squamous cell cancer (SCC) in the skin folds of the scrotum, which he termed soot wart [1]. This condition was predominantly found in young men who had worked as chimney sweeps as young boys, as they were able to do this work because of their small size. The cause of soot wart was thought to be coal tar, which also contained traces of arsenic. This finding was one factor which led to the introduction of the Chimney Sweepers Act in England in 1778, one of the first examples of legislation aiming to prevent health and safety problems in workplaces.

Skin neoplasms were later described among other occupations, such as mule spinners' disease found in the scrotal and vulva rugae of cotton workers, which was first described in the early twentieth century. This condition was thought to result from the groin area becoming soaked with mineral oil from straddling cotton-spinning machines [2].

Since these early examples of occupational cancer of the skin, many occupational cancers occurring in other parts of the body and linked to workplace exposures have been discovered and become more prominent as a focus of occupational cancer prevention. Yet occupational skin cancer continues to be an important problem in workplaces today in many countries around the world.

This chapter presents information on the main types of skin neoplasms, exposure to sunlight and other occupational risk factors known to increase the risk of developing skin neoplasms, surveillance data which monitors the incidence of workplace-related neoplasms, and the current state of evidence for the effectiveness of workplace preventive measures, with a focus on new and emerging risks.

Types of Malignant Neoplasms Related to Occupation

There are three main types of malignant neoplasms of the skin, plus one precursor condition, for which workplace risk factors are known. These are basal cell carcinoma (BCC), SCC, a precursor form of SCC (actinic keratosis), and malignant melanoma (MM). Skin neoplasms apart from MM are

M.R. Sim, BMedSc, MBBS, MSc, PhD, FAFOEM (✉)
Centre for Occupational & Environmental Health, Monash University, 99 Commercial Road, Melbourne, VIC 3004, Australia
e-mail: malcolm.sim@monash.edu

S.S.H. Tan, MBBS
Skin and Cancer Foundation, Inc., Melbourne, VIC, Australia

R.L. Nixon, BSc, MBBS, MPH, FACD, FAFOEM
Occupational Dermatology Education and Research Centre, Skin and Cancer Foundation, Inc., Melbourne, VIC, Australia

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_21, © Springer-Verlag London 2014

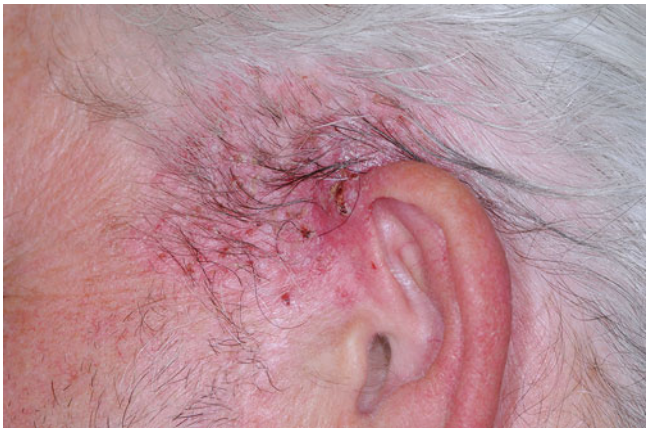


Fig. 21.1 Basal cell carcinoma on the ear

often given the umbrella term of non-melanoma skin cancer (NMSC). These four skin conditions have the following clinical features:

Basal Cell Carcinoma

BCC is the most common type of cutaneous malignancy, arising from the basal layers of the epidermis and its appendages. Although this tumor very rarely metastasizes, it is capable of extensive local invasion and tissue destruction. Ultraviolet (UV) light exposure is thought to be the major risk factor in the development of BCCs. About 85 % of BCCs occur on sun-exposed areas, particularly the head and neck (Fig. 21.1), while approximately 15 % of tumors occur on the skin protected from sun exposure [3, 4].

Genetic susceptibility is thought to play an important role in the development of BCCs [5]. Individuals with light skin color, blond or red hair, blue or green eyes, an inability to tan, a tendency to freckle easily, and a family history of skin cancer are at increased risk of developing BCCs. Race is also important, as BCC is extremely uncommon in dark-skinned races and uncommon in oriental populations compared with Caucasian populations [6, 7]. Approximately 40 % of patients who have had one BCC will develop another lesion within 5 years [8].

BCC may arise in the skin damaged by ionizing radiation, thermal injury, vaccination scars, and chronic inflammation. Immunocompromised patients have an increased BCC risk that is thought to be the result of impaired cell-mediated immunity and increased susceptibility to oncogenic viruses. However, immunosuppressed patients experience a greater relative increase in SCC than BCC [9].

BCCs usually appear as a flat, firm, pale area that is small, raised, pink or red, translucent, shiny, and waxy, and the area may bleed following minor injury. Tumor size can vary from a few millimeters to several centimeters in diameter. Characteristics vary for different clinical subtypes, which include nodular, superficial, morphoeic or fibrosing, pigmented, and the very rare variant, fibroepithelioma of Pinkus.

Nodular BCCs are the most common form of BCC, accounting for over 50 % of tumors. They are typically dome-shaped, pearly papules and nodules with rolled translucent borders and telangiectasia. Larger lesions with central necrosis are referred to by the historical term *rodent ulcer*, due to their tendency to invade surrounding tissue. Superficial BCCs occur most commonly on the trunk and appear as an erythematous patch (often well demarcated) that resembles eczema.

Morphoeic BCC is an aggressive variant. Clinically, it resembles a scar or a small patch of scleroderma and appears as whitish to yellowish fibrotic plaque with poorly defined margins. The appearance of scar tissue in the absence of trauma or previous surgical procedure or the appearance of atypical-appearing scar tissue at the site of a previously treated skin lesion should alert the clinician to the possibility of morphoeic BCC and the need for biopsy. Pigmented BCC is a subtype of nodular BCC that exhibits increased melanization. Clinically, the lesions are fairly well-defined papules or plaques with a translucent or pearly appearance and range in color from pink to dark brown or black.

Actinic Keratosis

Actinic keratosis (AK), also termed solar keratosis, represents the earliest lesion in the development of SCC in sun-damaged skin. AKs are very common and are more often seen in fair-skinned individuals, especially in those with a history of severe sunburn in childhood. The prevalence varies with geographical location and age with the highest rates of AK being found in sunny areas such as Queensland, Australia. Patients who are immunocompromised following organ transplantation are 250 times more likely to develop AK [10].

An AK may follow one of three paths: it may regress, it may remain unchanged, or it may progress to invasive SCC. The actual percentage that progresses to invasive SCC remains unknown, with estimates varying from as low as 0.1 % to as high as 10 % [11, 12].

AKs usually occur in middle-aged or elderly subjects on habitually sun-exposed areas such as the face, scalp, and dorsum of hands (Fig. 21.2). The sides of the neck are involved in both sexes, but the ears are predominantly involved in men, because of the cultural norm of shorter hair offering less protection from the sun.

AKs are often more easily palpated than seen. There are often multiple lesions, comprising either macules or papules with a rough scaly surface resulting from disorganized keratinization and with a variable degree of inflammation.

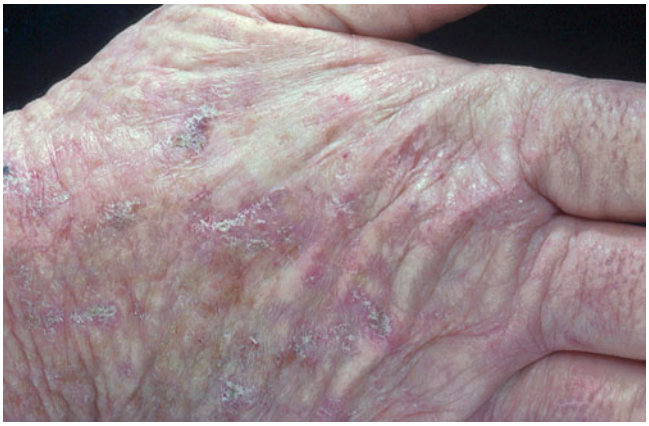


Fig. 21.2 Actinic keratosis on the dorsum of the hand

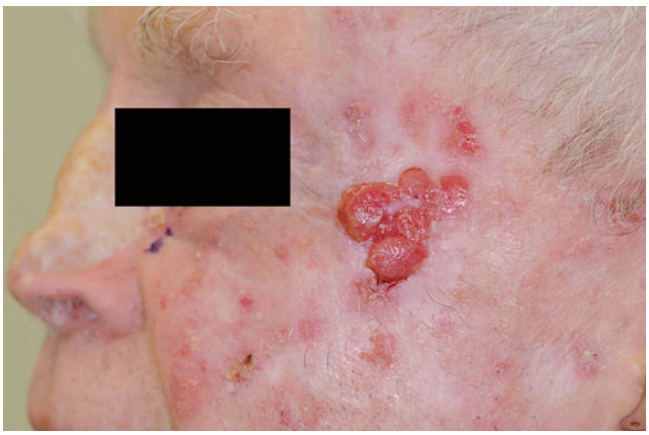


Fig. 21.3 Squamous cell carcinoma on the forehead

AKs are frequently 1–3 mm in size but can be as large as 1–2 cm. Lesions can develop significant thickening of the keratotic scale, and some may ultimately form a cutaneous horn. The edge of the keratosis is usually sharply demarcated and the reddening is usually closely confined to the area immediately below the area of abnormal scaling. While most AKs are asymptomatic, occasionally they may become pruritic or tender.

Squamous Cell Carcinoma

AKs can progress to become SCCs, which are related to cumulative sun exposure in fair-skinned people. Ultraviolet light exposure is the major risk factor in the development of SCC, which is reflected in the distribution of SCCs on sun-exposed areas. They usually arise in areas of damaged skin, including in areas previously damaged by ionizing radiation and chronic ulceration, such as in the rare inherited condition epidermolysis bullosa. Immunocompromised patients have a greatly increased risk of developing SCC, thought to relate to impaired cell-mediated immunity as well as increased susceptibility to oncogenic viruses [9].

SCCs arise from uncontrolled multiplication of malignant cells deriving from the epithelium. Invasive SCCs commence when atypical keratinocytes breach the dermal basement membrane and invade the dermis. Having traversed the epidermal basement membrane, the tumor acquires the ability to invade locally into fat, muscle, bone, or cartilage. Approximately 2 % of all SCCs metastasize, usually initially to the regional lymph nodes. The metastasis rate is higher from areas such as the lip, ear, and scalp.

SCCs rarely arise in healthy skin. There are usually signs of associated photodamage: nearby AKs, irregular pigmentation and telangiectasia, or leukokeratosis in cases of lip involvement. The first clinical evidence of malignancy is induration and lesions are often tender.

Approximately 70 % of all SCCs occur on the head and neck, most frequently involving the lower lip, external ear, periauricular region, or the forehead and scalp (Fig. 21.3). They also commonly occur on the dorsal hands and forearms. SCCs present clinically as scaly nodules or papules and less commonly as plaques that are skin-colored, pink, or red. The tumor surface may be smooth, keratotic, or ulcerated, and lesions may be exophytic or indurated. SCC must be excluded in any nonhealing erosion, ulcer, or skin lesion that repeatedly bleeds with minor trauma.

Malignant Melanoma

Both genetic and environmental factors are related to malignant melanoma (MM) pathogenesis. UV light exposure is a major environmental cause, especially in countries, such as Australia, which have high-risk fair-skinned populations and where UV light intensity is high. Malignant melanoma is the 5th most common cancer in Australia, behind NMSC, prostate, bowel, and breast cancer [13]. Australians have a one in 18 risk of being diagnosed with melanoma before the age of 85. Epidemiologic studies support the hypothesis that melanoma development is related to intermittent, intense sun exposure, particularly in childhood or adolescence [14]. Phenotypic features associated with increased risk of MM are light skin pigmentation, blond or red hair, blue or green eyes, a prominent freckling tendency, and tendency to sunburn with Fitzpatrick skin phototypes I–II [15].

Other risk factors for cutaneous melanoma include family history of melanoma or dysplastic nevus; history of prior melanoma; mutation in p16, BRAF, or MC1R; and xeroderma pigmentosum [16]. Nevi serve as genetic markers of increased risk rather than being premalignant lesions. Since there is an inverse relationship between the depth of invasion of MM and survival, it is important to recognize the early

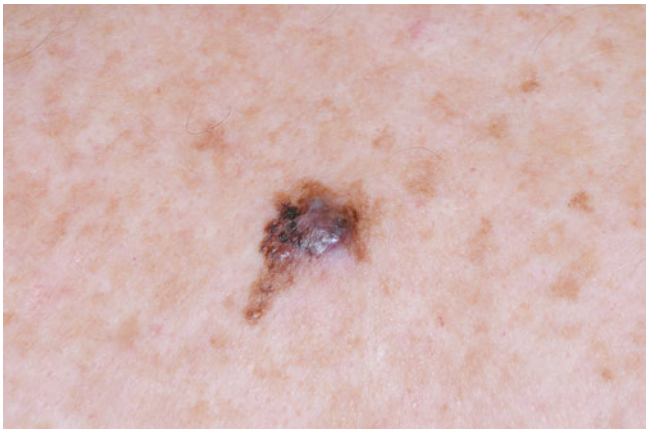


Fig. 21.4 Malignant melanoma on the trunk

clinical features of MM to facilitate early diagnosis and timely excision of the melanoma when there is a higher chance of cure.

Features used for melanoma recognition are A (asymmetry), B (irregular borders), C (color variegation), D (diameter >6 mm), and E (evolving over time). Four classic melanoma growth patterns with distinct clinical and pathologic features have been described: superficial spreading, nodular, acral lentiginous, and lentigo maligna melanoma.

Superficial spreading melanoma (SSM) is the most common type, accounting for approximately 70 % of all cutaneous melanomas. SSM has the appearance of flat, pigmented lesions, which become increasingly irregular in shape and color over time (Fig. 21.4). Variegation in color is a key feature of melanoma, and SSMs may become striking, with various hues of tan, brown, black, red, gray, and white. SSMs may arise in precursor nevi or dysplastic nevi, or they may develop de novo as a darkly pigmented macule or barely raised plaque.

Nodular melanoma (NM) is the second most common subtype and more commonly arises de novo than in a preexisting nevus. NM lacks the conventional criteria (ABCDE) that is helpful in clinical diagnosis of melanoma and it often presents as a symmetric papule or nodule with regular borders. The color is often uniform and is usually blue black or bluish red, but 5 % is amelanotic.

Acral lentiginous melanoma is the rarest form of malignant melanoma in Caucasians but represents the most common form in darker-pigmented individuals. The most typical presentation is of a flat, pigmented area on the palm or sole or a pigmented area under the fingernail or toenail. Pigmentation of the nail fold is suspicious of melanoma and termed Hutchinson's sign. Lentigo malignant melanoma typically occurs on chronically sun-exposed and photodamaged skin, particularly on the head and neck. The tumor can be present for long periods in its precursor form (lentigo maligna) before invasion occurs. Lentigo maligna begins as a small, brown smudge and gradually extends to produce an area of unevenly distributed pigmentation with an irregular edge. A discrete papular or nodular area developing within a lentigo maligna usually signals that invasion has occurred and may indicate the presence of a vertical-growth phase [17, 18].

While all of these types of skin neoplasm can be related to workplace exposures, the clinical features of an occupational skin neoplasm are no different from neoplasms related to sunlight and other exposures (such as arsenic in drinking water) outside the workplace. For this reason, the work-relatedness of these skin neoplasms can be unrecognized by treating clinicians, unless a careful occupational history is taken.

Occupational Factors

The most common exposure which increases the risk of malignant neoplasms of the skin in the general community is UV light from the sun, whether this exposure occurs in the workplace or during other leisure time activities. Apart from exposure to UV light through sunlight at work, many other established occupational risk factors have been identified for malignant skin neoplasms, many of which are now largely of historical interest in developed countries, although are still a problem in industrializing countries. These can be broken down into specific occupations and, in many cases, specific physical and chemical work exposures within those occupations. The main physical hazards of interest have been UV light and ionizing radiation, while the main chemical exposures of interest are metals (e.g., arsenic), metalworking fluids, and polycyclic aromatic hydrocarbons (PAHs), with some emerging hazards, such as shift work, where there may be a protective effect, but the evidence is less clear.

Most occupational skin neoplasm research has focused on BCC, SCC, and MM, but AKs have also been related to outdoor occupations [19]. Table 21.1 presents the results of some of the recently published studies investigating associations between occupational exposures and malignant skin neoplasms.

PAHs and Other Organic Compounds

An established chemical occupational skin carcinogen is the group of organic substances known as PAHs. This link has been well known since the time of the finding by Pott of scrotal cancer in chimney sweeps more than 200 years ago. More modern occupations where PAH exposure is known to occur include those in iron and steel foundries, coke production, roofers and asphalt workers, carbon black manufacture, and coal gasification. The main cancers of interest for these occupations have been lung and bladder, with considerations of skin cancer usually taking a secondary role [20].

Table 21.1 Recent studies of occupational exposures and malignant skin neoplasms

Author, year, country	Cohort description	Exposure assessment	Exposure categories	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Band et al. (2001), Canada	28,278 male pulp and paper mill workers; employed ≥1 year 1950–1992; follow-up to 1992; cancer incidence via linkage to National Cancer Registry	Work processes (kraft and sulfite) and duration	Overall <15 years ≥15 years	MM 1.59 (1.29–1.93) 1.25 (0.83–1.82) 1.78 (1.25–2.48)	Not adjusted for any confounding factors	Used 90 % CIs, association for MM stronger for kraft process
Hakansson et al. (2001), Sweden	323,860 male outdoor construction workers; cancer incidence from 1958 to 1993; linkage to Swedish Cancer Registry	Industrial hygienist assessed sunlight exposure for 200 work tasks: low medium, high	Head/face/neck Medium High Head/face/neck Medium High	MM 0.8 (0.4–1.5) 2.0 (0.8–5.2) NMSC 1.0 (0.7–1.3) 0.7 (0.3–1.6)	Age, smoking, magnetic field exposure	For cancer at different sites, RR of MM elevated for eye in high exposure group 3.4 (1.1–10.5)
Puntoni et al. (2004), Italy	2,101 male dockyard workers; employed 1933–1980; follow-up to 1996; incidence via linkage with Genova cancer registry	Occupational history, assessed into three carbon black exposure groups and year of first employment	All workers Low Moderate High <1958 ≥1958	MM 288 (125–568) 352 (96–901) 308 (63–900) 151 (4–840) 355 (130–772) 185 (22–668)	Age standardized	Small number of MM cases y, so limited power for subgroup analyses
Randem et al. (2004), four Nordic countries	22,362 male asphalt workers; employed >1 season; cancer incidence via linkage with national cancer registries	Assessment of job histories into 5 job groups	All countries	NMSC 0.59 (0.49–0.71) MM 0.50 (0.35–0.70)	Age, calendar period, and country	No association with job categories or years since first employment for NMSC
Yoshinaga et al. (2005), USA	65,304 US white radiologic technologists; SCC and BCC ascertained by questionnaire and physician confirmation	Ionizing radiation exposure estimated from year first worked (ref was 1960+)	Year first worked: 1950–1959 1940–1949 <1940	RR for BCC: 1.42 (1.12–1.80) 2.04 (1.44–2.88) 2.16 (1.14–4.09)	Gender, skin complexion, eye and hair color, lifetime UV exposure, total years worked	No association between year first worked and SCC
Sorahan 2007, UK	28,555 oil refinery and 16,477 petroleum distribution male workers; cancer incidence and mortality linkage	Work records; classified as refinery or distribution workers	Refinery Distribution Refinery Distribution	SSR for MM: 129 (103–159) 119 (88–158) SSR for other skin cancers: 117 (110–124) 113 (104–123)	Age	No association with longer period from first employment. Refinery operators, craftsmen, and administrative staff had significant excess of mortality from MM
Dennis et al. (2010), North Carolina, USA	24,704 pesticide applicators; follow-up 1993–2005 for incident cutaneous melanoma	Enrolment and follow-up questionnaire data on 50 pesticides	*Benomyl fungicide* <133 exp-days ≥ 133 exp-days *Carbaryl insecticide* <56 exp-days ≥56 exp-days *Maneb/mancozeb fungicide* <63 exp-days ≥63 exp-days *Parathion insecticide* <56 exp-days ≥56 exp-days	ORs 1.0 (0.4–2.2) 2.8 (1.2–6.5) 1.3 (0.9–2.1) 1.7 (1.1–2.5) 1.6 (0.8–3.4) 2.4 (1.2–4.9) 1.6 (0.8–3.1) 2.4 (1.3–4.4)	Age, gender, hours of sun exposure, BMI	No association with arsenic-based pesticides but significant effect modification when benomyl and maneb/mancozeb users were also exposed to lead arsenate As 50 pesticides examined, multiple comparisons need to be considered

(continued)

Table 21.1 (continued)

Author, year, country	Cohort description	Exposure assessment	Exposure categories	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Costello et al. (2011), USA	14,139 white males autoworkers, mortality and cancer incidence until 2004	Exposure groups based on work history and air monitoring data		MM HR (incidence)	Year of birth, year of hire, type of fluid	Linear dose response for straight oils
			Straight >4.62 mg/m^3-years	1.99 (1.00–3.96)		No associations with synthetic oils
			Soluble >10.41 mg/m^3-years	1.72 (0.69–4.27)		
Schernhammer et al. (2011), USA, Nurses' Health Study	68, 336 rotating night shift non-Hispanic white female nurses; follow-up 1988–2006	Number of years on rotating shift work collected by questionnaire	Rotating night shift	HR for all skin cancers	Age	Similar pattern for BCC, SCC, and MM when analyzed separately. Little difference when further adjusted by personal factors
			Never	1.0	No effect modification by history of UV light exposure	Dark hair color had lowest risk
			1–2 years	1.02 (0.97–1.07)		
			3–5 years	0.99 (0.94–1.05)		
			6–9 years	0.91 (0.84–0.99)		
			≥10 years	0.84 (0.78–0.89)		

Despite the large number of occupations involving PAH exposure, one review found few studies which investigated a link between PAH and skin cancers, but that the studies which included skin cancer found small, but statistically significant, increased risks of ORs ranging from 1.1 to 1.5 for different types of PAH exposure scenarios [21]. A more recent cohort study of workers exposed to bitumen found no convincing evidence of an increased risk of MM or NMSC by exposure or by duration of employment, but numbers were small [22].

Other organic compounds in the workplace have also been implicated as a cause of skin cancer. A meta-analysis of mortality from skin cancer in 350,000 oil refinery and petroleum distribution workers in cohort studies from several countries reported a slight overall excess, which did not quite reach statistical significance (SMR 110, 99–122) [23]. Most of the mortality data related to MM, as mortality is low from other types of skin cancers. There was some variation between the studies, with significant excesses found in the UK and Canadian cohorts. Specific exposures which may be related to excess skin cancer mortality were not clearly identified, especially as the highest SMR in the UK study was for administrative, clerical, and managerial employees.

The most recent update of the UK cohort study has found small, but significant, excesses for both MM and NMSC mortality among refinery workers [24] (Table 21.1). The most recent update of the Australian petroleum worker cancer incidence cohort study (Healthwatch) has also found an excess of MM incidence (SIR 1.37, 1.19–1.58), although no clear work factors could be identified [25]. PAH exposure and outdoor work are exposures of prime interest in these workers.

Arsenic

Another established skin carcinogen is inorganic arsenic, with exposure occurring both occupationally and environmentally, the latter usually through arsenic-contaminated drinking water in Bangladesh [26] but also in other counties, such as Taiwan [26]. Chronic exposure to arsenic increases the risk of keratoses, which are characteristically found on the palms and soles. Rarely, they may develop into SCCs in these areas, which are very unusual locations for this type of skin tumor. Arsenic exposure in workplaces usually occurs in the presence of other substances, and its carcinogenic effect on the skin can therefore be difficult to quantify. One case-control study of 1585 NMSC cases found elevated risks of SCC for some occupations which could involve exposure to inorganic arsenic, such as construction workers (OR 2.95, 1.12–7.74) and masons (OR 2.55, 1.36–4.78), although this work is often done outside [27].

Metalworking Fluids

A further chemical hazard which has received attention in the literature is exposure to metalworking fluids among metalworkers following some SCC case reports in the early part of the twentieth century. A 1998 systematic review of SCC in three cohort studies and one case-control study found conflicting results, with the case-control study showing the strongest risk, which was found among those involved in metal occupations (RR 10.5, 4.0–36.9) [28]. The review suggested

that the excess risk is more likely to be related to straight metalworking fluids than soluble fluids.

A more recent study of metalworking fluids and MM (Table 21.1) has also demonstrated the strongest evidence for straight metal fluids, which have higher oil contents than either soluble or synthetic metal fluids [29]. The most likely mechanism is that the excess skin cancer risk is related to direct contact of the fluid on the skin, and the metalworking fluid exposure metrics, based on air monitoring data, used in the MM study are thought to be acting as surrogate measures of dermal exposure. This mechanism would fit in better with what is known about the relationship between site of exposure and site of skin cancer in mule spinner's disease. However, the bodily distribution of the MM cases in the Costello et al.'s [29] study was consistent with the distribution in the US male population, which weakens the evidence for this mechanism.

Other Workplace Chemicals

Other studies have investigated different workplace chemicals and skin cancers, but the evidence generally is not clear (Table 21.1). A cohort study of male pulp and paper mill workers found an excess SIR for MM, with the highest risk occurring after 15 years of employment [30], but the likely causative exposure was not identified. Another cohort study investigated carbon black exposure and MM in dockyard workers, but the small size of the cohort and number of MM cases was small and no convincing associations were seen [31]. A cohort study of pesticide applicators within the Agricultural Health Study in the USA found increased risk of MM for the highest subgroups for several fungicides and insecticides, although a large number (about 50) of pesticides were examined and exposure was based on self-report [32].

UV Light

The other major category of occupational risk factors is physical hazards. Because of the well-established link between UV radiation from sunlight and skin neoplasms in the general community, there has been considerable interest in the level of risk among those workers in occupations which involve long periods and/or intense bursts of time in the sun. The wavelengths for UV radiation range between 100 and 400 nm and are broadly categorized into UVA (>315–400 nm), UVB (>280–315 nm), and UVC (100–280 nm). Most of the UV radiation that workers are exposed to is UVA, while UVB is a more potent cause of sunburn and DNA damage [33].

While some studies have not shown a role for occupational UV light exposure as a cause of MM, such as the study by Hakansson et al. [34] in Table 21.1, there is no debate about the role of occupational UV light exposure in causing SCC. A 2011 systematic review of six cohort studies and 12 case-control studies found that all but two studies reported an association between SCC and outdoor occupational UV light exposure [35]. The meta-estimate OR was 1.77 (1.40–2.30) and was of similar magnitude when the cohort and case-control studies were analyzed separately. The same research group has also published a systematic review of occupational UV exposure and BCC [36]. Twenty-three studies met the eligibility criteria and a weak to moderate association was found, as indicated by a pooled OR of 1.43 (1.23–1.66). Adjusting for nonoccupational UV exposure strengthened the association.

An important finding in both systematic reviews was the identification of considerable variation in what was defined as "occupational UV exposure" in the reviewed studies. This highlights the need for more standardized metrics for this type of workplace exposure, especially when the relevant pattern of exposure is thought to be different between BCCs and SCCs. A recent case-control study in Demark found no association between outdoor work and MM or NMSC, although UV intensity was low, which suggests that the association with outdoor work and NMSC is likely to vary geographically [37]. This indicates that the strength of the association of UV exposure and NMSC, particularly SCC, will relate to the cumulative UV levels experienced, and to date, much of the literature has emanated from Europe, which has lower levels of UV exposure than, say, Australia or southern USA, areas of the world where fair-skinned people predominate.

One limitation experienced in studies in geographical regions with high UV levels is differentiating occupational UV exposure from recreational UV light exposure, the latter likely to be influenced by socioeconomic status. Those with fairer skin and a tendency to sunburn may choose not to go into jobs which involve outdoor work, as found in a study in Queensland, Australia, which found no association between NMSC and outdoor work [38].

There can be other sources of UV light exposure, apart from sunlight, in workplaces. One example is welding which was investigated in a population-based case-control study of ocular melanoma in France [39]. Despite the small number of 50 cases, a strong association was found between ocular melanoma, a very unusual location for MM, and welding (OR 7.3, 2.6–20.1), as well as a relationship with job duration. IARC subsequently concluded that there is sufficient evidence for ocular melanoma in welders [40]. Other occupations, such as cooks and metalworkers, also showed elevated risks, although the mechanism for these occupations is less clear.

A growing trend, especially in developed countries, is the increasing use of tanning salons to obtain a fast tan. An IARC review has demonstrated that patrons who use these salons are at increased risk of melanoma and SCC [40], but there is no published research so far on the risk of skin cancer in workers at these salons.

Ionizing Radiation

A systematic review of five cohort studies of female flight attendants found an increased risk of MM, with a combined RR of 2.13 (1.58–2.88) [41]. However, it is not clear in this study whether ionizing radiation (IR) during flight or recreational UV exposure while on layover between flights was the more important exposure. This finding for women is supported by another systematic review of male civil and military pilots and male flight attendants which found that all three occupations had an excess risk of both MM and other skin cancer incidences [42]. The highest risk for both types of tumor was in male flight attendants; for MM, the meta-SIR was 3.42 (1.94–6.06), while for other skin cancers the meta-SIR was 7.46 (3.52–15.89).

There has been a long-standing interest in IR as a risk factor for skin neoplasms, which has been suggested as a possible cause of increased skin cancer risk among aircrews in the review papers referred to above [41, 42]. In addition to these reviews, the findings of the Yoshinaga et al.'s (2005) study (Table 21.1) indicate that long-term exposure to low to moderate ionizing radiation, based on a surrogate measure related to year first worked as a radiologic technician, increased the risk of BCC, but not SCC, with a strong dose-response relationship [43]. A strength of this study was the ability to adjust for UV exposure and personal characteristics, such as skin color.

A review of occupations with ionizing radiation and MM found stronger evidence for aircrew than in nuclear industry workers, although even among the aircrew, the findings from the various studies were inconsistent [44]. In addition, the authors concluded that any confounding or modifying effect from high leisure time UV exposure during time spent overseas by the aircrew could not be estimated.

The most recent review of medical radiation workers has documented the large drop in IR exposures among hospital medical radiation workers over the period from 1926 to 1984 [45]. Based on film badge data, the median annual dose fell from 71-mSv for the period before 1939 to 2.0 mSv in the period 1977–1984. However, Linet et al. [45] point out that ongoing monitoring of cancer, including skin cancer, in such workers is needed, in particular for those involved in more recently developed fluoroscopically guided interventional procedures which can result in higher IR exposure in those occupations.

Shift Work

A more contemporary exposure of increasing research interest is shift work, which has been investigated in the US Nurses' Health Study for a range of cancers. This study has found a reduction in risk with increasing years of rotating shift work in nurses for each of MM, BCC, and SCC and for all skin tumors combined [46]. The protective effect was strongest for MM, with a 44 % (37–87 %) reduction after 10 years of rotating shift work. Hair color was a significant effect modifier, with dark-haired nurses having the lowest risk, while there was no effect modification by history of sunlight exposure. These findings suggest that genetic and environmental factors may both act in melatonin suppression during night work, incurring a protective mechanism which is not well understood.

Epidemiology and Surveillance

The Global Burden of Disease Study has estimated, based on 2,000 data, that there were 211,921 incident cases of cutaneous MM, 65,161 deaths, and a total MM disease burden of 690,000 disability-adjusted life years (DALYs) [47]. It is also estimated that about 2,883,000 people developed incident SCC in 2000, with 13,534 deaths and the loss of 162,000 DALYs. For BCC it is estimated that ten million people developed new BCCs in 2000, although deaths from BCC are rare (estimated 3,245 worldwide in 2000) and therefore the total disease burden is lower than for MM or SCC, at about 58,000 DALYs lost in 2000.

This global burden of neoplasms of the skin is disproportionately carried by fair-skinned individuals and/or those who live in areas of the world with high UV exposure from the sun. With concerns about rising temperature and increased UV radiation through reduction of the ozone layer, it has been estimated that an elevation of temperature of 2° could increase the carcinogenic impact of UV light by a further 10 %, although there is some uncertainty about this figure [48]. In the USA, the rising incidence of MM has already been well documented, more than tripling in US men from about 7.5/110,000 in 1973 to 25.5/100,000 in 2004 [49]. Part of this apparent increase may be explained by greater recognition and improved diagnostic techniques for skin neoplasms, although greater UV intensity and increased outdoor activities may also play a role.

The global burden of disease estimates for skin neoplasms are not able to identify what proportion of this burden is related to work factors, as there is an absence of the necessary empirical data. However, estimates of the occupational contribution to cancer using a population attributable risk (PAR) approach have been performed in some countries. In Australia, it has been estimated that 192 MMs in males in 2000 (4.3 % of the total) were caused by occupation and that this was about 4.4 % of the estimated total number of 4,415 work-related cancers in Australian males in that year [50]. In addition, it was estimated that 28,000 NMSCs in males were

caused by occupation. Such calculations have acknowledged limitations, such as uncertainties in the numbers of exposed workers and levels of exposure as well as uncertainties in the PARs themselves, but these findings do help to identify skin neoplasm and work as an important problem to address.

A more recent estimate of the contribution of occupation to cancer in the UK based on attributable fractions for the IARC Group 1 and Group 2A carcinogens and using data from the CARcinogen EXposure (CAREX) database has been undertaken [51]. This study estimated that 2,928 NMSC registrations in 2004 were attributable to occupation, with almost all of the cases estimated to occur from three exposures: 1,541 from UV light, 902 from mineral oils, and 545 from PAHs. The number of NMSC was only exceeded by the estimated number of lung cancer cases attributable to occupation and was thought to be an underestimate, due to the known under-registration of NMSC in Britain.

Another approach is to try to obtain empirical data about the extent and risk factors for skin neoplasms by establishing notification programs. Such programs to monitor a wide range of occupational diseases, including skin neoplasms, have been established around the world. In the UK, The Health and Occupational Reporting (THOR) network, through its EPI-DERM program involving physician-notified occupational skin diseases, has found that about 12 % of cases ($n = 1468$) were skin neoplasms for the period 1995–2006 [52]. More recent analysis of the THOR data for 1988 skin cancer notifications until 2009 showed that 99 % of cases were thought to be related to sunlight/ultraviolet radiation, with the most frequently reported occupations being outdoors, such as armed services personnel (37 %), agricultural workers (18 %), and construction workers (9 %) [53].

It is interesting to note that the numbers of skin cancer cases notified in THOR are considerably lower than the estimates presented in the Rushton et al.'s (2010) study [51] and the spectrum of work-related exposures and occupations is also very different from those estimates. A more recent analysis of the EPI-DERM data indicates that the increased risks for skin cancers relate to roofers, those in the construction trades, laborers and painters, and decorators [54]. Inconsistencies in the numbers of cases and spectrum of occupations within different notification schemes may relate to factors such as different referral patterns and detection bias.

There is some evidence in the USA that workers with occupational exposure to UV light are less likely than other workers to have ever had a skin examination [55]. This may be due, in part, to the itinerant and seasonal nature of such work, leading to less regular contact with the healthcare system and may be an important factor in the known underestimate of the extent of the occupational skin neoplasm burden.

Use of Prevention Measures in Workers

There is evidence that the pattern of sun exposure related to skin neoplasms is different for the different types of cancers. MM appears to be more related to intermittent, more intense episodes of sun exposure leading to sunburn and blistering, whereas other types of skin cancer appear to be more related to chronic, cumulative sun exposure [56], which is the more relevant pattern of exposure for outdoor workers. In Australia, which has one of the highest incidences of skin cancer in the world, UV radiation exposure of workers in the building and construction industry was found to be well in excess of the occupational UVR exposure standard developed by the International Radiation Protection Association [57]. This indicates a strong need for sun protection programs, which need to be designed to take account of different patterns of sun exposure. In the case of UV light exposure, the usual workplace primary prevention measures, such as elimination or substitution, are not suitable options, so the main focus needs to be on measures lower in the hierarchy of controls, such as personal protection and administrative measures.

A 2007 systematic review assessed the extent of the use of measures to reduce sun exposure among outdoor workers [58]. The reviewed studies were published between 1991 and 2001 and found that measures to reduce sun exposure were variably used. For example, among Latino farm workers in California, it was common to wear long-sleeved shirts and hats, but using a sunscreen or wearing a wide-brimmed hat was much less common [59]. There were also gender differences among preventive measures, with men more likely to wear hats and women more likely to use sunscreens, so it is important that such differences are considered in designing sun protection programs in workplaces.

Interventions to Reduce Work Exposure

Most of the intervention research related to reducing the impact of skin neoplasms in workers has concentrated on ways to reduce UV light exposure, while interventions to reduce other occupational factors have received lesser attention. The 2007 systematic review by Glanz et al. assessed the evidence for the effectiveness of interventions to improve sun protection in outdoor workers [58]. Most interventions studied involved various forms of educational material and/or training programs with or without skin screening examinations. The authors concluded that there were too few well-designed studies with adequate documentation of changes in sun exposure and/or outcomes (rather than simply change in knowledge) to determine the effectiveness of skin protection programs to reduce the impact of UV light exposure in the occupational setting.

The best evidence comes from two intervention studies in the USA. The first of these was an evaluation of the Go Sun Smart (GSS) program, a worksite sun safety program largely based on the diffusion-of-innovations theory [60]. The GSS program was evaluated in a pair-matched, group-randomized, pretest/posttest-controlled design enrolling employees at 26 ski areas in Western North America. 2,119 employees completed both the pretest and posttest surveys. Employees at the intervention ski areas were more aware of GSS (OR = 8.27, $p < 0.05$) and reported less sunburning (adjusted OR = 1.63, $p < 0.05$) at posttest than employees at the control ski areas. A dose-response relationship was found (adjusted OR = 1.46, $p < .05$) with greater observed GSS program implementation associated with fewer episodes of sunburn among ski workers. Despite limitations, such as the short (5-month) period of follow-up, the 40 % dropout at posttest, and the seasonal nature of this work which means the findings may not necessarily be generalizable to other occupations with more regular schedules, this study provides some evidence that the GSS program can lead to short-term reductions in hazardous sun exposure.

A further 2-group randomized study assessed a sun safety intervention promoting the wearing of wide-brim hats and sunscreen use among US postal workers [61]. This study involved 2,662 workers and had a longer period of follow-up than the ski worker study: 3 months, 1 year, and 2 years. Intervention group workers were found to have significantly higher use of hats and sunscreen at 3 months, and this was maintained over the 2 years of follow-up with an OR of 2.9 (2.3–3.6) for wide-brim hat use and an OR of 2.0 (1.6–2.6) for sunscreen use at 2 years. A more recent study, using a Health Belief Model, found that the use of skin cancer videos and photos of sun damage in their own faces was associated with significant increases in sun protection behaviors and decreases in skin color measured by a spectrophotometer in 148 male highway workers which persisted for 1 year after the intervention [62]. This is clearly an important area of research in the future.

Conclusion

Occupational neoplasms of the skin have been recognized for more than 200 years since being first documented in chimney sweeps in eighteenth-century England. Since then, several other chemical and physical workplace exposures have been established as causes of malignant skin neoplasms; however, UV light has been shown to be the most important current cause, particularly for SCC. There are also some well-established chemical exposures in the workplace, such as PAH exposure and some other possible emerging hazards which require further research to investigate their relationship with skin neoplasms. Current methods to monitor trends in occupational skin neoplasms are inadequate, although the incidence of these cancers is probably on the rise, in line with skin cancer trends in the general community and related to increasing UV radiation levels [63]. The development of effective skin protection programs in the occupational setting is clearly an urgent priority and this will need to be an important focus of research in the future.

References

1. Pott P. Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures and the mortification of the toes and feet. London: T.J. Carnegy; 1775. p. 63–8.
2. Southam AH, Wilson SR. Cancer of the scrotum: the etiology, clinical features, and treatment of the disease. Br Med J. 1922; 2(3229):971–3.
3. Gallagher RP, Hill GB, Bajdik CD, et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. 1. Basal cell carcinoma. Arch Dermatol. 1995;131:157–63.
4. McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma: possible indicator of differing causes. Arch Dermatol. 1997;133:593–6.
5. Stacey SM, Sulam P, Masson G, et al. New common variants affecting susceptibility to basal cell carcinoma. Nat Genet. 2009;41(8):909–14. Epub 2009 Jul 5.
6. Miki Y. Basal cell epithelioma among Japanese. Australas J Dermatol. 1968;9:304–13.
7. Shanmugaranam K, Labrooy EB. Skin cancer in Singapore. Washington, DC: National Cancer Institute; 1963. p. 127–40. Monograph 10.
8. Robinson JK. Risk of developing a basal cell carcinoma. A 5 year prospective study. Cancer. 1987;60(1):118–20.
9. Lindelof B, Sigurgeirsson B, Gabel H, et al. Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol. 2000;143:513–9.
10. Euvrard S, Kanitakis J, Pouteil-Noble C, et al. Comparative epidemiologic study on premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. J Am Acad Dermatol. 1995;33:222–9.
11. Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol. 2000;42(1 Pt 2):23–4.
12. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet. 1988;1(8589):795–7.
13. Australian Institute of Health and Welfare. http://www.aihw.gov.au/cancer/#incidence. Accessed 15 Feb 2012.
14. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005;41:45–60.
15. Rhodes AR, Weinstock MA, Fitzpatrick TB, et al. Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals. JAMA. 1987;258:3146–54.
16. Piepkorn M. Melanoma genetics: an update with focus on the CDKN2A p1 tumor suppressors. J Am Acad Dermatol. 2000; 42:705–22.
17. Wolff K, Goldsmith LA, Katz SI, et al. Chapter 124: cutaneous melanoma. Fitzpatrick's Dermatology in General Medicine. 7th ed. United Kingdom: McGraw-Hill Medical, NY 2008.
18. Burns T, Breathnach S, Cox N, Griffiths C. Chapter 54: lentigos, melanocytic naevi and melanoma. Rook's Textbook of Dermatology. 8th ed. Boston: Wiley and Blackwell Publishing UK 2010.

19. Schwartz RA, Bridges TM, Butani AK, Ehrlich A. Actinic keratosis: an occupational and environmental disorder. J Eur Acad Dermatol Venereol. 2008;22:606–15.
20. Baan R, Grosse Y, Straif K, et al. A review of human carcinogens – Part F : chemical agents and related occupations. Lancet Oncol. 2009;10:1143–4.
21. Boffetta P, Jourenkova N, Gustavson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control. 1997;8:444–72.
22. Randem BG, Burstyn I, Langard S, Svane O, Jarvholm B, Kauppinen T, Bergdahl IA, Johansen C, Hansen J, Partanen T, Kromhout H, Ferro G, Boffetta P. Cancer incidence of Nordic asphalt workers. Scand J Work Environ Health. 2004;30(5): 350–5.
23. Wong O, Raabe GK. A critical review of cancer epidemiology in the petroleum industry, with a meta-analysis of a combined database of more than 350,000 workers. Regul Toxicol Pharmacol. 2000;32:78–98.
24. Sorahan T. Mortality of UK oil refinery and petroleum distribution workers, 1951–2003. Occup Med. 2007;57:177–85.
25. Gun RT, Pratt N, Ryan P, Roder D. Update of mortality and cancer incidence in the Australian petroleum industry cohort. Occup Environ Med. 2006;63:476–81.
26. Chen Y, Parvez F, Gamble M, Islam T, et al. Arsenic exposure at low-to-moderate levels and skin lesions, arsenic metabolism, neurological functions, and biomarkers for respiratory and cardiovascular diseases: review of recent findings from the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh. Toxicol Appl Pharmacol. 2009;239:184–92.
27. Suárez B, López-Abente G, Martínez C, Navarro C, et al. Occupation and skin cancer: the results of the HELIOS-I multicenter case-control study. BMC Public Health. 2007;7:180.
28. Calvert GM, Ward E, Schnorr TM, Fine LJ. Cancer risks among workers exposed to metalworking fluids: a systematic review. Am J Ind Med. 1998;33:282–92.
29. Costello S, Friesen MC, Christiani DC, Eisen EA. Metalworking fluids and malignant melanoma in autoworkers. Epidemiology. 2011;22:90–7.
30. Band PR, Le ND, Fang R, Astrakianakis G, Bert J, Keefe A, Krewski D. Cohort cancer incidence among pulp and paper mill workers in British Columbia. Scand J Work Environ Health. 2001; 27(2):113–9.
31. Puntoni R, Ceppi M, Gennaro V, Ugolini D, et al. Occupational exposure to carbon black and risk of cancer. Cancer Causes Control. 2004;15(5):511–6.
32. Dennis LK, Lynch CF, Sandier DP, Alavanja MCR. Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural health study. Environ Health Perspect. 2010;118(6):812–7.
33. Young C. Solar ultraviolet radiation and skin cancer. Occup Med. 2009;59:82–8.
34. Hakansson N, Floderus B, Gustavsson P, Feychting M, Hallin N. Occupational sunlight exposure and cancer incidence among Swedish construction workers. Epidemiology. 2001;12:552–7.
35. Schmitt J, Seidler A, Diepgen TL, Bauer A. Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis. Br J Dermatol. 2011;164:291–307.
36. Bauer A, Diepgen TL, Schmitt J. Is occupational solar ultraviolet irradiation a relevant risk factor for basal cell carcinoma? A systematic review and meta-analysis of the epidemiological literature. Br J Dermatol. 2011;165:612–25.
37. Kenborg L, Jørgensen AD, Budtz-Jørgensen E, Knudsen LE, Hansen J. Occupational exposure to the sun and risk of skin and lip cancer among male wage earners in Denmark: a population-based case–control study. Cancer Causes Control. 2010;21: 1347–55.
38. Green A, Battistutta D, Hart V, Leslie D, Weedon D, Nambour Study Group. Skin cancer in sub-tropical Australian population: incidence and lack of association with occupation. Am J Epidemiol. 1996;144:1034–40.
39. Guénel P, Laforest L, Cyr D, Févotte J. Occupational risk factors, ultraviolet radiation, and ocular melanoma: a case-control study in France. Cancer Causes Control. 2001;12(5):451–9.
40. Ghissassi FE, Baan R, Straif K, et al. A review of human carcinogens – part D: radiation. Lancet Oncol. 2009;10:751–2.
41. Tokumaru O, Haruki K, Bacal K, Katagiri T, Yamamoto T, Sakurai Y. Incidence of cancer among female flight attendants: a meta-analysis. J Travel Med. 2006;13:127–32.
42. Buja A, Lange JH, Perissinotto E, Rausa G, et al. Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. Toxicol Ind Health. 2005;21: 273–82.
43. Yoshinaga S, Hauptmann M, Sigurdson AJ, Doody MM, Freedman DM, Alexander BH, Linet MS, Ron E, Mabuchi K. Nonmelanoma skin cancer in relation to ionising radiation exposure among U.S. radiologic technologists. Int J Cancer. 2005;115:828–34.
44. Fink CA, Bates MN. Melanoma and ionizing radiation: is there a causal relationship? Radiat Res. 2005;164(5):701–10.
45. Linet MS, Kim KP, Miller DL, Kleinerman RA, et al. Historical review of occupational exposures and cancer risks in medical radiation workers. Radiat Res. 2010;174:793–808.
46. Schernhammer ES, Razavi P, Li TY, Qureshi AA, Han J. Rotating night shifts and risk of skin cancer in the nurses' health study. J Natl Cancer Inst. 2011;103:602–6.
47. Lucas RM, McMichael AJ, Armstrong BK, Smith WT. Estimating the global disease burden due to ultraviolet radiation exposure. Int J Epidemiol. 2008;37(3):654–67.
48. Van der Leun JC, de Gruijl FR. Climate change and skin cancer. Photochem Photobiol Sci. 2002;1:324–6.
49. Kalia S, Haiducu ML. The burden of skin disease in the United States and Canada. Dermatol Clin. 2012;30:5–18.
50. Fritschi L, Driscoll T. Cancer due to occupation in Australia. Aust NZ J Public Health. 2006;30:213–9.
51. Rushton L, Bagga S, Bevan R, Brown TP. Occupation and cancer in Britain. Br J Cancer. 2010;102(9):1428–37.
52. McNamee R, Carder M, Chen Y, Agius R. Measurement of trends in incidence of work-related skin and respiratory diseases, UK 1996–2005. Occup Environ Med. 2008;65:808–14.
53. Turner S, Forman S, McNamee R, Carder M, Agius R. Investigating skin cancer case reporting to The Health and Occupation Reporting (THOR) network. Occup Environ Med. 2011;68:A38.
54. Stocks SJ, Turner S, McNamee R, Carder M, Hussey L, Agius RM. Occupation and work-related ill-health in UK construction workers. Occup Med. 2011;61:407–15.
55. LeBlanc WG Ph.D, Vidal L, Kirsner RS, Lee DJ. Reported skin cancer screening of US adult workers. J Am Acad Dermatol. 2008;59:55–63.
56. Kütting B, Drexler H. UV-induced skin cancer at workplace and evidence-based prevention. Int Arch Occup Environ Health. 2010;83:843–54.
57. Giles P, Wright J. Measured solar ultraviolet radiation exposures of outdoor workers in Queensland in the building and construction industry. Photochem Photobiol. 2003;78:342–8.
58. Glanz K, Buller DB, Saraiya M. Reducing ultraviolet radiation exposure among outdoor workers: state of the evidence and recommendations. Environ Health. 2007;6:22. doi:10.1186/1476-069X-6-22.
59. Salas R, Mayer JA, Hoerster KD. Sun-protective behaviours of California farmworkers. J Occup Environ Med. 2005;47:1244–9.
60. Buller DB, Andersen PA, Walkosz BJ, Scott MD. Randomized trial testing a worksite sun protection program in an outdoor recreation industry. Health Educ Behav. 2005;32:514–35.

61. Mayer JA, Slymen DJ, Clapp EJ, Pichon LC. Promoting sun safety among US postal service letter carriers: impact of a 2-year intervention. Am J Public Health. 2007;97:559–65.
62. Stock ML, Gerrard M, Gibbons FX. Sun protection intervention for highway workers: long-term efficacy of UV photography and skin cancer information on men's protective cognitions and behaviour. Ann Behav Med. 2009;38:225–36.
63. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of non-melanoma skin cancer. Br J Dermatol. 2012;166:1069–80.

Breast Cancer

22

France Labrèche, Mark S. Goldberg,
and Elisabete Weiderpass

Keywords
Breast cancer • Occupational exposure • Risk factors • Shift work • Work schedule tolerance • Ethylene oxide

Female Breast Cancer

Descriptive Epidemiology

Breast cancer is the most common malignancy affecting women. Indeed, among all cancers affecting women, breast cancer has the highest incidence and mortality both in high-income and low- and middle-income countries. In 2008, 1.38 million new cases were reported, corresponding to 23 % of all cancers occurring in women that year. The incidence of female breast cancer varies greatly, being highest among white women in the United States, in Australia and New Zealand, and in Western and Northern Europe (greater than 75 new cases per 100,000 women). Incidence is lowest among Asian women living in Asia, and African women living in sub-Saharan Africa (incidence around or below 30 new cases per 100,000 women). The range of mortality rates for female breast cancer is narrower than that of incidence rates, due to better survival in high-income countries as compared to low- and middle-income countries (Fig. 22.1) [1].

The incidence of female breast cancer has been increasing worldwide over the last five decades, including in Asia and in Europe. In the United States, incidence rates have been declining over the last few years, probably due to the reduction of large-scale hormone replacement therapy prescription [2, 3]. Secular time trends in mortality rates have generally been more stable than those of incidence [4].

F. Labrèche, MSc, PhD
Research and Expertise Division, Institut de recherche Robert-Sauvé en santé et en sécurité du travail, Montreal, QC, Canada

Département de Santé environnementale et santé au travail, École de santé publique, Université de Montréal, Montreal, QC, Canada

M.S. Goldberg, MSc, PhD
Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, QC, Canada

E. Weiderpass, MD, MSc, PhD (✉)
Cancer Registry of Norway, Oslo, Norway

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway

Department of Genetic Epidemiology, Folkhälsan Research Center, Helsinki, Finland
e-mail: elisabete.weiderpass@ki.se

General Epidemiology and Lifestyle-Related Risk Factors

As is the case for most cancers, breast cancer is a multifactorial disease. Several nonoccupational factors have been found to be consistently associated with increased risks of developing breast cancer; a selection of these is presented in Table 22.1.

Reproductive Factors

Early age at menarche (≤11 vs. ≥15 years, 1.1–1.9-fold increased risk) [5, 6], late age at menopause (≥55 vs. ≤45 years, 1.1–1.9-fold increased risk) [5, 6], nulliparity (nulliparous vs. parous women: one to twofold increase in risk, inconclusive after one full-term pregnancy) [7], and age at first full-term pregnancy above 30 years (one to twofold increased risk compared to women with first full-term pregnancy

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_22, © Springer-Verlag London 2014

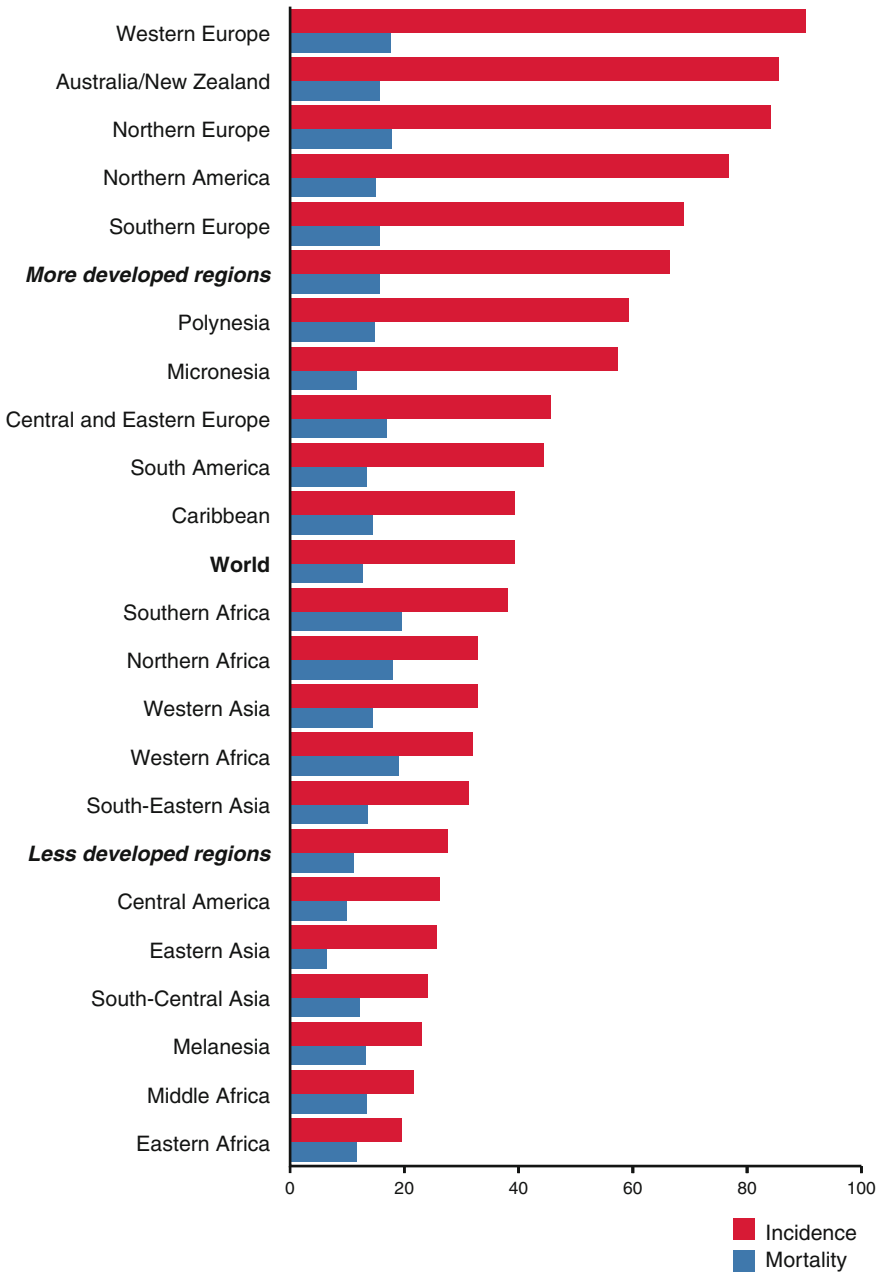


Fig. 22.1 World age-standardized incidence and mortality rates of female breast cancer in different world regions. GLOBOCAN 2008

>20 years of age) [6–11] have been consistently associated with an increased risk of breast cancer. Breastfeeding reduces risk in both pre- and postmenopausal women [15, 20]; a pooled analysis showed a decreased risk of 4 % for every 12 months a woman breastfeeds, regardless of whether a woman breastfeeds in consecutive children or not [12].

Use of Exogenous Hormones

According to the International Agency for Research on Cancer (IARC), diethylstilbestrol causes cancer of the breast in women exposed while pregnant [21]. The use of oral contraceptives comprising estrogen and progestogen among current and recent users only is also associated with an increased risk of developing breast cancer in young women [21]; the risk is particularly increased among women with benign breast disease who use oral contraceptives, and among women who used oral contraceptives either before 20 years of age (relative risk ~2.1) or before their first full-term pregnancy (relative risk ~1.6) [6, 7, 21]. The use of hormone replacement therapy containing estrogen and progestogen also increases the risk of developing breast cancer (relative risk <2 for women who took them for several years or in high doses), as does hormone replacement therapy containing estrogen only [6, 7, 13, 14, 16].

Diet, Body Size, and Physical Activity

The World Cancer Research Fund [15] evaluated the available evidence on the risk of cancer and several aspects of diet,

Table 22.1 Selected nonoccupational risk factors associated with the development of breast cancer

Risk factor	Definition	Range of risk	Menopausal status	References
Reproductive risk factors				
Age at menarche	≤11 vs. ≥15 years old	1.1–1.9	Any	[5, 6]
Age at first full-term pregnancy	≥30 vs. <20 years old	1.1–1.9	Any	[6–11]
Parity	Nulliparous vs. ≥1 child	1–2	Any	[7]
Breastfeeding	Per 12 months (continuous or not)	Decrease of 4 % in risk	Any	[5, 7]
Age at menopause	≥55 years vs. ≤45 years old	1.1–1.9	Postmenopausal	[5, 6]
Medication				
Diethylstilbestrol	Use during pregnancy	1.3–1.5	Not specified	[12]
Oral contraceptives with combined estrogen-progestogen	Ever vs. never	1.6–2.1	Premenopausal	[6, 7, 12, 13]
Hormone replacement therapy (estrogen alone or in combination with progestogen)	Several years or in high doses	<2	Postmenopausal	[6, 7, 14]
Lifestyle and personal risk factors				
Height	Per 5 cm increase	Increase of 3 % in risk	Any	[15]
High body fat	Exposure-response relationship	Decrease in risk	Premenopausal	[11, 16]
High body fat	Exposure-response relationship	Increase in risk	Postmenopausal	[15, 17]
Physical activity	Per 7 MET h/week	Decrease of 3 % in risk	Any	[15–17]
Alcohol consumption	Per 10 g ethanol consumed daily	Increase of 10 % in risk	Any	[15, 18]
Total fat consumption		Increased risk	Postmenopausal	[7, 15]
Other exposures				
Chest irradiation (X- and γ-radiation)	High doses vs. minimal (irradiation from puberty to childbearing years)	2–4	Any	[7, 19]

METs describe the energy cost of physical activity relative to a person's resting metabolic rate

physical activity, and body size. The IARC Handbooks of Cancer Prevention series also includes similar evaluations [17, 18]. The results from the World Cancer Research Fund and the IARC are of major importance and are summarized below.

There is evidence suggesting that total fat consumption may be associated with the risk of developing postmenopausal breast cancer, although firm conclusions cannot be drawn as there are a limited number of studies available [15]. No other dietary factor has been compellingly linked to breast cancer risk in either pre- or postmenopausal women [15, 18]. There are consistent epidemiological data that support an exposure-response relationship, indicating that high body fat protects against breast cancer risk among premenopausal women, but the mechanistic evidence is unknown [11, 17]. In contrast, there are consistent epidemiological data and a clear exposure-response relationship, with robust evidence for mechanisms operating in humans, indicating that greater body adiposity after menopause is associated with higher risk of developing breast cancer [15, 18]. According to the evaluation of the World Cancer Research Fund, increased abdominal fat is associated with increased risk of developing postmenopausal breast cancer (relative risk 1.19, 95 % confidence interval [CI] 1.10–1.28 per 0.1 increment in waist-to-hip ratio), as is weight gain in adults (relative risk 1.05, 95 % CI 1.04–1.07 per 5 kg gained), whereas higher birth weight is associated with an increased risk of premenopausal breast cancer (relative risk 1.08, 95 % CI 1.04–1.13) [15].

With respect to height, there are abundant and generally consistent prospective epidemiological studies showing a clear exposure-response relationship as well as evidence for plausible mechanisms in humans. The World Cancer Research Fund considers that there is convincing evidence that factors that lead to greater adult attained height (relative risk 1.03, 95 % CI 1.01–1.04 per 5 cm increase) are associated with increased incidence among both pre- and postmenopausal women [15].

Results from prospective studies on physical activity are inconsistent, but in general suggest a protective effect against both pre- and postmenopausal breast cancer. The evidence for postmenopausal breast cancer is stronger than for premenopausal breast cancer, although there is some heterogeneity in the exposure-response relationship depending on the study design. There are little data regarding frequency, duration, or intensity of activity, but the evidence is robust for mechanisms operating in humans. In summary, physical activity probably protects against postmenopausal breast cancer [15, 18].

Alcoholic Beverages

In agreement with the IARC evaluation, which considered alcohol as carcinogenic (Group 1 agent) to the human breast [22], the World Cancer Research Fund also classified as convincing the evidence that consumption of alcoholic beverages increases incidence in both pre- and postmenopausal breast cancer, irrespective of the type of alcoholic beverage (i.e., no difference between wine, beer, liquor, etc.). An exposure-response relationship is apparent: all studies in which an exposure gradient was investigated found that risks

increased with increasing alcohol consumption (relative risk 1.10, 95 % CI 1.06–1.14 per 10 g/day increase). In addition, no threshold was identified, and there is robust evidence for mechanisms operating in humans [15].

Tobacco Smoking

The IARC considers that there is limited evidence suggesting that tobacco smoking may be associated with increasing incidence of breast cancer, in particular when smoking starts early and before a woman's first full-term pregnancy (before the breast tissue matures) and continues for several decades [22].

Ionizing Radiation

The IARC classified X-radiation and γ-radiation as carcinogenic agents with sufficient evidence in humans in relation to developing breast cancer (two- to fourfold increase in risk for high doses compared to minimal exposure; risk may be higher when exposure occurs between puberty and childbearing years, when breast tissue is still proliferating) [7, 19, 23]. The evidence on which the evaluation was based emanates from many studies in special populations, such as atomic bomb survivors, medical patients, and women who were exposed in utero (offspring of atomic bomb survivors and pregnant medical patients) (see Table 22.1) [19, 23, 24].

Family History of Breast Cancer and Genetic Factors

Family history of breast cancer increases a woman's risk substantially depending on the age at which affected relatives were diagnosed, as well as the age of the woman herself, the number of affected relatives, and the generational distance between the relatives and the women. The familial relative risk (FRR) for first-degree relatives of breast cancer patients is about twice that of women without a family history of breast cancer [25, 26] and increases more than fourfold for women who have a first-degree relative with premenopausal bilateral breast cancer or who have two first-degree relatives with any form of breast cancer [5–11, 27, 28]; most of this FRR appears to be due to inherited susceptibility [26, 29, 30].

Several important genetic variants have been found, ranging from high-penetrance but rare mutations that confer very high risks (ranging from 5 to more than 20), moderate-penetrance mutations that are associated with risks between 1.5 and 5, and low-penetrance but frequent polymorphisms associated with lower risks (see Table 22.2) [28, 31]. Based on recent evidence, it appears that genetic susceptibility is involved in a large proportion of breast cancer cases. According to a polygenic model, about half of all breast cancer cases arise in a small, highly susceptible subgroup comprising about 12 % of women (those with a risk above 10 % by age 70 years). In fact, half of the female population has a breast cancer risk of only 3 % or less, accounting for about 12 % of all breast cancer cases [32].

Table 22.2 Known breast cancer susceptibility alleles

Susceptibility alleles	Frequency in European populations	% of familial relative risk explained
High risk		
BRCA1, BRCA2, TP53, PTEN, STK11/LKB1	0.0006–0.001	20–25 %
Intermediate risk		
CHEK2, ATM, BRIP1, PALB2	0.005–0.01	5 %
Low risk		
FGFR2, TOX3, MAP3K1, FAM84B/c-MYC, LSP1, NEK10/SLC4A7, COX11, CASP8 (D302H), TNP1/IGFBP5/IGFBP2/TNS1, NOTCH2/FCGR1B, RAD51L1, MRPS30/FGFR10, ESR1d	0.13–0.52	8–10 %

Adapted from Mavaddat et al. [28], Copyright 2010, with permission from Elsevier

About 25 % of the FRR is explained by high-risk alleles such as BRCA1, BRCA2, PTEN, and TP53. When the rare intermediate-risk alleles (CHEK2, ATM, BRIP1, PALB2) are also considered, another 2–3 % of the FRR is accounted for (see Table 22.2) [33]. In addition to these high- and intermediate-risk alleles, genetic studies have identified 19 common low-risk susceptibility alleles that explain yet another 10 % of the FRR [34–43]. Many of these genes are involved in DNA repair mechanisms (see Table 22.2) [28].

In summary, the known susceptibility alleles account for only about one-third of the overall FRR. Recent genome-wide linkage studies did not identify any additional rare variants that confer large breast cancer risks (relative risk >2) [28]. Thus, the remainder of the FRR could likely be explained by some combination of common variants, although certain authors consider that including newly discovered common variants would only modestly improve the performance of risk models for breast cancer [44].

Occupational Exposures

The IARC Monographs on the Evaluation of Carcinogenic Risks to Humans series is recognized worldwide as a dependable source when it comes to identifying carcinogenic agents and circumstances. Possible carcinogenic agents are classified using a five-category classification system: Group 1 agents are deemed carcinogenic to humans; Group 2A agents probably carcinogenic to humans; Group 2B agents possibly carcinogenic to humans; Group 3 agents not classifiable as to their carcinogenicity to humans; and Group 4 agents probably not carcinogenic to humans [45]. The evidence considered by the working groups to classify the agents comes mainly from human and animal studies. Thus, some agents may be classified as carcinogenic to humans based on sufficient evidence

Table 22.3 Weight of the evidence of carcinogenicity to the human breast for selected lifestyle and occupational agents or exposure circumstances, as identified in the International Agency for Research on Cancer (IARC) Monographs, Volumes 1–102

Agent	IARC classification[a]	Weight of evidence[b] for breast cancer		
		In humans	In animals	From occupational exposure studies
Lifestyle factors				
Alcoholic beverages	1	S	S	N/A
Tobacco smoking (active)	1	L	L	N/A
Pharmaceuticals				
Diethylstilbestrol	1	S	S	N/A
Estrogen-progestogen contraceptives	1	S	S	N/A
Estrogen-progestogen menopausal therapy	1	S	S	N/A
Estrogen menopausal therapy	1	L	S	N/A
Mixed exposures (environmental and occupational)				
X-radiation, γ-radiation	1	S	S	L
Tobacco smoking (passive)	1	I	I	I
Occupational exposures				
Ethylene oxide	1	L	S	L
Shift work that involves circadian disruption	2A	L	S	L
Pharmaceuticals				
Estrogens	1	S	S	L, I
Antineoplastics	1, 2A	S	S	L, I
Organic solvents				
Mixtures	1,2A, 2B, 3	L, I	L	L, I
Tetrachloroethylene	2A	I	L	I
Trichloroethylene	2A	I	L	I
Aromatic hydrocarbons				
Benzene	1	L	L	I
PAHs	1, 2A, 2B, 3	I	L	I
ELF-EMF	2B	I	L, I	L, I
Pesticides, PCBs	1, 2A, 2B, 3	S, L, I	S, L, I	L, I

This table does not include risk factors not covered in IARC Monographs Volumes 1–102, notably reproductive and other hormonal factors, diet and nutritional factors, and genetic susceptibility traits

Abbreviations: *PAH* polycyclic aromatic hydrocarbons, *ELF-EMF* Extremely-Low-Frequency Electric and Magnetic Fields, *PCB* polychlorinated biphenyls

[a]Group 1 = carcinogenic to humans, Group 2A = probably carcinogenic to humans, Group 2B = possibly carcinogenic to humans, Group 3 = not classifiable as to its carcinogenicity to humans

[b]*S* sufficient evidence, *L* limited evidence, *I* inadequate evidence, *N/A* not applicable to occupational exposures

in humans, or limited evidence in humans, but sufficient evidence in animals. Finally, an agent can be considered carcinogenic to a certain organ, but not necessarily to another one. Table 22.3 shows the known or suspected causes of breast cancer abstracted from the IARC Monographs [46].

According to the different IARC Working Groups, the existing Group 1 agents with *sufficient* evidence of carcinogenicity to the human breast are not related to occupational exposures. For example, the available evidence for alcoholic beverages, diethylstilbestrol, and combined estrogen-progestogen oral contraceptives or hormone replacement therapy derives from personal use, not exposures in occupational settings. The rationale presented for X-radiation and γ-radiation essentially derives from studies carried out on atomic bomb survivors and women who underwent radiation therapy before menopause (for conditions such as acute postpartum mastitis, benign breast disease, and follow-up of tuberculosis by chest fluoroscopies) [47]. Only one Group 1 agent, ethylene oxide, is essentially an occupational exposure; the evidence for its carcinogenicity to the human breast is, however, *limited*. It is important to appreciate that in fact few studies of occupational risk factors for breast cancer have been carried out, so the paucity of occupational carcinogens may be due to lack of research.

Estrogen-only hormone replacement therapy and active tobacco smoking have been classified by the IARC as probably carcinogenic to the human female breast, with *limited* evidence in humans, but again, these exposures are not considered to be related to occupation.

Occupational Agents with Limited Evidence for Carcinogenicity to the Human Breast

Two agents, ethylene oxide (Group 1 agent) [48] and shift work that involves circadian disruption (Group 2A agent) [49], are considered to be related to occupation (see Table 22.4).

Ethylene Oxide

Ethylene oxide is used mainly as a raw material for the production of several industrial chemicals, including glycols, which are used in the production of a number of consumer goods [64]. Less than 1 % is used as a sterilizing agent, a fumigant, or a pesticide by different healthcare facilities, spice manufacturers, or sterilization contractors [64]. In the early 2000s, the approximate estimates of the number of exposed workers in the United States was in the order of 48,000 [65]. In the European Union in the early 1990s, the corresponding estimate was around 47,000 workers [66].

The data used by the IARC to classify ethylene oxide [48] derive mainly from four occupational cohort studies on mortality [50–53]. Because death from breast cancer is highly misclassified, one must rely on the corresponding incidence studies of three of the four aforementioned cohort studies [50–52]. More weight was given to a US National Institute for Occupational Safety and Health cohort study of 7,500 women [52], which had accounted for several important potential confounding variables. That study showed a clear

Table 22.4 Known and suspected occupational[a] causes of female breast cancer, as identified in the IARC Monographs

Agents with limited evidence for *occupational exposures* in humans			
Agents	Major industries/occupations	Range of risk ratios considered	References
Ethylene oxide	Ethylene oxide production	Cohort studies	[50–53]
	Chemical manufacture of ethylene glycols	Any duration of exposure: 0.5–1.7	
	Medical facilities with sterilization unit (hospitals, medical and dental clinics)	>14,620 ppm days: 1.9	
	Manufacturers of sterile medical supplies		
	Industrial sterilization contractors (spices, tobacco, furs, museum artifacts, etc.)		
Shift work that involves circadian disruption	Healthcare sector	Cohort studies	[54–57]
	Transportation	Any duration: ~1.0	
	Accommodation and food services	≥20–30 years (nurses): 1.4–1.8	
	Agriculture	Nested case-control studies	[58–60]
	Manufacturing industry	Any duration: 1.0–1.5	
		≥7–30 years: 1.7–2.2	
		Case-control studies	[61–63]
		Any duration: 0.5–1.6	
		≥5–20 years: 2.3–2.5	

[a]Among carcinogenic agents with sufficient evidence in humans, the following were not considered work-related: diethylstilbestrol and (active) tobacco smoking

exposure-response relationship between exposure to ethylene oxide and breast cancer incidence, with a risk of 1.87 among women in the highest quintile of cumulative exposure. A smaller study from the United States also showed increased risks (standardized morbidity ratios 1.57–1.72) among women from a sterilization company [51]. A Swedish study [50] did not report an increase in risk, but the follow-up period was rather short (11.8 years), which is a major limitation of the study. A few animal studies concluded that there were increased risks of mammary tumors in rodents. Additional mechanistic studies showed alkylation, gene mutations, and chromosomal alterations following binding to cellular macromolecules resulting in DNA, RNA, and protein (including hemoglobin) adducts; these led the IARC Working Group to classify ethylene oxide as carcinogenic to humans (Group 1 agent) but with *limited* human evidence for breast cancer and lymphoid tumors [48, 67].

Shift Work Involving Circadian Disruption

Although shift work corresponds to several definitions of work schedules, including hours other than the traditional daytime work period [68], it is generally considered as "… the organization of working time by different teams in succession to cover more than the usual 8-h day, up to and including the whole 24-h period" [69]. The most important factor of shift work that disrupts biological rhythms appears to be the proportion of time worked at night [70, 71]. The industrial sectors with the largest percentages of workers on a non-daytime shift are accommodation and food services, agriculture, health services, and transportation and communication [72]. It was estimated in 2005 that 9–30 % of workers in the European Union, depending on the country, worked shifts that included night work [73]; in 2004 that proportion was estimated to be about 15 % in the United States [74].

The IARC Working Group cited data from eight studies designed specifically to evaluate the relationship between shift work involving night work and the risk of breast cancer [49]. Six of these studies reported a modest increase in risk (generally <2) among women who worked night shifts for a long period of time, or who did rotating work including night shifts. These studies used several definitions of shift work and different designs (two prospective cohort studies among nurses [54, 55], three nested case-control studies [58–60], and one retrospective case-control study [61]). Two studies showed negative results, but one of these, a census-based cohort study [56], suffered from important design limitations, and the other, a retrospective case-control study, had an unusually high percentage of night and evening workers [62]. The available studies included mainly Caucasian women and women with postmenopausal breast cancer. In some of the studies, potential uncontrolled confounding and problems in exposure assessment may have biased the results toward an absence of association, thus underestimating the risk. Studies of aircraft personnel, some of whom are subjected to circadian disruption as well as cosmic radiation (pilots, flight attendants) and electromagnetic fields (all), were considered to support the previously mentioned findings [49].

The main theory underlying the detrimental effects of shift work is that light at night can disrupt circadian rhythms through its effect on melatonin synthesis and on the circadian gene function of the suprachiasmatic nucleus, and that this disruption might increase cancer risk through several pathways [75], including an indirect decrease of melatonin's possible oncostatic and free radical scavenging properties and perturbation of the involvement of circadian genes in cell

proliferation, apoptosis, cell cycle control, and DNA-damage response [49]. A case-control study nested in a cohort of nurses reported an inverse relationship between the urinary concentration of 6-sulphatoxymelatonin, a biomarker of melatonin concentration, and breast cancer incidence [76]; levels of 6-sulphatoxymelatonin decreased with increasing number of nights worked in the 2 weeks prior to urine collection [77]. However, another cohort study in the general population did not find such a relationship [78]. The additional evidence considered by the IARC Working Group to classify shift work that involves circadian disruption as probably carcinogenic to humans was *sufficient* in experimental animals for the carcinogenicity of light during the daily dark period (biological night) [79].

Since the IARC evaluation, a few additional studies have been published, the majority reporting increased risks. A population-based prospective cohort study of Chinese women reported no relationship between the incidence of breast cancer and night shift work as estimated from self-reports and a job-exposure matrix [57]. A group of researchers commented that these results may be consistent with the melatonin hypothesis, as women of Asian descent have been shown to have less suppression of their melatonin levels than Caucasians [80]. A population-based case-control study conducted among German women, the GENICA study, reported an increase in the incidence of breast cancer risk among women who had been night shift workers for 20 years or more (odds ratio (OR) 2.48), but it was based on only 12 cases [63]. A second population-based case-control study, conducted in France (the CECILE study), found a twofold increased risk among women who had worked the night shift more than 4.5 years prior to their first pregnancy [81]. Finally, a case-control study nested within a cohort of Danish military personnel reported increasing breast cancer incidence with the number of years of night shift work, with a fourfold increase among women who defined themselves as being a "morning" person [82]. An additional publication supported an inverse relationship between urinary concentrations of a melatonin metabolite and breast cancer risk [83].

Clearly more studies in humans are needed to allow a thorough understanding of the possible association between shift work and breast cancer risk. A working group convened by the IARC recently identified several major domains of non-day shift schedules that needed to be captured in a consistent manner to increase the validity of future studies on shift work and cancer [72].

Occupational Agents with Insufficient Evidence for Carcinogenicity to the Human Breast

A few additional agents have been associated with an increased breast cancer risk in women in more than one study, but the weight of evidence was not deemed sufficient to support their classification as carcinogenic to the human breast (see Table 22.5).

Ionizing Radiation

Although all forms of ionizing radiation are accepted carcinogens, as they cause direct DNA mutagenesis (in particular double-stranded DNA breaks) and genomic instability [47], studies of occupational exposures to X-radiation or γ-radiation, neutron radiation, or radionuclides emitting α- or β-particles have been largely negative. Limitations of these studies were that the studied cohorts were small and their exposures were much lower than those of atomic bomb survivors or women who underwent radiation therapy.

Occupational exposures occur when either handling radioactive materials or being exposed to natural sources of radiation at work. Aircraft personnel are exposed to natural sources of γ-radiation and neutrons, and underground miners to natural radionuclides emitting essentially α-particles. Workers handling radioactive materials or machinery can be exposed to several types of radiation; for example, healthcare workers are exposed in larger numbers to X-radiation, but some may be exposed to radionuclides emitting α- or β-particles, industrial radiographers are exposed to X-radiation, and nuclear energy or nuclear weapon workers are essentially exposed to γ-radiation and α- or β-particles [128]. In 2008, the United Nations Scientific Committee on Exposure to Atomic Radiation estimated that about 22.8 million workers were exposed to ionizing radiation, with 13 million exposed to natural sources and 9.8 million to artificial sources; medical workers are considered to constitute about two-thirds of exposed workers [129]. However, the annual occupational effective doses have been diminishing and were estimated to vary between 0.1 and 1.0 mSv per year in 2000–2002 for exposures to artificial sources, compared to 2.9 mSv per year for exposure to radon gas [129].

The IARC Working Group that assessed the available evidence of a relationship between breast cancer and occupational exposure to ionizing radiation (X-radiation and γ-radiation) among radiologists and radiology technicians remarked that increased risks appeared to be restricted to women exposed before the 1940s and to women who had been working for more than 30 years as certified radiology technicians [47]. A study of Chinese medical X-ray workers reported increased risks that were more elevated among women who began working before 1970 and before 30 years of age and those with more than 25 years of employment [84]. This particular pattern was also confirmed in a study of radiology technicians in the United States [85]. Indeed, studies of more recent cohorts have not shown evidence of increased risks at current exposure levels [24, 86, 130]. A recent review of epidemiological studies of medical radiation workers concluded that information on average annual exposure to occupational radiation, time trends in radia-

Table 22.5 Agents or exposure circumstances that have been associated with female breast cancer, but with insufficient evidence

Agents with some, but insufficient, evidence in humans			
Agents	Examples of industries/occupations	Range of risk ratios	References
X- and γ-radiation	Diagnostic radiology Nuclear medicine Industrial radiology Nuclear workers Uranium workers	0.9–5.3 (depending on cumulative exposure)	[84–93]
Organic solvents (including halogenated solvents), other chemicals	Painting Metal products fabrication Wood and furniture industry Printing and publishing Chemical industry Textile and clothing industry Electronics workers Laundry and dry cleaning Aircraft and automotive industries Gasoline service station workers Electronics workers Semiconductor plant workers Manufacturers of electronic capacitors and of electronic coils and transformers Printing machine operators and tenders	0.5–2.4 (depending on type of solvent and cumulative exposure)	[89, 94–107]
ELF-EMFs	Telephone and telegraph operators Electronic data processing operators Sewing machine operators, textile workers Denturists Machinists	1.0–4.6 (depending on cumulative exposure, age at first exposure, and tumor hormonal status)	[99, 108–112]
PAHs	Paving and roofing (with coal tar) Wood preservation with creosote Aluminum production and anode manufacturing Carbon electrode manufacturing Calcium carbide production Thermoelectric power plants Deep frying Traffic booth attendants	1.1–3.0 (depending on cumulative exposure, age at first exposure, and tumor hormonal status)	[96, 105]
Pharmaceutical drugs	Pharmaceutical workers	0.3–4.1	[99, 107, 113–115]
Several chemicals	Laboratory technicians, chemical workers	1.1–2.3	[106, 107, 116, 117]
Pesticides and agrochemicals, solvents, etc.	Farmers and farm workers	0.7–2.8	[106, 107, 110, 118]
EMFs, solvents, pigments, textile fibers	Working in textile and clothing	0.5–4.1	[89, 99, 106, 107, 119]
EMFs, cosmic radiations, shift work	Flight personnel	0.8–3.3	[120–124]
Organic solvents, EMFs, metals, welding fumes	Semiconductor and computer manufacturing industries	0.7–1.3	[102, 107, 125]
PAHs, EMFs, cleaning chemicals	Chefs and cooks	0.7–1.6	[99, 106, 107, 126]
Organic solvents, glues, etc.	Cosmetologists and manicurists	0.7–1.2	[89, 107, 127]

Abbreviations: *ELF-EMF* Extremely-Low-Frequency Electric and Magnetic Fields, *PAH* polycyclic aromatic hydrocarbons

tion exposure, and organ-specific doses was insufficient in most of the available studies to assess the lifetime cancer risk of these workers. The authors stressed the importance of conducting large-scale studies where individual cumulative occupational radiation dose estimates are used to assess dose–response relationships [131].

A cohort study of workers at a uranium production facility in the United States (primarily α-radiation) did not show any increased risk of breast cancer among exposed workers, and a small increase was observed among nonexposed workers. However, there were only five deaths and seven incident cases in the group of female workers exposed to radiation

[87]. A cohort study of French nuclear energy production workers reported a small increased risk of death due to breast cancer (standardized mortality ratio 1.14, 90 % CI 0.94–1.37) [88]. A recent case-control study showed a large increased risk (OR 5.3, 95 % CI 2.4–14.1) associated with exposure to ionizing radiation, but used rather crude exposure assessment methods (expert assessment based on occupational history) [89]. An analysis of the Canadian National Dose Registry did not show an excess risk of breast cancer in women with occupational exposure to ionizing radiation [132]. As exposure decreases over the years, risks are presumably being reduced and very large studies will be needed to detect excess risks.

Occupational Exposure to Hormones, Antineoplastic Drugs, or Other Pharmaceuticals

So far, a dozen pharmaceutical drugs have been classified as carcinogenic or probably carcinogenic to the female breast. Among these, diethylstilbestrol used during pregnancy, oral contraceptives or hormone replacement therapy containing estrogens only or estrogen-progestogen combinations [14], and several anti-neoplastic drugs [133] have been classified as carcinogenic (Group 1 agents) by the IARC. However, occupational exposures to these pharmaceuticals were not addressed in the corresponding issue of the IARC Monographs.

Additional data not considered by IARC are now available. Several studies among pharmaceutical workers reported evidence of elevated levels of urinary metabolites of antineoplastic drugs [133], or of effects linked to exposure to steroids (e.g., gynecomastia and loss of libido in men and menstrual problems in women) [134]. Elevated risks of breast cancer in the order of 1.5–2.9 were reported in a Danish record-linkage study [113] and in two of four cohort studies of pharmaceutical workers [135, 136]. Another well-designed cohort study reported a small increase in incidence among women in the highest exposure groups [114], whereas in the fourth cohort study, only mortality was assessed and there were too few deaths to draw conclusions (four breast cancer deaths) [115]. Thus, there are not enough data to draw conclusions about whether the fabrication or handling of pharmaceutical drugs is associated with an increased risk of breast cancer.

Other Occupational Exposures

The available evidence for other occupations or occupational exposures comes from studies that have varying levels of precision. Linkage studies combining records or registries have usually relied on occupation and/or industry titles, whereas other designs such as case-control or cohort studies have complemented job titles and industry with information on specific exposures gathered by questionnaires or derived from job-exposure matrices. During the last 10 years, few studies have been conducted on the role of occupational exposures in female breast cancer.

Organic Solvents and Aromatic Hydrocarbons

There is some evidence of increased breast cancer risk associated with exposures to several categories of organic solvents, including halogenated solvents [94, 95] and solvents that metabolize into reactive oxygen species [96]. Moreover, evidence derives from studies in which specific organic solvents could not be identified [97]. Industries and occupations that entail exposure to organic solvents have also been associated with increased breast cancer risk [98]: laundry and dry cleaning occupations; working in the aircraft and automotive industries, including service attendants at gasoline stations [99]; electronic workers and those in semiconductor plants [95]; manufacturers of electronic capacitors and electronic coils and transformers; and printing machine operators and tenders [100]. However, in some studies the risks were very low [101, 102] or even nonexistent, such as for styrene [103]. The relationship between exposures to solvents and breast cancer appears to be modulated by the hormonal receptor status of the tumor, as well as by age at first exposure [94–97].

Aromatic hydrocarbons are a large family of molecules containing at least one benzene ring (i.e., a 6-carbon structure with alternating double and single bonds between carbon atoms). Some of these are also considered organic solvents, and the simplest of these chemicals is benzene; aromatic hydrocarbons with one benzene ring are called monocyclic aromatic hydrocarbons (MAHs), whereas those with two or more fused benzene rings are referred to as polycyclic aromatic hydrocarbons (PAHs) [137]. PAHs derive from incomplete combustion of organic material, and their concentrations are influenced particularly by industrial and traffic-related sources [138]. Some PAHs are accepted carcinogens, while a few others are classified as probably or possibly carcinogenic to humans.

Exposure to benzene [104], to MAHs as a group [96], and to PAHs [105] has been associated with an increased incidence of about 30 %. The increased risk has been observed in both premenopausal [105] and postmenopausal women [96]. The effects of exposure to PAHs appear to be influenced by genetic susceptibility [139]. Aromatic amines, a subgroup of aromatic hydrocarbons often used as pigments, have also been found to be associated with an increased risk of breast cancer, with a clear exposure-response relationship [140], and with risk patterns that may differ according to the hormonal receptor status of the tumor [141]. Finally, a small risk has also been reported for exposure to soluble metalworking fluids [142].

Extremely-Low-Frequency Electric and Magnetic Fields

In 2000, a review of the literature concluded that occupational exposure to extremely-low-frequency electric and

magnetic fields (ELF-EMFs) could possibly be associated with female breast cancer [143]. However, in its 2002 monograph on nonionizing radiation, the IARC mentioned such a possible increased risk of breast cancer among men, without referring to female breast cancer. It was also pointed out that the available studies on women from the 1980s and early 1990s had presented methodological limitations, including lack of appropriate exposure measurements, and a possible publication bias toward those studies showing positive associations [144]. Moreover, Goodman and colleagues studied the effect of uncontrolled potential confounding factors in early studies of EMF exposure and concluded that they could account for an OR of about 1.2–1.3 [145].

More recent studies, including meta-analyses, do not support the hypothesis that exposure to EMFs increases the risk of female breast cancer [108, 146–148]. A large population-based case-control study showed a slight increase in risk [109], whereas another case-control study showed a fourfold increased risk among telephone and telegraph operators [110]. A few additional studies suggested a moderately increased risk for postmenopausal breast cancer in certain subgroups of women, such as those exposed before age 36 years and whose tumor was progesterone-positive [111], and premenopausal women with estrogen receptor-positive breast cancer associated with a long duration of high occupational exposure [112].

Pesticides, Polychlorinated Biphenyls, and Other Organochlorines

Results from most of the recent studies show either none, or only a very small increased risk of breast cancer [149, 150] after exposure to pesticides [151], polychlorinated biphenyls (PCBs), or other organochlorines [152–154]. However, one cohort study of chemical workers exposed to dioxins showed an increase of breast cancer mortality (standardized mortality ratio (SMR) = 1.86) based on 19 deaths, but no clear exposure-response pattern [155]. In a few recent papers, increased risks, especially with exposure to PCBs, were linked to certain polymorphisms, notably of cytochrome P-450 1A1 [149, 156] and GSTM1 [157]: it is possible that small increased risks of breast cancer do exist, but probably only in the presence of certain polymorphisms.

Specific Job Titles

The first mention of an "occupational" increased risk of breast cancer was probably published more than 300 years ago by Bernardino Ramazzini, who reported on increased occurrence of breast cancer among nuns, which he attributed to their celibate life, sensing a relationship with nulliparity [158]. Several clerical and professional occupations, such as those of administrators, teachers, librarians, journalists, inspectors, and others, have repeatedly been associated with an increased risk of incidence or mortality in different settings, often in studies based on routinely collected data [106, 107, 110, 126, 159–162]. The increased risk presented by these professional occupations has been ascribed by most authors to peculiar reproductive and other lifestyle factors and residual confounding associated with indicators of higher socioeconomic status that would be more frequent among women occupying these professions: high education level; having less children, at a later age; higher use of hormone replacement therapy; and higher alcohol consumption [106, 107, 126, 161–163].

Increased risks have also been reported, albeit inconsistently, for farming occupations [110, 118], textile and clothing workers [89, 107], leather and fur processors and glass-manufacturing workers [110], nurses [60], dentists [164], electricity power plant workers [165], semiconductor and computer manufacturing industries [102, 125], metal-working and automotive plastics manufacturing [166], and scientists [126]. However, similar occupations have also been associated with absence of risk, for example, the occupation of farm worker [107, 167, 168], garment worker [119], glass manufacturer [106], dentist [164], and cosmetologist and manicurist [127].

Air transport crews, particularly flight attendants, showed increased risks of female breast cancer in several studies in the Nordic countries and in the United States [169]. After adjusting for possible confounding by reproductive factors, a few studies still showed an increased risk [120, 121], although there were a few negative studies [122–124].

In summary, several high-quality studies have been conducted during the last 20 years, but our understanding of how occupational and environmental agents affect female breast cancer risk is still limited partly because of inconsistencies in the findings and partly because only a handful of potentially hazardous agents have been investigated. In many of the studies on specific industries or occupations, possible confounding due to lifestyle factors known to be associated with breast cancer (such as alcohol consumption, lower parity, and late age at first full-term pregnancy) was most often not taken into account, so that confounding could not be ruled out. Subtleties of the mechanistic relationships are difficult to capture in epidemiological analyses, because of difficulties in assessing past exposures, not knowing the ages at which women may be highly susceptible, and because effects may be restricted to a subset of women with specific genotypes.

Other Inconclusive Environmental Exposures

Cadmium and other heavy metals that have estrogenic activity in animal studies have been postulated to be associated with increased risks [170], but little human data are available [171].

A handful of studies, using rather crude estimates of exposure, suggested that exposure to traffic-related air pollution may be associated with increased breast cancer risk [172–174]. Using a more refined design, Crouse and colleagues

Table 22.6 Estimated proportions of female breast cancer attributable to occupation

Population	Occupational exposures considered	Attributable proportions (95 % confidence interval)	Comments	References
Finland	Ionizing radiation, hair dyes (hairdressers)	1.7	Proportion of attributable deaths by breast cancer	[191]
Great Britain	Shift work	4.6 (3.3–6.0)	Proportion of attributable deaths by breast cancer	[192]

[175] recently reported increased risks of postmenopausal breast cancer with exposure to traffic-related air pollution in Montreal, using a reliable marker of traffic-related air pollution and ground-level concentrations of nitrogen dioxide. Air pollution is composed of many chemicals that are also found in the workplace. Indeed, a few studies have shown associations between the incidence of breast cancer and occupational exposure to chemicals that are present in vehicular exhaust and thus in urban air pollution, such as benzene and PAHs [96, 104]. Should traffic-related air pollution prove to be a risk factor, a very large number of cases may be attributed to it, as exposure is ubiquitous in both working and nonworking populations.

Interaction Between Genetic Susceptibility and Various Exposures

The study of joint effects of genetic and environmental factors is crucial in understanding the etiology of breast cancer because it allows the identification of subgroups of women with specific genotypes who may be at higher risk after exposure to xenobiotics or whose risk may be reduced by other exposures [176]. These studies provide insights into mechanisms and can help to determine possible enzymes or proteins that can act on potential carcinogens [176]. For example, if null alleles are present in detoxification reactions (e.g., no enzyme synthesized), carcinogens or carcinogenic metabolites, especially lipophilic ones, may concentrate in adipose breast tissue.

A few gene-environment studies have reported that certain single-nucleotide polymorphisms (SNPs) involved in the biotransformation of xenobiotics are associated with increased breast cancer risk. Numerous polymorphisms of P-450 cytochromes have been identified, and further study of gene-environment interactions has been recommended [177]. Urinary concentrations of PAH metabolites were associated with certain polymorphisms of CYP1A1 and GSTP1 in a German study [178], but another case-control study did not find any association between occupation and CYP1A1*2 polymorphisms [179]. Elevated relative risks were found for high levels of plasma PCBs and CYP1A1 variants in case-control studies [156, 180] and in the Nurses' Health Study [181]. Results are inconsistent for active and passive smoking in relation to slow and rapid NAT2 acetylators [182–184] and with exposures to aromatic and heterocyclic amines [141]. Elevated risks were suggested for current alcohol consumption with certain glutathione S-transferase genotypes (null GSTM1, GSTT1, and GSTM3) [185–187], and there was an inverse association between breast cancer risk and frequency of alcohol consumption with alcohol dehydrogenase II polymorphism [188].

It has also been determined that carriers of two high-risk alleles, BRCA1 and BRCA2, show increased sensitivity to the effect of clastogens as measured by micronucleus formation [189]. Polymorphisms of p53, a protein involved in the regulation of the cell cycle and apoptosis, were associated with increased risks in association with exposures to ionizing radiation in the Carolina Breast Cancer Study [190].

In summary, several studies have shown that interactions between certain genetic variants and exposure to xenobiotics can affect the risk of breast cancer, but the findings still need to be replicated before any firm etiologic conclusion can be drawn.

Proportion of Female Breast Cancer Attributable to Occupation

A prerequisite for calculating the proportion of cancers that are attributable to occupational exposures is that a causal association has been firmly established. As of 2011, only two groups of researchers had published estimates of the burden of breast cancer attributable to occupational exposures. The first study included ionizing radiation and exposure to hair dyes among hairdressers and concluded that 1.7 % of breast cancer could be attributed to occupational exposures [191]. The second study considered only shift work and estimated that 4.6 % of female breast cancers could be attributed to occupational exposures [192] (see Table 22.6).

Male Breast Cancer

Descriptive Epidemiology

Male breast cancer is a very rare disease, with incidence rates varying from 5 to 15 per 1,000,000. Rates are higher in North America and Europe and extremely low in Asian populations. Indeed, female breast cancer incidence is 100 times higher than male breast cancer incidence, which represents less than 1 % of cancers affecting men worldwide [193]. Studies on the time trends of male breast cancer indicate that

its incidence is increasing in North America, the United Kingdom, Singapore, and possibly some African countries, mimicking time trends of female breast cancer, although on a much smaller scale. Conversely, in the Nordic countries and Switzerland, incidence has been stable over the last 40 years [194–196].

General Epidemiology and Lifestyle-Related Risk Factors

The etiology of male breast cancer is poorly understood. This may be due to the relative rarity of male breast cancer and, consequently, the scarcity of published studies. Genetic, hormonal, and environmental risk factors have been reported to be associated with male breast cancer risk. Family history of breast cancer has been associated with an increased risk of male breast cancer [27]. In particular, genetic susceptibilities related to male breast cancer include mutations in BRCA1, BRCA2, and possibly other genes (CYP17, AR gene, CHEK2) [197]. Klinefelter's syndrome and a few other rare disorders have also been associated with increased risk. Similarly, associations with education, religion, marital status, clinical disorders related to hormonal imbalance (e.g., infertility, testicular injury, gynecomastia), and estrogen intake are controversial. Hormonal imbalance appears to lend to an increased risk [193].

Among the environmental exposures studied, alcohol consumption and related liver cirrhosis, heavy tobacco smoking, and obesity were associated with increased male breast cancer risk in a few studies, but results were equivocal. There are an insufficient number of studies to allow any conclusions about the effect of exposure to ionizing radiation or electromagnetic fields on male breast cancer [193, 198–201]. So far, the IARC has not identified any carcinogens for male breast cancer.

Occupational Exposures

Some evidence of carcinogenicity to the male human breast has been gathered for Group 1 agents outside the occupational setting, e.g., alcoholic beverages [199] and X-radiation and γ-radiation [90, 202]. Some evidence of a relationship with occupational ionizing radiation exposure has also been reported [91].

Inconclusive Occupational Exposures

A few occupational exposures have been associated, albeit inconclusively, with male breast cancer [193, 197].

Extremely-Low-Frequency Electric and Magnetic Fields

In its 2002 monograph, the IARC Working Group on nonionizing radiation mentioned a possible increased risk of male breast cancer in association with ELF-EMFs. The committee also pointed out that the available studies from the 1980s and early 1990s presented methodological limitations, lack of appropriate exposure measurements, and a possible positive publication bias [144]. Since then very few studies have been published. A modest increased risk of male breast cancer (OR of 1.31) has been reported in men exposed to ELF-EMFs, but those exposed intermittently showed indications of an exposure-response trend, which led the authors to conclude that variations in exposure levels within work days could be associated with an increased risk [203]. Thus, the available evidence does not allow to draw firm conclusions on the effect of exposure to ELF-EMFs on male breast cancer risk.

Polycyclic Aromatic Hydrocarbons

The few epidemiological studies in which the relationship between exposure to PAHs and male breast cancer was investigated did not show consistent findings. In a record-linkage study, Hansen [204] reported a significantly increased risk among workers potentially exposed to combustion products (as a proxy for PAHs) when compared with other workers; the risk was particularly elevated for exposures starting before age 40 years [204]. However, in an Italian case-control study, no association was found between male breast cancer and occupational exposure to PAHs [205].

Heat

A few reviews mentioned that occupational exposure to high temperatures has been associated with increased risk of breast cancer in men, possibly because of testicular dysfunction resulting from high temperatures [193, 197]. However, these reviews refer to a small number of studies with a number of methodological limitations. Three small case-control studies (52, 91, and 71 cases) reported an increased risk for men "with occupations that involved heat exposure" [206–208], whereas a larger one reported that working in blast furnaces, steel works, and rolling and finishing mills (occupations with elevated heat exposures) conveyed a threefold increased risk of male breast cancer [205]. Nevertheless, several other carcinogens are also found in these workplaces and their potential confounding effects cannot be excluded.

Various Occupations

In 1842, Domenico Antonio Rigoni-Stern reported an increased occurrence of breast cancer among male priests, but his findings have not been confirmed in more recent studies [198, 209–211]. A cohort study of men exposed to ethylene oxide (a carcinogen linked to breast cancer in women) did not report the occurrence of breast cancer in the studied workers [212]. A large study carried out in the Nordic countries reported higher than expected standardized incidence rates among journalists, cooks, stewards, printers, artistic workers, and building caretakers [106]; the authors underline

that a common characteristic of these occupations is that they usually include shift work, which has been associated with increased breast cancer risk in women [79]. A significantly increased risk of dying from breast cancer has been reported in policemen [213] and in professional firefighters [214], but the incidence of breast cancer was not increased in the same cohort [215]. A recent European case-control study found a twofold increased risk, possibly due to petroleum and other organic solvents, especially among motor vehicle mechanics and painters. The risk was also increased for elevated exposure to alkylphenolic compounds, which are known endocrine-disrupting chemicals (OR 3.8, 95 % CI 1.5–9.5) [216]. One study reported a relationship between carrier status for BRCA1/2 mutations and the occupation of truck driver in male breast cancer risk [217].

Conclusion

In conclusion, a handful of occupational exposures have been linked, with reasonable evidence, to an increased risk of breast cancer in women, but none have yet been linked to male breast cancer. As the most common cancer among women, breast cancer represents an important burden on our societies. There are no certainties regarding the importance of occupational or environmental exposures in the etiology and development of breast cancer, but the fact that only about 30 % of the risk is explained by known risk factors [216] means that continuous research on the relationship between occupational exposures and breast cancer is warranted.

Breast cancer risk is obviously influenced by a number of hormonal factors and may thus be influenced by endocrine-disrupting agents. These exposures may be mediated by environmental determinants, such as lifestyle (hormone therapy, diet, alcohol consumption, smoking), work schedule (e.g., shift work), and various medical conditions. As the mammary gland passes through certain critical periods during development, adverse effects may necessitate exposure to carcinogens during the short window of time when the structures of the gland are sensitive. These toxicants could lead to an increase in the incidence of mammary tumors if they alter circulating or tissue-localized hormone levels. This could happen through mechanisms such as hormonal disruption, mutations in critical genes caused by alkylating carcinogens during key stages of development, or influences on hormone transport and receptor expression patterns.

While there are many critical periods during mammary gland development and a large array of potential toxicants which may be able to act as cancer-causing agents under some conditions in experimental models, there are not many that have been shown to do so in humans. However, it is ultimately the observations in humans that will dictate if what is possible from a theoretical point of view can happen in real-life situations. The issues involved, such as the possible interactions between potential risk factors, including critical exposures before complete maturation of the breast gland, and the great diversity of breast cancer itself, are very complex and challenging to study in humans.

The absence of specific molecular markers and genetic susceptibility tests hampers early identification of women and men who would be particularly susceptible to occupation-related breast cancer, but does not preclude preventive activities that are well known to the industrial hygiene field: anticipation of potential carcinogens, followed by their recognition, evaluation, communication, and control (elimination, substitution, and reduction of exposure) in the workplace.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893–917.
2. Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. Breast Cancer Res. 2007;9:R28.
3. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med. 2007;356:1670–4.
4. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973–1997. Int J Epidemiol. 2005;34:405–12.
5. Kelsey JL, Bernstein L. Epidemiology and prevention of breast cancer. Annu Rev Public Health. 1996;17:47–67.
6. Harris JR, Lippman ME, Veronesi U, Willett W. Breast cancer (1). N Engl J Med. 1992;327:319–28.
7. Byrne C, Harris A. Cancer rates and risks. 4th ed. Bethesda: US Department of Health and Human Services, National Institutes of Health; 1996.
8. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81:1879–86.
9. Rockhill B, Weinberg CR, Newman B. Population attributable fraction estimation for established breast cancer risk factors: considering the issues of high prevalence and unmodifiability. Am J Epidemiol. 1998;147:826–33.
10. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst. 1995;87:1681–5.
11. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol. 1985;122:904–14.
12. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002;360:187–95.
13. IARC. Monographs on the evaluation on carcinogenic risks to humans, Hormonal contraception and post-menopausal hormone therapy, vol. 72. Lyon: International Agency for Research on Cancer; 1999.

14. IARC. Monographs on the evaluation on carcinogenic risks to humans, Combined estrogen-progestogen contraceptives, vol. 91. Lyon: International Agency for Research on Cancer; 2007.
15. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2007.
16. Ewertz M. Hormone therapy in the menopause and breast cancer risk–a review. Maturitas. 1996;23:241–6.
17. IARC. IARC handbooks of cancer prevention, Weight control and physical activity, vol. 6. Lyon: International Agency for Research on Cancer; 2002.
18. IARC. IARC handbooks of cancer prevention, Fruit and vegetables, vol. 8. Lyon: International Agency for Research on Cancer; 2003.
19. El Ghissassi F, Baan R, Straif K, et al. A review of human carcinogens–part D: radiation. Lancet Oncol. 2009;10:751–2.
20. Hankinson S, Hunter D. Breast cancer. In: Hunter H, Trichopoulos D, Adami HO, editors. Textbook of cancer epidemiology. Oxford: Oxford University Press; 2002.
21. IARC. Monographs on the evaluation on carcinogenic risks to humans, A review of human carcinogens. Part A: pharmaceuticals, vol. 100. Lyon: International Agency for Research on Cancer; 2011.
22. Secretan B, Straif K, Baan R, et al. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009;10:1033–4.
23. Boice Jr JD, Monson RR. Breast cancer in women after repeated fluoroscopic examinations of the chest. J Natl Cancer Inst. 1977;59:823–32.
24. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers exposed to ionizing radiation in Korea. J Occup Environ Med. 2008;50:791–803.
25. Antoniou AC, Easton DF. Models of genetic susceptibility to breast cancer. Oncogene. 2006;25:5898–905.
26. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst. 1994;86:1600–8.
27. Slattery ML, Kerber RA. A comprehensive evaluation of family history and breast cancer risk. The Utah population database. JAMA. 1993;270:1563–8.
28. Mavaddat N, Antoniou AC, Easton DF, Garcia-Closas M. Genetic susceptibility to breast cancer. Mol Oncol. 2010;4:174–91.
29. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. PLoS Med. 2004;1:e65.
30. Kerber RA, O'Brien E. A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. Cancer. 2005;103:1906–15.
31. Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. Nat Genet. 2008;40:17–22.
32. Pharoah PD, Antoniou A, Bobrow M, Zimmern RL, Easton DF, Ponder BA. Polygenic susceptibility to breast cancer and implications for prevention. Nat Genet. 2002;31:33–6.
33. Rahman N, Seal S, Thompson D, et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet. 2007;39:165–7.
34. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature. 2007;447:1087–93.
35. Hunter DJ, Kraft P, Jacobs KB, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet. 2007;39:870–4.
36. Ahmed S, Thomas G, Ghoussaini M, et al. Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. Nat Genet. 2009;41:585–90.
37. Stacey SN, Manolescu A, Sulem P, et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet. 2008;40:703–6.
38. Thomas G, Jacobs KB, Kraft P, et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet. 2009;41:579–84.
39. Turnbull C, Ahmed S, Morrison J, et al. Genome-wide association study identifies five new breast cancer susceptibility loci. Nat Genet. 2010;42:504–7.
40. Zheng W, Long J, Gao YT, et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. Nat Genet. 2009;41:324–8.
41. Cox A, Dunning AM, Garcia-Closas M, et al. A common coding variant in CASP8 is associated with breast cancer risk. Nat Genet. 2007;39:352–8.
42. Milne RL, Benitez J, Nevanlinna H, et al. Risk of estrogen receptor-positive and -negative breast cancer and single-nucleotide polymorphism 2q35-rs13387042. J Natl Cancer Inst. 2009;101:1012–8.
43. Antoniou AC, Wang X, Fredericksen ZS, et al. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. Nat Genet. 2010;42:885–92.
44. Wacholder S, Hartge P, Prentice R, et al. Performance of common genetic variants in breast-cancer risk models. N Engl J Med. 2010;362:986–93.
45. IARC. Agents classified by the IARC monographs, volumes 1–102. Lyon: International Agency for Research on Cancer. Available at: http://monographs.iarc.fr/ENG/Classification/ClassificationsGroupOrder.pdf. Last update 17 Jun 2011.
46. IARC. Website of the IARC monographs on the evaluation of carcinogenic risks to humans. http://monographs.iarc.fr/. Accessed 5 Sept 2011.
47. IARC. Monographs on the evaluation on carcinogenic risks to humans, Ionizing radiation. Part 1: X and gamma (γ) radiation, and neutrons, vol. 75. Lyon: International Agency for Research on Cancer; 2000.
48. IARC. Monographs on the evaluation on carcinogenic risks to humans, 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide), vol. 97. Lyon: International Agency for Research on Cancer; 2008.
49. IARC. Monographs on the evaluation on carcinogenic risks to humans, Painting, firefighting and shiftwork, vol. 98. Lyon: International Agency for Research on Cancer; 2010.
50. Hagmar L, Mikoczy Z, Welinder H. Cancer incidence in Swedish sterilant workers exposed to ethylene oxide. Occup Environ Med. 1995;52:154–6.
51. Norman SA, Berlin JA, Soper KA, Middendorf BF, Stolley PD. Cancer incidence in a group of workers potentially exposed to ethylene oxide. Int J Epidemiol. 1995;24:276–84.
52. Steenland K, Whelan E, Deddens J, Stayner L, Ward E. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control. 2003;14:531–9.
53. Coggon D, Harris EC, Poole J, Palmer KT. Mortality of workers exposed to ethylene oxide: extended follow up of a British cohort. Occup Environ Med. 2004;61:358–62.
54. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Colditz GA. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. J Natl Cancer Inst. 2001;93:1563–8.
55. Schernhammer ES, Kroenke CH, Laden F, Hankinson SE. Night work and risk of breast cancer. Epidemiology. 2006;17:108–11.
56. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. Scand J Work Environ Health. 2007;33:336–43.

57. Pronk A, Ji BT, Shu XO, et al. Night-shift work and breast cancer risk in a cohort of Chinese women. Am J Epidemiol. 2010;171:953–9.
58. Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. Incidence of breast cancer in Norwegian female radio and telegraph operators. Cancer Causes Control. 1996;7:197–204.
59. Hansen J. Increased breast cancer risk among women who work predominantly at night. Epidemiology. 2001;12:74–7.
60. Lie JA, Roessink J, Kjaerheim K. Breast cancer and night work among Norwegian nurses. Cancer Causes Control. 2006;17:39–44.
61. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst. 2001;93:1557–62.
62. O'Leary ES, Schoenfeld ER, Stevens RG, et al. Shift work, light at night, and breast cancer on Long Island, New York. Am J Epidemiol. 2006;164:358–66.
63. Pesch B, Harth V, Rabstein S, et al. Night work and breast cancer – results from the German GENICA study. Scand J Work Environ Health. 2010;36:134–41.
64. NTP. Report on carcinogens. 12th ed. Research Triangle Park: US Department of Health and Human Services, Public Health Service, National Toxicology Program; 2011.
65. Occupational Safety and Health Commission. Regulatory review of the occupational safety and health administration's ethylene oxide standard. Washington, DC: OSHA; 2005.
66. Kauppinen T, Toikkanen J, Pedersen D, et al. Occupational exposure to carcinogens in the European union. Occup Environ Med. 2000;57:10–8.
67. Grosse Y, Baan R, Straif K, et al. Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. Lancet Oncol. 2007;8:679–80.
68. Grosswald B. The effects of shiftwork on family satisfaction. Families in society. J Contemp Soc Serv. 2004;85:413–23.
69. Costa G, Haus E, Stevens R. Shift work and cancer – considerations on rationale, mechanisms, and epidemiology. Scand J Work Environ Health. 2010;36:163–79.
70. Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES. Night work and breast cancer risk: a systematic review and meta-analysis. Eur J Cancer. 2005;41:2023–32.
71. Brainard GC, Sliney D, Hanifin JP, et al. Sensitivity of the human circadian system to short-wavelength (420-nm) light. J Biol Rhythms. 2008;23:379–86.
72. Stevens RG, Hansen J, Costa G, et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC working group report. Occup Environ Med. 2011;68:154–62.
73. Parent-Thirion A, Fernandez Macias E, Huntly J, Vermeylen G. Fourth European working conditions survey. Luxembourg: Office for Official Publications of the European Communities; 2007.
74. McMenamin TM. A time to work: recent trends in shift work and flexible schedules. Mon Labor Rev. 2007;130:3–15.
75. Stevens RG. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. Int J Epidemiol. 2009;38:963–70.
76. Schernhammer ES, Hankinson SE. Urinary melatonin levels and breast cancer risk. J Natl Cancer Inst. 2005;97:1084–7.
77. Schernhammer ES, Rosner B, Willett WC, Laden F, Colditz GA, Hankinson SE. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. Cancer Epidemiol Biomarkers Prev. 2004;13:936–43.
78. Travis RC, Allen DS, Fentiman IS, Key TJ. Melatonin and breast cancer: a prospective study. J Natl Cancer Inst. 2004;96:475–82.
79. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. Lancet Oncol. 2007;8:1065–6.
80. Girschik J, Heyworth J, Fritschi L. Re: "Night-shift work and breast cancer risk in a cohort of Chinese women". Am J Epidemiol. 2010;172:865–6.
81. Menegaux F, Truong T, Anger A, et al. Night work and breast cancer: a population-based case-control study in France (the CECILE study). Int J Cancer. 2013;132:924–31.
82. Hansen J, Lassen CF. Nested case-control study of night shift work and breast cancer risk among women in the Danish military. Occup Environ Med. 2012;69:551–6.
83. Schernhammer ES, Hankinson SE. Urinary melatonin levels and postmenopausal breast cancer risk in the nurses' health study cohort. Cancer Epidemiol Biomarkers Prev. 2009;18:74–9.
84. Wang JX, Zhang LA, Li BX, Zhao YC, Wang ZQ, Zhang JY, Aoyama T. Cancer incidence and risk estimation among medical x-ray workers in China, 1950-1995. Health Phys. 2002;82:455–66.
85. Doody MM, Freedman DM, Alexander BH, et al. Breast cancer incidence in U.S. radiologic technologists. Cancer. 2006;106:2707–15.
86. Linet MS, Hauptmann M, Freedman DM, Alexander BH, Miller J, Sigurdson AJ, Doody MM. Interventional radiography and mortality risks in U.S. radiologic technologists. Pediatr Radiol. 2006;36 Suppl 2:113–20.
87. McGeoghegan D, Binks K. The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946–95. J Radiol Prot. 2000;20:111–37.
88. Telle-Lamberton M, Bergot D, Gagneau M, Samson E, Giraud JM, Neron MO, Hubert P. Cancer mortality among French atomic energy commission workers. Am J Ind Med. 2004;45:34–44.
89. Shaham J, Gurvich R, Goral A, Czerniak A. The risk of breast cancer in relation to health habits and occupational exposures. Am J Ind Med. 2006;49:1021–30.
90. Sont WN, Zielinski JM, Ashmore JP, et al. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. Am J Epidemiol. 2001; 153:309–18.
91. Ashmore JP, Krewski D, Zielinski JM, Jiang H, Semenciw R, Band PR. First analysis of mortality and occupational radiation exposure based on the National Dose Registry of Canada. Am J Epidemiol. 1998;148:564–74.
92. McGeoghegan D, Binks K. The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946–95. J Radiol Prot. 2000;20:381–401.
93. McGeoghegan D, Gillies M, Riddell AE, Binks K. Mortality and cancer morbidity experience of female workers at the British nuclear fuels sellafield plant, 1946–1998. Am J Ind Med. 2003;44:653–63.
94. Rennix CP, Quinn MM, Amoroso PJ, Eisen EA, Wegman DH. Risk of breast cancer among enlisted army women occupationally exposed to volatile organic compounds. Am J Ind Med.2005;48:157–67.
95. Sung TI, Chen PC, Jyuhn-Hsiarn LL, Lin YP, Hsieh GY, Wang JD. Increased standardized incidence ratio of breast cancer in female electronics workers. BMC Public Health. 2007;7:102.
96. Labreche F, Goldberg MS, Valois MF, Nadon L. Postmenopausal breast cancer and occupational exposures. Occup Environ Med. 2010;67:263–9.
97. Peplonska B, Stewart P, Szeszenia-Dabrowska N, et al. Occupational exposure to organic solvents and breast cancer in women. Occup Environ Med. 2010;67:722–9.
98. Hansen J. Breast cancer risk among relatively young women employed in solvent-using industries. Am J Ind Med. 1999;36: 43–7.
99. Band PR, Le ND, Fang R, Deschamps M, Gallagher RP, Yang P. Identification of occupational cancer risks in British Columbia. A population-based case-control study of 995 incident breast cancer cases by menopausal status, controlling for confounding factors. J Occup Environ Med. 2000;42:284–310.
100. Peplonska B, Stewart P, Szeszenia-Dabrowska N, et al. Occupation and breast cancer risk in Polish women: a population-based case-control study. Am J Ind Med. 2007;50:97–111.
101. Chang YM, Tai CF, Yang SC, Chen CJ, Shih TS, Lin RS, Liou SH. A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan. Ann Epidemiol. 2003;13: 652–60.

102. McElvenny DM, Darnton AJ, Hodgson JT, Clarke SD, Elliott RC, Osman J. Investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility. Occup Med (Lond). 2003;53:419–30.
103. Boffetta P, Adami HO, Cole P, Trichopoulos D, Mandel JS. Epidemiologic studies of styrene and cancer: a review of the literature. J Occup Environ Med. 2009;51:1275–87.
104. Costantini AS, Gorini G, Consonni D, Miligi L, Giovannetti L, Quinn M. Exposure to benzene and risk of breast cancer among shoe factory workers in Italy. Tumori. 2009;95:8–12.
105. Petralia SA, Vena JE, Freudenheim JL, et al. Risk of premenopausal breast cancer in association with occupational exposure to polycyclic aromatic hydrocarbons and benzene. Scand J Work Environ Health. 1999;25:215–21.
106. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48:646–790.
107. Villeneuve S, Fevotte J, Anger A, et al. Breast cancer risk by occupation and industry: analysis of the CECILE study, a population-based case-control study in France. Am J Ind Med. 2011;54:499–509.
108. Forssen UM, Rutqvist LE, Ahlbom A, Feychting M. Occupational magnetic fields and female breast cancer: a case-control study using Swedish population registers and new exposure data. Am J Epidemiol. 2005;161:250–9.
109. McElroy JA, Egan KM, Titus-Ernstoff L, Anderson HA, Trentham-Dietz A, Hampton JM, Newcomb PA. Occupational exposure to electromagnetic field and breast cancer risk in a large, population-based, case-control study in the United States. J Occup Environ Med. 2007;49:266–74.
110. Gardner KM, Ou SX, Jin F, et al. Occupations and breast cancer risk among Chinese women in urban Shanghai. Am J Ind Med. 2002;42:296–308.
111. Labreche F, Goldberg MS, Valois MF, Nadon L, Richardson L, Lakhani R, Latreille B. Occupational exposures to extremely low frequency magnetic fields and postmenopausal breast cancer. Am J Ind Med. 2003;44:643–52.
112. Van Wijngaarden E, Nylander-French LA, Millikan RC, Savitz DA, Loomis D. Population-based case-control study of occupational exposure to electromagnetic fields and breast cancer. Ann Epidemiol. 2001;11:297–303.
113. Hansen J, Olsen JH, Larsen AI. Cancer morbidity among employees in a Danish pharmaceutical plant. Int J Epidemiol. 1994;23:891–8.
114. Edling C, Friis L, Mikoczy Z, Hagmar L, Lindfors P. Cancer incidence among pharmaceutical workers. Scand J Work Environ Health. 1995;21:116–23.
115. Harrington JM, Goldblatt P. Census based mortality study of pharmaceutical industry workers. Br J Ind Med. 1986;43:206–11.
116. Hansen J, Olsen JH. Cancer morbidity among Danish female pharmacy technicians. Scand J Work Environ Health. 1994;20:22–6.
117. Shaham J, Gurvich R, Kneshet Y. Cancer incidence among laboratory workers in biomedical research and routine laboratories in Israel: part II-nested case-control study. Am J Ind Med. 2003;44:611–26.
118. Brophy JT, Keith MM, Gorey KM, et al. Occupation and breast cancer: a Canadian case-control study. Ann N Y Acad Sci. 2006;1076:765–77.
119. Pinkerton LE, Hein MJ, Stayner LT. Mortality among a cohort of garment workers exposed to formaldehyde: an update. Occup Environ Med. 2004;61:193–200.
120. Rafnsson V, Sulem P, Tulinius H, Hrafnkelsson J. Breast cancer risk in airline cabin attendants: a nested case-control study in Iceland. Occup Environ Med. 2003;60:807–9.
121. Linnersjo A, Hammar N, Dammstrom BG, Johansson M, Eliasch H. Cancer incidence in airline cabin crew: experience from Sweden. Occup Environ Med. 2003;60:810–4.
122. Haldorsen T, Reitan JB, Tveten U. Cancer incidence among Norwegian airline cabin attendants. Int J Epidemiol. 2001;30:825–30.
123. Zeeb H, Blettner M, Langner I, et al. Mortality from cancer and other causes among airline cabin attendants in Europe: a collaborative cohort study in eight countries. Am J Epidemiol. 2003;158:35–46.
124. Kojo K, Pukkala E, Auvinen A. Breast cancer risk among Finnish cabin attendants: a nested case-control study. Occup Environ Med. 2005;62:488–93.
125. Clapp RW, Hoffman K. Cancer mortality in IBM Endicott plant workers, 1969–2001: an update on a NY production plant. Environ Health. 2008;7:13.
126. MacArthur AC, Le ND, Abanto ZU, Gallagher RP. Occupational female breast and reproductive cancer mortality in British Columbia, Canada, 1950–94. Occup Med (Lond). 2007;57:246–53.
127. Quach T, Doan-Billing PA, Layefsky M, et al. Cancer incidence in female cosmetologists and manicurists in California, 1988–2005. Am J Epidemiol. 2010;172:691–9.
128. IARC. Monographs on the evaluation on carcinogenic risks to humans, A review of human carcinogens. Part D: radiation, vol. 100. Lyon: International Agency for Research on Cancer; 2012.
129. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. UNSCEAR 2008 report to the general assembly with scientific annexes, vo. 1. New York: United Nations; 2010.
130. Yoshinaga S, Mabuchi K, Sigurdson AJ, Doody MM, Ron E. Cancer risks among radiologists and radiologic technologists: review of epidemiologic studies. Radiology. 2004;233:313–21.
131. Linet MS, Kim KP, Miller DL, Kleinerman RA, Simon SL, Berrington de Gonzalez A. Historical review of occupational exposures and cancer risks in medical radiation workers. Radiat Res. 2010;174:793–808.
132. Sont WN, Zielinski JM, Ashmore JP, et al. Sont et al. Respond to "studies of workers exposed to low doses of radiation". Am J Epidemiol. 2001;153:323–4.
133. Connor TH, McDiarmid MA. Preventing occupational exposures to antineoplastic drugs in health care settings. CA Cancer J Clin. 2006;56:354–65.
134. Heron RJ, Pickering FC. Health effects of exposure to Active Pharmaceutical Ingredients (APIs). Occup Med (Lond). 2003;53:357–62.
135. Thomas TL, Decoufle P. Mortality among workers employed in the pharmaceutical industry: a preliminary investigation. J Occup Med. 1979;21:619–23.
136. Baker CC, Russell RA, Roder DM, Esterman AJ. A nine year retrospective mortality study of workers in a British pharmaceutical company. J Soc Occup Med. 1986;36:95–8.
137. IARC. Monographs on the evaluation on carcinogenic risks to humans, Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures, vol. 92. Lyon: International Agency for Research on Cancer; 2010.
138. Straif K, Baan R, Grosse Y, Secretan B, El GF, Cogliano V. Carcinogenicity of polycyclic aromatic hydrocarbons. Lancet Oncol. 2005;6:931–2.
139. Jeffy BD, Chirnomas RB, Romagnolo DF. Epigenetics of breast cancer: polycyclic aromatic hydrocarbons as risk factors. Environ Mol Mutagen. 2002;39:235–44.
140. de Vocht F, Sobala W, Wilczynska U, Kromhout H, Szeszenia-Dabrowska N, Peplonska B. Cancer mortality and occupational exposure to aromatic amines and inhalable aerosols in rubber tire manufacturing in Poland. Cancer Epidemiol. 2009;33:94–102.
141. Rabstein S, Bruning T, Harth V, et al. N-acetyltransferase 2, exposure to aromatic and heterocyclic amines, and receptor-defined breast cancer. Eur J Cancer Prev. 2010;19:100–9.
142. Thompson D, Kriebel D, Quinn MM, Wegman DH, Eisen EA. Occupational exposure to metalworking fluids and risk of breast cancer among female autoworkers. Am J Ind Med. 2005;47:153–60.

143. Caplan LS, Schoenfeld ER, O'Leary ES, Leske MC. Breast cancer and electromagnetic fields–a review. Ann Epidemiol. 2000;10: 31–44.
144. IARC. Monographs on the evaluation on carcinogenic risks to humans, Non-ionizing radiation. Part 1: static and Extremely Low-Frequency (ELF) electric and magnetic fields, vol. 80. Lyon: International Agency for Research on Cancer; 2002.
145. Goodman M, Kelsh M, Ebi K, Iannuzzi J, Langholz B. Evaluation of potential confounders in planning a study of occupational magnetic field exposure and female breast cancer. Epidemiology. 2002;13:50–8.
146. Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A. Review of the epidemiologic literature on EMF and Health. Environ Health Perspect. 2001;109 Suppl 6:911–33.
147. Johansen C. Electromagnetic fields and health effects–epidemiologic studies of cancer, diseases of the central nervous system and arrhythmia-related heart disease. Scand J Work Environ Health. 2004;30 Suppl 1:1–30.
148. Feychting M, Forssen U. Electromagnetic fields and female breast cancer. Cancer Causes Control. 2006;17:553–8.
149. Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. Environmental pollutants and breast cancer: epidemiologic studies. Cancer. 2007;109 Suppl 12:2667–711.
150. Silver SR, Whelan EA, Deddens JA, et al. Occupational exposure to polychlorinated biphenyls and risk of breast cancer. Environ Health Perspect. 2009;117:276–82.
151. Engel LS, Hill DA, Hoppin JA, et al. Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. Am J Epidemiol. 2005;161:121–35.
152. Ward EM, Schulte P, Grajewski B, et al. Serum organochlorine levels and breast cancer: a nested case-control study of Norwegian women. Cancer Epidemiol Biomarkers Prev. 2000;9: 1357–67.
153. Rusiecki JA, Holford TR, Zahm SH, Zheng T. Polychlorinated biphenyls and breast cancer risk by combined estrogen and progesterone receptor status. Eur J Epidemiol. 2004;19:793–801.
154. Salehi F, Turner MC, Phillips KP, Wigle DT, Krewski D, Aronson KJ. Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors. J Toxicol Environ Health B Crit Rev. 2008;11:276–300.
155. Manuwald U, Velasco GM, Berger J, Manz A, Baur X. Mortality study of chemical workers exposed to dioxins: follow-up 23 years after chemical plant closure. Occup Environ Med. 2012;69: 636–42.
156. Zhang Y, Wise JP, Holford TR, et al. Serum polychlorinated biphenyls, cytochrome P-450 1A1 polymorphisms, and risk of breast cancer in Connecticut women. Am J Epidemiol. 2004;160:1177–83.
157. McCready D, Aronson KJ, Chu W, Fan W, Vesprini D, Narod SA. Breast tissue organochlorine levels and metabolic genotypes in relation to breast cancer risk Canada. Cancer Causes Control. 2004;15:399–418.
158. Franco G. Bernardino Ramazzini and women workers' health in the second half of the XVIIth century. J Public Health (Oxf). 2012;34:305–8.
159. Goldberg MS, Labreche F. Occupational risk factors for female breast cancer: a review. Occup Environ Med. 1996;53:145–56.
160. Carpenter L, Roman E. Cancer and occupation in women: identifying associations using routinely collected national data. Environ Health Perspect. 1999;107 Suppl 2:299–303.
161. Bernstein L, Allen M, Anton-Culver H, et al. High breast cancer incidence rates among California teachers: results from the California teachers study (United States). Cancer Causes Control. 2002;13:625–35.
162. Teitelbaum SL, Britton JA, Gammon MD, et al. Occupation and breast cancer in women 20–44 years of age (United States). Cancer Causes Control. 2003;14:627–37.
163. Larsen SB, Olsen A, Lynch J, et al. Socioeconomic position and lifestyle in relation to breast cancer incidence among postmenopausal women: a prospective cohort study, Denmark, 1993–2006. Cancer Epidemiol. 2011;35:438–41.
164. Simning A, Van WE. Literature review of cancer mortality and incidence among dentists. Occup Environ Med. 2007;64:432–8.
165. Nichols L, Sorahan T. Mortality of UK electricity generation and transmission workers, 1973–2002. Occup Med (Lond). 2005;55:541–8.
166. Brophy JT, Keith MM, Watterson A, et al. Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: a Canadian case-control study. Environ Health. 2012;11:87.
167. Colt JS, Stallones L, Cameron LL, Dosemeci M, Zahm SH. Proportionate mortality among US migrant and seasonal farmworkers in twenty-four states. Am J Ind Med. 2001;40:604–11.
168. Nanni O, Ravaioli A, Bucchi L, Falcini F, Ricci R, Buiatti E, Amadori D. Relative and absolute cancer mortality of women in agriculture in Northern Italy. Eur J Cancer Prev. 2005;14: 337–444.
169. Whelan EA. Cancer incidence in airline cabin crew. Occup Environ Med. 2003;60:805–6.
170. Coyle YM. The effect of environment on breast cancer risk. Breast Cancer Res Treat. 2004;84:273–88.
171. McElroy JA, Shafer MM, Trentham-Dietz A, Hampton JM, Newcomb PA. Cadmium exposure and breast cancer risk. J Natl Cancer Inst. 2006;98:869–73.
172. Lewis-Michl EL, Melius JM, Kallenbach LR, Ju CL, Talbot TO, Orr MF, Lauridsen PE. Breast cancer risk and residence near industry or traffic in Nassau and Suffolk Counties, Long Island, New York. Arch Environ Health. 1996;51:255–65.
173. Bonner MR, Han D, Nie J, et al. Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. Cancer Epidemiol Biomarkers Prev. 2005;14:53–60.
174. Nie J, Beyea J, Bonner MR, et al. Exposure to traffic emissions throughout life and risk of breast cancer: the Western New York Exposures and Breast Cancer (WEB) study. Cancer Causes Control. 2007;18:947–55.
175. Crouse DL, Goldberg MS, Ross NA, Chen H, Labreche F. Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case-control study. Environ Health Perspect. 2010;118:1578–83.
176. Rothman N, Wacholder S, Caporaso NE, Garcia-Closas M, Buetow K, Fraumeni Jr JF. The use of common genetic polymorphisms to enhance the epidemiologic study of environmental carcinogens. Biochim Biophys Acta. 2001;1471:C1–10.
177. Masson LF, Sharp L, Cotton SC, Little J. Cytochrome P-450 1A1 gene polymorphisms and risk of breast cancer: a HuGE review. Am J Epidemiol. 2005;161:901–15.
178. Rihs HP, Pesch B, Kappler M, et al. Occupational exposure to polycyclic aromatic hydrocarbons in German industries: association between exogenous exposure and urinary metabolites and its modulation by enzyme polymorphisms. Toxicol Lett. 2005;157:241–55.
179. Surekha D, Sailaja K, Rao DN, Padma T, Raghunadharao D, Vishnupriya S. Association of CYP1A1*2 polymorphisms with breast cancer risk: a case control study. Indian J Med Sci. 2009;63:13–20.
180. Moysich KB, Shields PG, Freudenheim JL, et al. Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev. 1999;8:41–4.
181. Laden F, Ishibe N, Hankinson SE, Wolff MS, Gertig DM, Hunter DJ, Kelsey KT. Polychlorinated biphenyls, cytochrome P450 1A1, and breast cancer risk in the nurses' health study. Cancer Epidemiol Biomarkers Prev. 2002;11:1560–5.
182. Chang-Claude J, Kropp S, Jager B, Bartsch H, Risch A. Differential effect of NAT2 on the association between active and

passive smoke exposure and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2002;11:698–704.
183. Terry PD, Goodman M. Is the association between cigarette smoking and breast cancer modified by genotype? A review of epidemiologic studies and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15:602–11.
184. Conlon MS, Johnson KC, Bewick MA, Lafrenie RM, Donner A. Smoking (active and passive), N-acetyltransferase 2, and risk of breast cancer. Cancer Epidemiol. 2010;34:142–9.
185. Mitrunen K, Jourenkova N, Kataja V, et al. Glutathione S-transferase M1, M3, P1, and T1 genetic polymorphisms and susceptibility to breast cancer. Cancer Epidemiol Biomarkers Prev. 2001;10:229–36.
186. Park SK, Yoo KY, Lee SJ, et al. Alcohol consumption, glutathione S-transferase M1 and T1 genetic polymorphisms and breast cancer risk. Pharmacogenetics. 2000;10:301–9.
187. Helzlsouer KJ, Selmin O, Huang HY, et al. Association between glutathione S-transferase M1, P1, and T1 genetic polymorphisms and development of breast cancer. J Natl Cancer Inst. 1998;90:512–8.
188. Sturmer T, Wang-Gohrke S, Arndt V, Boeing H, Kong X, Kreienberg R, Brenner H. Interaction between alcohol dehydrogenase II gene, alcohol consumption, and risk for breast cancer. Br J Cancer. 2002;87:519–23.
189. Iarmarcovai G, Bonassi S, Botta A, Baan RA, Orsiere T. Genetic polymorphisms and micronucleus formation: a review of the literature. Mutat Res. 2008;658:215–33.
190. Furberg H, Millikan RC, Geradts J, Gammon MD, Dressler LG, Ambrosone CB, Newman B. Environmental factors in relation to breast cancer characterized by p53 protein expression. Cancer Epidemiol Biomarkers Prev. 2002;11:829–35.
191. Nurminen M, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. Scand J Work Environ Health. 2001;27:161–213.
192. Rushton L, Bagga S, Bevan R, et al. Occupation and cancer in Britain. Br J Cancer. 2010;102:1428–37.
193. Ottini L, Palli D, Rizzo S, Federico M, Bazan V, Russo A. Male breast cancer. Crit Rev Oncol Hematol. 2010;73:141–55.
194. Stang A, Thomssen C. Decline in breast cancer incidence in the United States: what about male breast cancer? Breast Cancer Res Treat. 2008;112:595–6.
195. Contractor KB, Kaur K, Rodrigues GS, Kulkarni DM, Singhal H. Male breast cancer: is the scenario changing. World J Surg Oncol. 2008;6:58.
196. Miao H, Verkooijen H, Chia KS, et al. Incidence and outcome of male breast cancer: an international population-based study. J Clin Oncol. 2011;29:4381–6.
197. Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. Cancer Epidemiol Biomarkers Prev. 2005;14:20–6.
198. Ewertz M, Holmberg L, Tretli S, Pedersen BV, Kristensen A. Risk factors for male breast cancer–a case-control study from Scandinavia. Acta Oncol. 2001;40:467–71.
199. Guenel P, Cyr D, Sabroe S, et al. Alcohol drinking may increase risk of breast cancer in men: a European population-based case-control study. Cancer Causes Control. 2004;15:571–80.
200. Lynge E, Afonso N, Kaerlev L, et al. European multi-centre case-control study on risk factors for rare cancers of unknown aetiology. Eur J Cancer. 2005;41:601–12.
201. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet. 2006;367:595–604.
202. Thomas DB, Rosenblatt K, Jimenez LM, et al. Ionizing radiation and breast cancer in men (United States). Cancer Causes Control. 1994;5:9–14.
203. Pollan M, Gustavsson P, Floderus B. Breast cancer, occupation, and exposure to electromagnetic fields among Swedish men. Am J Ind Med. 2001;39:276–85.
204. Hansen J. Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. Am J Ind Med. 2000;37:349–52.
205. Cocco P, Figgs L, Dosemeci M, Hayes R, Linet MS, Hsing AW. Case-control study of occupational exposures and male breast cancer. Occup Environ Med. 1998;55:599–604.
206. Mabuchi K, Bross DS, Kessler II. Risk factors for male breast cancer. J Natl Cancer Inst. 1985;74:371–5.
207. Lenfant-Pejovic MH, Mlika-Cabanne N, Bouchardy C, Auquier A. Risk factors for male breast cancer: a Franco-Swiss case-control study. Int J Cancer. 1990;45:661–5.
208. Rosenbaum PF, Vena JE, Zielezny MA, Michalek AM. Occupational exposures associated with male breast cancer. Am J Epidemiol. 1994;139:30–6.
209. Kaplan SD. Retrospective cohort mortality study of Roman Catholic priests. Prev Med. 1988;17:335–43.
210. Rigoni S. Statistical facts about cancers on which Doctor Rigoni-Stern based his contribution to the Surgeons' Subgroup of the IV Congress of the Italian Scientists on 23 September 1842. Stat Med. 1987;6:881–4. translation.
211. Fritschi L, Guenel P, Ahrens W. Breast cancer in priests: follow-up of an observation made 167 years ago. Eur J Epidemiol. 2010;25:219–21.
212. Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM. Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J Occup Environ Med. 2009;51:714–23.
213. Wirth M, Vena JE, Smith EK, Bauer SE, Violanti J, Burch J. The epidemiology of cancer among police officers. Am J Ind Med. 2013;56:439–53.
214. Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA, Lai H, Lai S. Mortality in Florida professional firefighters, 1972 to 1999. Am J Ind Med. 2005;47:509–17.
215. Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA. Cancer incidence in Florida professional firefighters, 1981 to 1999. J Occup Environ Med. 2006;48:883–8.
216. Villeneuve S, Cyr D, Lynge E, et al. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe. Occup Environ Med. 2010;67:837–44.
217. Palli D, Masala G, Mariani-Costantini R, et al. A gene-environment interaction between occupation and BRCA1/BRCA2 mutations in male breast cancer? Eur J Cancer. 2004;40:2474–9.

Malignant Tumors of the Female Reproductive System

23

Elisabete Weiderpass and France Labrèche

Keywords
Cervix • Endometrial cancer • Ovarian cancer • Vulva • Vagina • Fallopian tube • Women • Cervical cancer • Asbestos • Occupational exposures • Tetrachloroethylene

Descriptive Epidemiology

Cancers of the female reproductive system – namely, cancer of the cervix uteri (cervical cancer); cancer of the corpus uteri (which includes mostly adenocarcinomas originating in the endometrium and some other rarer cancers, such as sarcomas); ovarian, vulvar, vaginal, and fallopian tube cancers; and choriocarcinoma – are an important cause of cancer morbidity and mortality worldwide. Cervical, endometrial, and ovarian cancers are relatively common (Fig. 23.1), while the other cancers of the female reproductive system are very rare.

Cervical cancer is the third most common cancer in women worldwide, behind breast and colorectal cancers, and the seventh most common cancer overall, with an estimated 530,232 new cases in 2008 (Table 23.1). More than 85 % of the global burden occurs in less developed regions (Fig. 23.2), where it accounts for 13 % of all cancers in women. Cervical cancer remains the most common female cancer in Eastern Africa, South-Central Asia, and Melanesia. Incidence is high in Eastern and Western Africa (standardized incidence rates greater than 30 new cases per 100,000 women), Southern Africa (26.8 per 100,000), South-Central Asia (24.6 per 100,000), and South America, Melanesia, and Central Africa (between 23.9 and 23.0 new cases per 100,000 women). Rates are lowest in Western Asia, North America, and Australia/New Zealand (less than 6 per 100,000). The overall mortality to incidence ratio of cervical cancer is 52 %; it was responsible for 275,000 deaths in 2008, about 88 % of which occurred in less developed regions: 53,000 in Africa (standardized mortality rate of 17.6 deaths per 100,000 women), 31,700 in Latin America and the Caribbean (10.8 deaths per 100,000 women), and 159,800 in Asia (7.9 deaths per 100,000 women) (Fig. 23.3).

Endometrial cancer is the sixth most common cancer in women, with an estimated 288,387 new cases in 2008, and a standardized incidence rate of 8.2 per 100,000 women (Table 23.1). While the global burden in terms of number of cases is evenly distributed between less developed and more developed regions (Fig. 23.3a), incidence and mortality are higher in more developed regions (Fig. 23.3b). North America and Western Europe show some of the highest standardized incidence rates (more than 10 new cases per 100,000 women), with the lowest rates occurring in Asia and Africa (less than 10 per 100,000) [1]. Overall, the mortality to incidence ratio of endometrial cancer is 26 %, and it was responsible for 73,854 deaths in 2008. This relatively low ratio is probably due to the fact that symptoms of endometrial cancer are easily recognizable (consisting of postmenopausal bleeding in the majority of cases), and the cure rate is high when surgical treatment is performed during the early stages of the disease.

E. Weiderpass, MD, MSc, PhD (✉)
Cancer Registry of Norway, Oslo, Norway

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway

Department of Genetic Epidemiology, Folkhälsan Research Center, Helsinki, Finland
e-mail: elisabete.weiderpass@ki.se

F. Labrèche, PhD
Département de Santé environnementale et santé au travail, École de santé publique, Université de Montréal, Montreal, QC, Canada

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_23, © Springer-Verlag London 2014

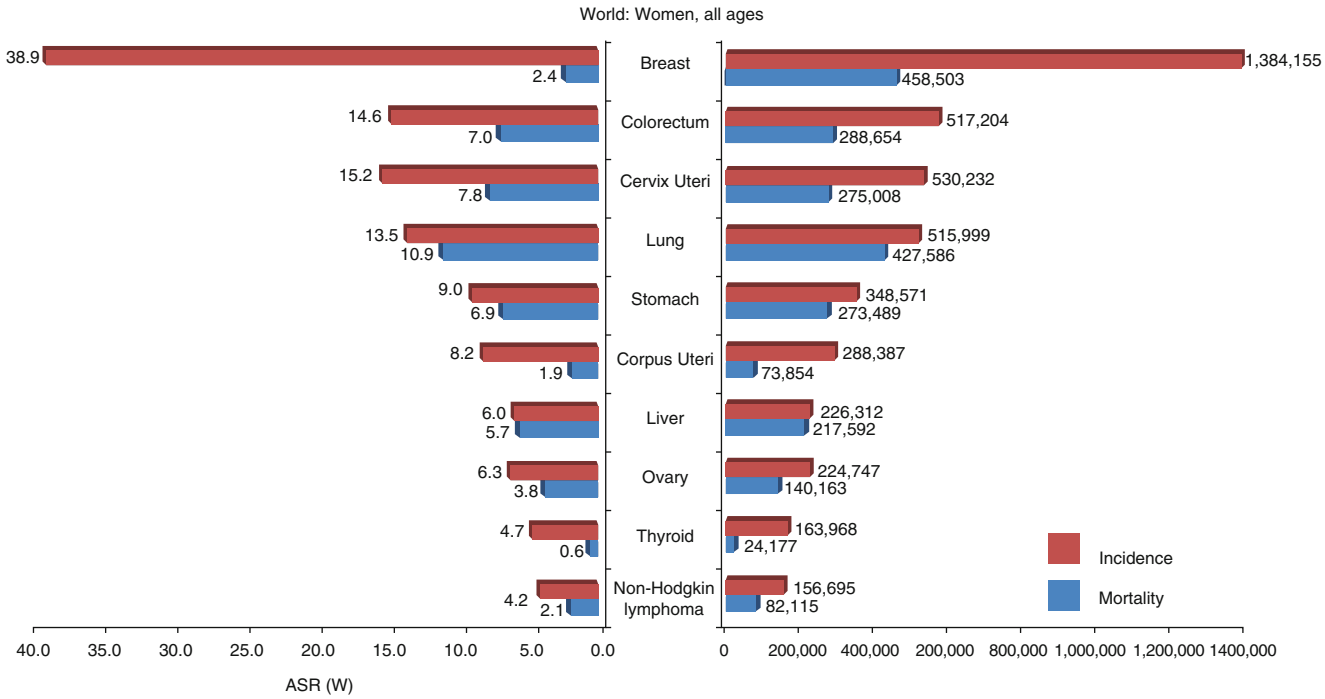


Fig. 23.1 World age-standardized cancer incidence and mortality rates, and number of cases and deaths among women. GLOBOCAN 2008. *ASR (W)* world age-standardized rate

Table 23.1 Statistics on selected cancer sites among women worldwide, GLOBOCAN 2008

	Cancer incidence			Cancer mortality		
Cancer site	Annual estimated number of new cases	Standardized incidence rate per 100,000 women (world standard)	Cumulative risk per 100 women (age 0–74 years old)	Annual total number of deaths	Standardized mortality rate per 100,000 women (world standard)	Cumulative risk per 100 women (age 0–74 years old)
All cancers	6,044,710	164.4	16.48	3,345,176	87.2	9.06
Breast	1,384,155	38.9	4.13	458,503	12.4	1.33
Cervix uteri	530,232	15.2	1.56	275,008	7.8	0.87
Corpus uteri	288,387	8.2	0.96	73,854	1.9	0.23
Ovary and ovarian adnexa	224,747	6.3	0.68	140,163	3.8	0.43

Data on cancer of the ovary and ovarian adnexa, including fallopian tube cancer (which is rare), are combined in the cancer statistics of the International Agency for Research on Cancer (IARC, www.iarc.fr). Together, they constitute the eighth most common cancers among women worldwide (Fig. 23.1), with 224,747 incident cases (standardized incidence rate of 6.3 per 100,000 women) and 140,163 deaths (standardized mortality rate of 3.8 per 100,000 women) estimated to have occurred in 2008. Both more developed and less developed regions of the world are affected (Fig. 23.3a, b), although the incidence rates are at least twice as high in Europe and North America as in Asia and Africa [1, 2]. The mortality to incidence ratio is 62 % (Table 23.1).

The number of new cancers of the female genitalia worldwide is unknown for most countries. However, this number can be estimated from incidence rates in countries where information is available [3]. In 2002, the estimated number of new cancers of the female genitalia worldwide was 40,000.

Vulvar and vaginal cancers are relatively rare. The age-standardized incidence rates of vulvar cancer worldwide are estimated to vary between 0.5 and 1.5 new cases per 100,000 women, without any clear geographical pattern. The standardized incidence rates of vaginal cancer are estimated to be between 0.3 and 0.7 per 100,000 in most countries [4, 5].

Choriocarcinomas constitute about 0.6 % of all cancers of the female reproductive system. In 2002 there were about 5,800 cases reported worldwide, with the vast majority occurring in less developed regions. Age-standardized incidence rates range from 0.04 new case per 100,000 women in Southern Africa and Northern Europe to 0.43 per 100,000 in Southeast Asia [6, 7]. In Vietnam, the incidence rate has been reported to be 1.98 per 100,000 women [7].

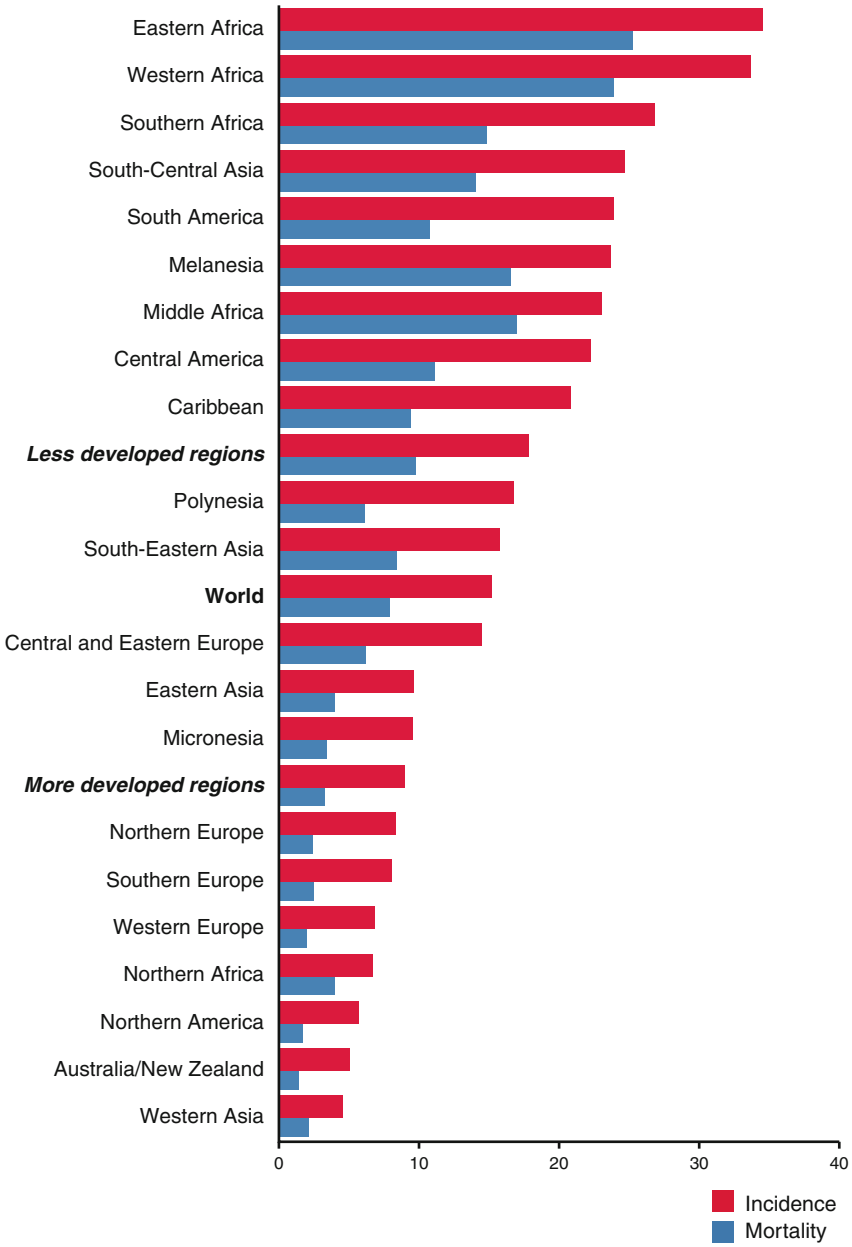


Fig. 23.2 World age-standardized incidence and mortality rates of cervical cancer in different world regions. GLOBOCAN 2008

Etiology and Lifestyle-Related Risk Factors

Cervical Cancer

There are two main histological types of cervical cancer: squamous cell carcinoma and adenocarcinoma. As for several other cancer types, when diagnosed in early stages, the prognosis of patients with cervical cancer is good (5-year survival rate above 90 %), but when diagnosed in advanced stages, the prognosis is extremely poor, even in countries with high-quality healthcare facilities available to all patients. The introduction of cervical cancer screening has dramatically reduced cervical cancer mortality in several countries where mortality is concentrated among women who do not participate in screening or those above the recommended screening age [8]. However, in areas where screening is not available, such as less developed regions, cervical cancer is a major cause of cancer death among women [2].

Cervical cancer is caused by persistent infection with human papillomavirus (HPV) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, or 59, and persistent infections with HPV16 and 18 are responsible for about 70 % of all cervical cancers worldwide. Persistent infection with HPV types 26, 53, 66, 67, 68, 70, 73, or 82 may also be causally related to cervical cancer. The recent introduction of mass vaccination against HPV16 and 18 in several countries is expected, in the

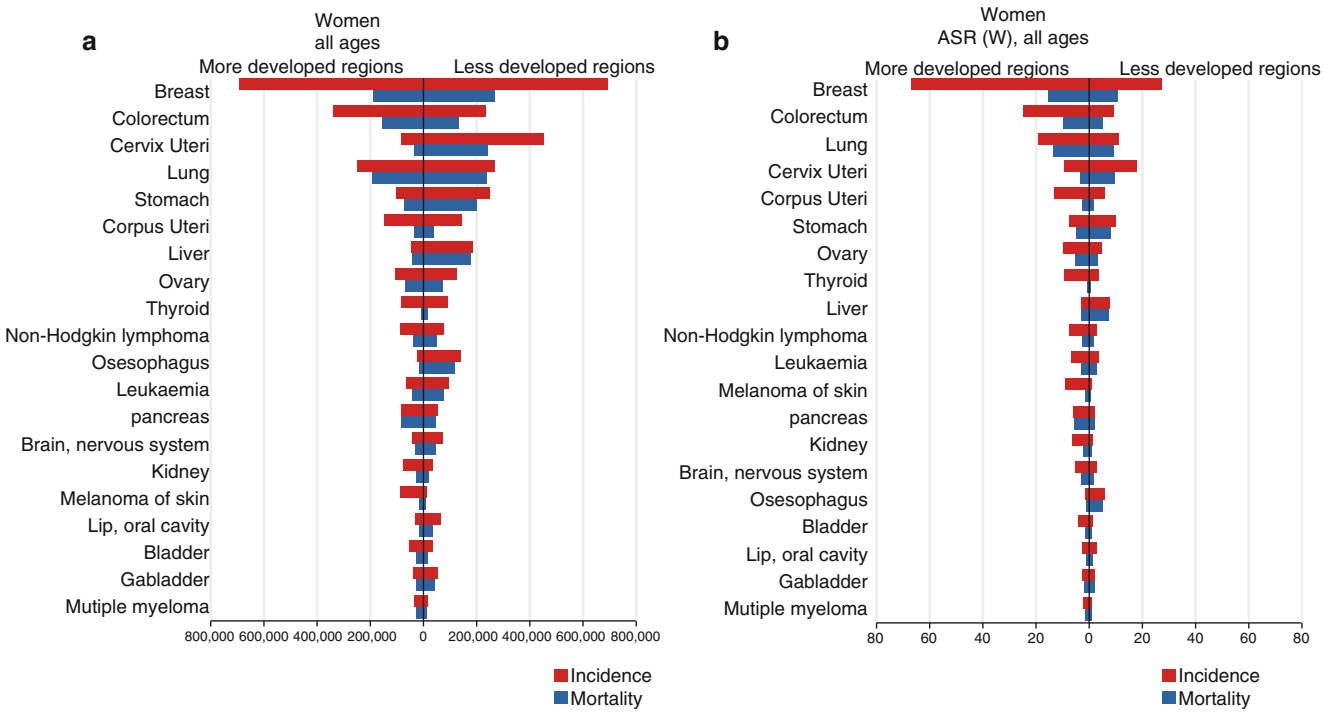


Fig. 23.3 (**a**) Number of cases and deaths. (**b**) World age-standardized cancer incidence and mortality rates. Women in more and less developed world regions. GLOBOCAN 2008. *ASR* (*W*) world age-standardized rate

long term, to dramatically decrease the incidence of and mortality from cervical cancer. However, the full benefit of mass HPV vaccination will not be observed for several decades. Therefore, screening will remain an essential tool to reduce cervical cancer mortality.

Other exposures that are considered carcinogenic to the cervix uteri are in utero exposure to diethylstilbestrol (associated with squamous cell carcinoma of the cervix), use of combined estrogen-progestogen oral contraceptives (associated with both in situ and invasive cervical cancers), human immunodeficiency virus type 1 (HIV1) infection, and tobacco smoking [9].

Endometrial Cancer

Endometrial cancer affects almost exclusively postmenopausal women. There are several histological subtypes of endometrial cancer, the most common being of epithelial origin, which can be further classified as adenocarcinomas of endometrioid type (Type I, 70–80 % of all endometrial cancers, including mucinous and adenosquamous tumors) or as adenocarcinomas of non-endometrioid type (Type II, 20–30 % of all endometrial cancers, including serous, mucinous, and clear cell histology, as well as rarer types such as carcinosarcomas and undifferentiated carcinomas) [9]. Type I endometrial cancer is usually hormone sensitive and occurs in women exposed to estrogens unopposed by progesterone. It is well differentiated with mild to moderate nuclear pleomorphism and has a low potential for myometrial invasion and metastasis [10]. Type II endometrial cancer usually arises from atrophic endometrial tissues and is poorly differentiated. It is not associated with estrogen or progestogen stimulation and has a high probability of myometrial invasion and metastasis and a very poor prognosis [11–15]. Overall, 5-year survival for endometrial adenocarcinomas is over 90 % when diagnosed in early stages (i.e., localized disease), but less than 50 % when the disease is diagnosed at advanced stages (with distant metastases).

Endometrial cancer risk has been previously associated with several host factors, including high body mass index, nulliparity or low parity, early age at first birth, history of type 2 diabetes mellitus (non-insulin dependent), and family history of cancer, particularly endometrial cancer. In addition, endogenous hormone levels have been positively associated with endometrial cancer risk in several prospective cohort studies [16], while cigarette smoking has been associated with a decreased risk [17]. Although high body mass index has been associated with endometrial cancer risk, no dietary factor has been singled out as being etiologically associated with any certainty [18]. Alcohol consumption does not appear to be associated with endometrial cancer risk [19].

Both estrogen-only and combined estrogen-progestogen hormone replacement therapies are classified as recognized causes of endometrial cancer [9]. The increased risk for estrogen-induced endometrial cancer decreases with the number of days per month that progestogens are added to the regi-

men. Tamoxifen, a drug mainly used to prevent breast cancer recurrence, has also been linked to endometrial cancer with sufficient evidence in humans [9]. There is evidence suggesting lack of carcinogenicity, with an inverse relationship observed between the use of combined estrogen-progestogen oral contraceptives and endometrial cancer. Also, a positive association has been observed between exposure to diethylstilbestrol and endometrial cancer [9].

Mesenchymal tumors occurring in the corpus uteri are aggressive and rare. The main histological types are carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma, and undifferentiated endometrial sarcoma [20]. Some studies define carcinosarcomas as poorly differentiated metaplastic carcinomas [21]. Depending upon the histological classification used, uterine sarcomas represent about 3–9 % of cancers of the corpus uteri and 1 % of all cancers of the female reproductive system [20, 22, 23]. The prognosis for certain histological types, such as uterine sarcoma, is quite poor; overall 5-year survival ranges from 17 to 53 % [22–25]. For endometrial stromal sarcoma, the prognosis is better than for other uterine sarcomas.

Uterine sarcomas are of largely unknown etiology. The incidence of uterine sarcoma varies between races; the age-adjusted incidence for Blacks has been reported to be twice that of Whites and more than twice that of women of other races [26, 27]. Possible etiological factors include a history of pelvic radiation, obesity, prolonged use of estrogen hormone replacement therapy or tamoxifen, and use of oral contraceptives [26, 28–30].

Ovarian Cancer

The etiology of ovarian cancer is not well understood. An excellent in-depth review on this subject has recently been published [31], and we refer interested readers to this review for more detailed information. Briefly, ovarian cancers are usually classified according to the cell types they originate from: epithelial (about 90 %), stromal (5 %), or germ cell (less than 5 %) [32]. Epithelial ovarian cancer can be further classified into the histological subtypes of serous, mucinous, endometrioid, and clear cell [33].

According to the IARC, there is sufficient human evidence that epithelial ovarian cancer is caused by estrogen hormone replacement therapy and tobacco smoking, and limited evidence regarding perineal use of talc-based body powder and exposure to X-radiation and γ-radiation (for medical purposes) [9]. Besides these risk factors, having a family history of the disease increases risk, as does being a carrier of mutations in the BRCA1/BRCA2 genes [34] or being affected by hereditary nonpolyposis colorectal cancer syndrome. Several studies indicate that height and body weight are associated with risk, in particular among nonusers of hormone replacement therapy. On the other hand, there are a few factors known to be associated with a decreased risk of ovarian cancer, such as high parity and use of oral contraceptives, and possibly breastfeeding, incomplete pregnancies, hysterectomy, and tubal ligation [31].

Studies on other potential risk factors, such as obesity, sedentary lifestyle, and alcohol consumption, have yielded inconsistent results [9, 18].

Other Cancers of the Female Reproductive System

The majority of vulvar cancers are squamous cell carcinomas, of which three histological subtypes (basaloid, warty, and verrucous) and the precursor lesion vulvar intraepithelial neoplasia are associated with HPV infection [4, 35]. There is sufficient human evidence that infection with HPV16 causes vulvar cancer and limited evidence regarding infection with HPV18 or 33 and with HIV1.

There are two main histological types of vaginal cancer, squamous cell carcinoma (the most frequent) and adenocarcinoma, and a rarer histological subtype, clear cell carcinoma. Many vaginal cancers are preceded by vaginal intraepithelial neoplasia. There is sufficient evidence that HPV16 is causally related to vaginal cancer and limited evidence that HIV1 is also associated with risk [9]. Diethylstilbestrol causes clear cell adenocarcinoma in the vagina of women who were exposed in utero [9, 36]; simultaneous or prior cancers of the female reproductive system confer an increased risk, especially if the women have been treated with pelvic irradiation [35].

The etiology of fallopian tube cancer is not well understood, probably because of the rarity of the disease, which makes studies rather difficult. The vast majority of reported cases are serous adenocarcinomas; clinical patterns, diagnosis, treatment, and prognosis are similar to those of ovarian cancers. Parity and sterilization procedures seem to decrease risk. Infections with *Chlamydia trachomatis* (which may cause salpingitis) or HPV do not seem to be associated with increased risk [37].

Most choriocarcinomas derive from the placental trophoblastic tissue. Known risk factors include maternal age (women younger than 20 or over 40 years), a previous history of hydatidiform mole (another trophoblastic disease), and possibly the use of oral contraceptives [7].

Occupational Exposures

The IARC Monographs on the Evaluation of Carcinogenic Risks to Humans series are recognized worldwide as dependable sources when it comes to identifying carcinogenic

Table 23.2 Known and suspected causes of cancers of the female reproductive system[a], as identified in the International Agency for Research on Cancer (IARC) Monographs, Volumes 1–102

Cancer site	Agent	IARC classification[b]	Sufficient evidence for cancer in humans	Limited evidence for cancer in humans
Cervix uteri	Diethylstilbestrol (in utero exposure)	1	X	
	Estrogen-progestogen oral contraceptives	1	X	
	Human immunodeficiency virus type 1	1	X	
	Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	1	X	
	Tobacco smoking (active)	1	X	
	Human papillomavirus types 26, 53, 66, 67, 68, 70, 73, 82	1		X
	Tetrachloroethylene	2A		X
Corpus uteri	Estrogen hormone replacement therapy	1	X	
	Estrogen-progestogen hormone replacement therapy	1	X	
	Tamoxifen	1	X	
	Diethylstilbestrol	1		X
Ovary	Asbestos (all forms)	1	X	
	Estrogen hormone replacement therapy	1	X	
	Tobacco smoking (active)	1	X	
	Talc-based body powder (perineal use)	2B		X
	X-radiation, γ-radiation	1		X
Vulva	Human papillomavirus type 16	1	X	
	Human immunodeficiency virus type 1	1		X
	Human papillomavirus types 18, 33	1		X
Vagina	Diethylstilbestrol (in utero exposure)	1	X	
	Human papillomavirus type 16	1	X	
	Human immunodeficiency virus type 1	1		X

This table is extracted from Cogliano et al. [9] and does not include risk factors not covered in the IARC Monographs Volumes 1–102, notably reproductive and other hormonal factors, diet and nutritional factors, and genetic susceptibility traits

[a]As of the end of 2011, the IARC has not classified any agent as a recognized or suspected carcinogen (Groups 1, 2A, or 2B) to the human fallopian tube

[b]Group 1 = carcinogenic to humans; Group 2A = probably carcinogenic to humans; Group 2B = possibly carcinogenic to humans

agents and circumstances. Possible carcinogenic agents are classified using a five-category classification system: Group 1 agents are deemed carcinogenic to humans; Group 2A agents probably carcinogenic to humans; Group 2B agents possibly carcinogenic to humans; Group 3 agents not classifiable as to their carcinogenicity to humans; and Group 4 agents probably not carcinogenic to humans [38]. The evidence considered by the working groups to classify the agents comes mainly from human and animal studies. Thus, some agents may be classified as carcinogenic to humans based on sufficient evidence in humans or limited evidence in humans but sufficient evidence in animals. Finally, an agent can be considered carcinogenic to a certain organ, but not necessarily to another one.

Table 23.2 shows the known or suspected causes of cancers of the female reproductive system abstracted from a summary of the IARC Monographs [9]. Two of these agents or exposure circumstances are directly related to occupational exposures: asbestos (Group 1 agent), which is considered to be carcinogenic to the human ovary [39], and tetrachloroethylene (Group 2A agent), which is considered to be probably carcinogenic to the human cervix uteri [40] (Table 23.3). Exposure to other agents with sufficient evidence of carcinogenicity (Group 1 agents) to the human cervix uteri, corpus uteri, ovary, vulva, or vagina generally occurs through medical treatments (diethylstilbestrol, oral contraceptives or hormone replacement therapy, X-radiation, and γ-radiation), environmental exposure (atomic bomb survivors), personal lifestyle habits (smoking, perineal use of talc-based body powder), or infections with other viruses (HIV1 and several HPV types) [50].

Cervical Cancer

Tetrachloroethylene

Tetrachloroethylene (or perchloroethylene) has been used as one of the main dry cleaning fluids around the world since the early 1950s. It is also currently used as a solvent in metal cleaning and in the textile industry; is a component of paint removers, printing inks, adhesives, paper coatings, and leather treatments; and is a carrier solvent for silicones [40]. In the early 1980s, it was estimated that 688,000 workers in the United States had potentially been exposed to

Table 23.3 Known and suspected occupational causes of cancers of the female reproductive system, as identified in the International Agency for Research on Cancer Monographs

Agents with sufficient or limited evidence in humans				
Agents	Industries/occupations	Cancer site	Range of risk ratios	References
Tetrachloroethylene	Metal cleaning	Cervix uteri	SMR 1.89–1.98	[45, 49]
	Textile industry		SMR 1.4–1.8	[46, 48]
	Manufacturing and use of paint removers, printing inks, adhesives, paper coatings, leather treatments, silicones		RR 1.09–1.34	[50]
			SIR 1.19–1.59	[51]
Asbestos	World War II gas mask manufacturing	Ovary	Compared to UK population: SMR 1.48–2.75 Compared to local population: SMR 1.74–2.96	[75]
	Manufacturing and use of asbestos products: asbestos cement, brake pads, roof tiles, etc.		SMR 1.2	[76]
	Mining and milling of asbestos fibers.		SIR 1.0–1.3	[78]
	Construction workers in insulation work, building maintenance or demolition, asbestos abatement work			

SIR standardized incidence ratio, *SMR* standardized mortality ratio, *RR* relative risk

tetrachloroethylene [51]. Approximate estimates of the number of exposed in the European Union were in the order of 820,000 in the early 1990s [52].

The mechanisms possibly responsible for the carcinogenicity of tetrachloroethylene have not yet been elucidated. A few pathways have been proposed for organs other than the cervix uteri based on animal models (e.g., peroxisome proliferation), but humans are relatively insensitive to those pathways [53]. However, it appears that the solvent is probably not genotoxic [40, 53]. The available human evidence used by the IARC Working Group to classify tetrachloroethylene as probably carcinogenic to the cervix uteri comes from three cohort studies. However, exposure to other chlorinated solvents in these studies could not be excluded, and potential confounding factors could not be controlled for [40]. Two cohort studies of dry cleaners showed an excess risk of 60–70 %, based on eight [41] and 21 deaths [43], respectively, while a cohort of workers monitored for tetrachloroethylene exposure reported two cases of cervical cancer [54].

Since the publication of the IARC Monographs, updates of the two cohorts of dry cleaners confirmed the increased risk of cervical cancer with exposure to tetrachloroethylene, with excess risks of 60 % (standardized mortality ratio [SMR] 1.6, 95 % confidence interval [CI] 1.0–2.3, based on 27 deaths) [44] and 95 % (SMR 1.95, 95 % CI 1.00–3.40) [42]. A Swedish record-linkage study reported a small increased risk for women registered as dry cleaning workers at the time of either the 1960 or the 1970 censuses. However, women who were registered as working in the industry at the time of both censuses showed no such increase [45]. A recent cohort study of Swedish dry cleaners and laundry workers found a small excess risk of cervical cancer, based on 25 cases (standardized incidence ratio [SIR] 1.25, 95 % CI 0.81–1.85), but the 19 cases exposed exclusively to tetrachloroethylene had an even smaller risk [46]. The studies published since the IARC's last evaluation in 1995 unfortunately did not take into account potential confounding factors for cervical cancer, such as HPV infection and other socioeconomic factors. Therefore recent studies do not strengthen the evidence for an association between the dry cleaning industry, in which tetrachloroethylene is the main solvent used, and an increased risk of cervical cancer.

Other Occupational Exposures

Several job titles have been associated with an increased risk of cervical cancer in more than one study, but most of these studies were exploratory in nature and did not adjust for important potential confounders such as socioeconomic status and HPV infection. Examples of those job titles are hotel/restaurant personnel and waitresses, food preparers, machine operators, cleaners, upholsterers, dry cleaners, beverage workers, other construction workers, and drivers [41–44, 55–58]. Women working in agriculture also appear to be at increased risk [56–61]. A cohort study of professional firefighters in Florida reported a fivefold increased risk of cervical cancer, unadjusted for lifestyle habits [62]. A Swedish registry-based cohort study found a 39 % nonsignificant increase in risk associated with shift work; however, the definition of shift work used in the study was very rough, including occupations in which at least 40 % of the workers reported working rotating shifts (three shifts per day) or workers who worked at least one night in the week preceding interview [63].

A Finnish record-linkage study reported excess risks of cervical cancer of about 20–40 % with exposure to a large group of aliphatic and alicyclic, aromatic, and chlorinated hydrocarbon solvents. The authors reported similar excess risks with silica and wood dust exposures, after standardization by birth cohort, follow-up period, and socioeconomic status [64]. A study using a similar design reported a 48 %

increased risk of cervical cancer among Swedish workers exposed to diesel exhaust fumes, with suggestion of a dose-response relationship [65]. Certain textile workers exposed to organic dusts, solvents, and dyes have been found to present small increases in cervical cancer risk in record-linkage studies [56, 64]. A cohort study of textile workers also reported an excess risk (SIR 1.82, 95 % CI 1.19–2.67) that was further increased in women who had worked in the industry for 10 years or more (SIR 2.44, 95 % CI 1.21–4.35); again, the estimates were not adjusted for potential confounding factors [66]. A cohort study of auto-manufacturing workers in Michigan showed an excess risk of cervical cancer (relative risk [RR] 2.96, 95 % CI 2.11–4.02) based on 40 cases. Although the risk estimates were not adjusted for reproductive and behavioral risk factors for cervical cancer, a comparison of workers exposed and unexposed to certain metal working fluids showed an increased risk for soluble fluids (RR = 1.55) [67].

An exposure circumstance that had not been identified previously is also worth mentioning. A Finnish record-linkage study explored cancer risk among workers exposed to molds of agricultural and industrial origin and to bacteria of nonhuman origin, attributing exposures using a job-exposure matrix. The authors reported that women in the highest category of mold and of bacterial exposure had cervical cancer RR of 3.1 (95 % CI 1.0–9.2) and 2.6 (95 % CI 1.5–4.7), respectively [68].

In conclusion for cervical cancer, apart from occupational exposure to tetrachloroethylene, which has been classified as probably carcinogenic to the human cervix uteri (Group 2A agent), all the other occupational exposures for which there is some evidence of an association require well-designed confirmatory studies, with proper adjustment for potential confounding factors.

Endometrial Cancer

None of the agents or circumstances classified as carcinogenic to the corpus uteri by the IARC are related to occupational exposures. Some occupational exposures have been associated with an increased risk of endometrial cancer in a few studies, but the evidence was not solid enough to support their classification as carcinogenic to the human corpus uteri. It is generally believed that the role of further environmental or occupational factors in the causation of endometrial cancer is unclear and probably small [64].

For example, occupations involving professional or administrative tasks, such as the occupation of teacher, secretary, telephone operator, and musician [56, 58, 69–71], have all been associated with increased risks of endometrial cancer. A Swedish registry-based cohort study did not find increased risks associated with shift work, but the definition of shift work used in the study was very rough, including occupations in which at least 40 % of the workers reported working rotating shifts (three shifts per day) or workers who worked at least one night in the week preceding interview [63]. A cohort study in the United States reported an increased risk among nurses who worked at least 20 years in rotating shifts; the risk was larger in a subgroup of obese nurses, after adjustment for potential confounders (body mass index >30 kg/m^2; RR 2.09, 95 % CI 1.24–3.52), and increased with the duration of shift work [72]. All of these occupations are sedentary, which is consistent with the idea that physical activity is a protective factor for endometrial cancer [73].

A case-control study among Italian agricultural communities reported an increased risk of corpus uteri cancer among women who worked in farming occupations for 10–19 years (odds ratio [OR] 2.4, 95 % CI 1.0–5.9) [60].

A record-linkage study reported an excess endometrial cancer risk of 1.2 among Finnish women in jobs that involved exposure to animal dust and of 1.3 for women working in sedentary jobs, after standardization by birth cohort, follow-up period, socioeconomic status, mean parity, and mean age at first birth by occupation [64].

Most studies did not look at specific subtypes of corpus uteri cancers. One record-linkage study in the Nordic countries focused on the possible occupational etiology of uterine sarcomas. SIRs of leiomyosarcoma and endometrial stromal sarcoma were computed for 53 occupational categories [58]. The occupational groups with increased SIRs of leiomyosarcoma were shoe and leather workers (SIR 2.59, 95 % CI 1.12–5.11), farmers (SIR 1.62, 95 % CI 1.18–2.17), and teachers (SIR 1.38, 95 % CI 1.07–1.76), whereas the SIR for domestic assistants was 0.64 (95 % CI 0.41–0.96). For endometrial stromal sarcoma, no occupation with elevated SIRs was observed [74].

In conclusion for endometrial cancer, no particular occupational exposure appears to convey an excess risk. However, as physical activity is a modifiable lifestyle factor affecting the risk of endometrial cancer, occupations with a moderate to high intensity of physical activity may help reduce the risk by contributing to the total amount of regular physical activity.

Ovarian Cancer

Asbestos

Although asbestos has been banned or restricted in several countries, it is estimated that 125 million people are still exposed to asbestos fibers in the workplace [75]. Apart from the mining and milling of asbestos fibers, occupational exposures mainly occur during the manufacturing and use of asbestos products (asbestos cement, brake pads, roof tiles, etc.), building insulation, maintenance and demolition, and asbestos abatement work [51]. With respect to lung cancer or

mesothelioma risk, there appears to be differences in potency according to the type and dimension of the fibers, but the overall conclusion is that all types of asbestos fibers are carcinogenic to humans [39]. Approximate estimates of the number of exposed workers in the early 1990s were in the order of 682,000 in the United States [76] and 1.2 million in the European Union [52].

The mechanisms of carcinogenesis have been described extensively for asbestos fibers, essentially in the lungs and the pleura; they include impaired fiber clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signaling pathways, and resistance to apoptosis [39]. As translocation of fibers to the ovaries has been demonstrated [77], it can be presumed that similar mechanisms are responsible for ovarian carcinogenesis and could eventually be associated with other reproductive cancers.

The available human evidence used by the IARC to classify asbestos fibers as carcinogenic to the ovary [39] comes from cohort studies of women who manufactured gas masks during World War II [47, 48] and from studies suggesting that asbestos can accumulate in the ovaries of occupationally exposed women [77]. In particular, the study of two cohorts of women in the United Kingdom who manufactured gas masks reported a larger mortality risk from ovarian cancer for women exposed to crocidolite and chrysotile fibers than for those exposed to chrysotile fibers only: the former group had a risk of dying from ovarian cancer 2.96 times that of non-exposed women in the area, and women exposed to chrysotile only had a risk 1.74 times that of non-exposed women in the area [47]. A smaller cohort study of another group of United Kingdom workers also showed a borderline significant increased risk of 1.8 (95 % CI 0.9–3.3) of dying from ovarian cancer [48]. A meta-analysis following IARC's classification in 2010 confirmed an excess mortality from ovarian cancer among asbestos-exposed workers (aggregate SMR 1.77, 95 % CI 1.37–2.28) [78].

A borderline increased risk of 1.3 (95 % CI 0.9–1.8) was reported by a study linking census-based job titles of Finnish women with subsequent risk of incident ovarian cancer, after translating job titles into exposure to asbestos using a national job-exposure matrix, FINJEM, and after adjustment for reproductive factors [49]. A Russian study also reported a significantly elevated risk of mortality among bookbinders (SMR 2.9, 95 % CI 1.5–5.0) who were exposed to asbestos-contaminated talc fillers in paper [79].

Ionizing Radiation

Healthcare workers and industrial radiographers are exposed to X-radiation (some healthcare workers may also be exposed to radionuclides emitting α- or β-particles), whereas nuclear energy or nuclear weapons workers are essentially exposed to γ-radiation and α- or β-particles when handling radioactive materials. However, workers can also be exposed because of natural sources of radiation (e.g., aircraft personnel exposed to γ-radiation and neutrons from cosmic radiation or underground miners exposed to natural radionuclides emitting essentially α-particles) [80]. The United Nations Scientific Committee on Exposure to Atomic Radiation estimated in 2008 that about 13 million workers were exposed to natural sources of ionizing radiation, whereas another 9.8 million were exposed to artificial sources; medical workers are considered to constitute about two-thirds of the latter group of workers [81]. It appears that the annual occupational effective doses have been diminishing regularly, and in 2000–2002 they were estimated to vary between 0.1 and 1.0 millisieverts annually for exposures to artificial sources, compared to an annual average of 2.9 millisieverts for exposure to natural sources [81].

The available human evidence of a relationship between ovarian cancer and exposure to X-radiation and γ-radiation has been classified as limited (Table 23.2) [9], and no mention of increased ovarian cancer risk was suggested in relation to occupational exposures by the IARC Working Group [50].

Studies published since the last IARC evaluation still report inconsistent results. A death certificate study of healthcare workers in the United States reported a statistically significant risk of mortality among radiologic technicians (mortality OR 1.8, 95 % CI 1.2–2.8) [69]. However, a cohort study of radiologic technologists in the United States did not report any increased risk of incidence of [82], or mortality from [83] ovarian cancer. A study of Chinese medical X-ray workers mentioned a small, non-statistically significant, increased risk but did not provide the actual risk estimates for ovarian cancer [84]. A cohort study of workers at a United States uranium production facility did not show an increased risk among the workers exposed to radiation, but there was only one death from ovarian cancer and no incident case between 1946 and 1995 [85]. A cohort study of French nuclear energy production workers reported a small increased risk of ovarian cancer and cancer of other and unspecified female genital organs (International Classification of Diseases 9th revision codes 183 and 184, SMR 1.1, 90 % CI 0.76–1.56) [86]. Analyses of the Canadian National Dose Registry did not find increased risks of incident ovarian cancer in women exposed to ionizing radiation in the workplace [87, 88]. A few other studies using various methods did not find increased risks of ovarian cancer incidence or mortality with exposure to ionizing radiation or with the occupation of radiologic technician [49, 58, 84, 89]. In summary, if occupational exposures to ionizing radiation do confer an increased risk of ovarian cancer, their overall impact is likely to be limited compared to other risk factors.

Other Occupational Exposures

During the last 10 years, relatively few studies reported on occupational exposures in relation to ovarian cancer. Many of these studies were record-linkage studies from the Nordic countries, and it is worth mentioning that risks obtained with these designs are likely to be diluted toward the null value because of aggregate-level data and possible misclassification of exposures and job titles [49].

Hormones, Antineoplastic Drugs, or Other Pharmaceuticals

Estrogen hormone replacement therapy has been classified as carcinogenic to the human ovary [90], but occupational exposures to these pharmaceuticals were not considered by the IARC Working Group. Very little additional data are available. Hormonal effects have been reported in workers exposed to steroids (e.g., gynecomastia and loss of libido in men and menstrual problems in women) [91]. A well-designed cohort study among employees with possible exposure to chemical, pharmacological, or biological agents in a pharmaceutical company in Sweden reported two cases of ovarian cancer, as expected [92]. A few record-linkage studies reported small or nonexistent increased risks of incident ovarian cancer in pharmacy technicians or workers in the pharmaceutical industry [58, 89, 93, 94]. A death certificate study reported an increased risk of mortality among pharmacists (mortality OR 2.4, 95 % CI 1.6–3.7) [69]. Thus there is not enough evidence to conclude that fabrication or handling of pharmaceutical drugs is associated with an increased risk of ovarian cancer.

Organic Solvents, Aromatic Hydrocarbons, and Exhaust Fumes

Increased risks of ovarian cancer have been associated with occupational exposure to several organic solvents in studies of different designs. Record-linkage studies conducted in the Nordic countries showed indications of increased risks for exposure to aromatic hydrocarbon solvents (SIR 1.3, 95 % CI 1.0–1.7) [49] or that solvent use among occupations associated with ovarian cancer suggests an etiologic role of aliphatic and aromatic hydrocarbons [89]. The latter study reported increased risks for several job titles that are associated with solvent exposure, such as shoe worker (RR 1.82, 95 % CI 1.01–3.3), graphic worker (RR 1.58, 95 % CI 1.02–2.5), and worker in the machine and electronics industry (RR 1.26, 95 % CI 1.01–1.6) [89]. Another record-linkage study found a small increased risk for printers [58]. A cohort study of printing industry workers reported an increased risk among bookbinders; the authors pointed out that bookbinders were exposed to solvents, glues, and paper dust [79]. Results for dry cleaners were inconsistent: one study reported no increase in risk of ovarian cancer in Finland [49], whereas a small increased risk was found in a Swedish study [89] of similar design. In summary, although several studies have found an excess risk of ovarian cancer among women occupationally exposed to organic solvents or to aromatic hydrocarbons, the available evidence is still limited, owing to the scanty exposure information in most studies.

Two Finnish record-linkage studies reported a two- to threefold increased risk of ovarian cancer associated with exposure to diesel engine exhaust fumes [49, 95]; the same studies also reported a 50–70 % increased risk associated with exposure to gasoline exhaust fumes. These findings have to be replicated in other contexts and with other study designs before definite conclusions can be drawn on the effect of exposure to exhaust fumes on ovarian cancer.

Specific Job Titles

Several clerical and professional occupations, such as teacher, librarian, nurse, secretary, retail sales clerk, and others, have repeatedly been associated with a small excess risk of ovarian cancer incidence or mortality in different settings, often in studies based on routinely collected data [56, 58, 69–71, 94]. The small increased risk presented by these professional occupations could be partly, if not wholly attributed to peculiar reproductive and other lifestyle factors and residual confounding associated with higher socioeconomic status that could be more frequent among women occupying these professions (having less children, at a later age, taking more hormone replacement therapy, etc.) [70, 71]. A cohort study of agricultural workers in Northern Italy did not find an increased risk of mortality from ovarian cancer among women working on farms [60], and a multicenter case-control study found similar results for cancer incidence [97], whereas a large cohort study of agricultural workers in the United States recently reported an increased risk among private pesticide applicators (relative SIR 2.88, 95 % CI 1.50–5.54, based on nine cases) [98].

An IARC Working Group recently concluded that a modest excess risk of ovarian cancer appeared to be linked to the occupation of hairdresser and related occupations, but that the lack of adjustment for potential confounders did not allow confounding to be ruled out [99]. A recent meta-analysis of 10 studies published between 1977 and 2003 on ovarian cancer among hairdressers and related occupations concluded that there was a small excess risk of about 16 % [100]. An excess risk of the same magnitude was also reported by a recent record-linkage study [58]. A large cohort study of female cosmetologists and manicurists in California did not find an increased risk of incident ovarian cancer, but the cohort was young (less than 20 % of the cohort was 50 years of age or older), and there was no adjustment for reproductive factors [101].

In conclusion for ovarian cancer, apart from occupational exposure to asbestos fibers, which is recognized by the IARC as

being carcinogenic to the human ovary, the other occupational exposures evoked so far have to be considered as hypotheses that need confirmation in carefully designed studies adjusting for potential confounding factors.

Other Cancers of the Female Reproductive System

A recent review of the IARC Monographs did not identify any other occupational exposure that could be causally related to the other cancers of the female reproductive system [9] (Table 23.2). Very little additional information is available on the possible role of occupational factors in the etiology of these cancers. Primary cancers of the vulva, vagina, and fallopian tube and choriocarcinoma are rare, and very few studies mention them individually or even as a group. We found one record-linkage cohort study of Swedish hairdressers that reported no increased risk for cancers of the female reproductive system other than ovarian, cervical, and endometrial cancers [102].

A more recent record-linkage study reported elevated SIRs of less than 20 % for cancer of the vulva among domestic assistants and building caretakers [58]. The other available evidence linking occupational exposures to vulvar cancer relies on single studies, the findings of which have not been replicated. One case-control study reported excess risks among private household maids and servants (OR = 2.54) and workers in laundry, cleaning, and other garment services (OR = 3.81) [103].

An excess risk of 2.6 was found for vaginal cancer among chemical process workers, whereas the risk was lower for building caretakers (SIR 1.30). The authors noted that no occupational risk factors had been previously identified for these cancers and that HPV infection was a well-known risk factor that could not be adjusted for in the study [58].

Using the same study design, Riska and colleagues recently reported two- to fourfold increased risks of fallopian tube cancer among smelting workers (based on six cases), artistic workers ($n = 14$), and hairdressers ($n = 25$) [104]. The authors stressed that their results have to be validated by studies with individual information on important potential confounding factors, such as socioeconomic status, reproductive history, and lifestyle factors [104].

Finally, an elevated risk of choriocarcinoma has been reported among nurses (based on four cases) and agricultural workers ($n = 2$), but only in one study (a Finnish record-linkage study) [105]. A cluster of three cases of choriocarcinoma was reported among women exposed to crocidolite, an amphibole asbestos fiber (two of the women were mine workers) [106].

In conclusion for the other cancers of the female reproductive system, there is no solid evidence of increased risks from occupational exposures. It is however a challenge to conduct powerful studies on these rare cancers while properly adjusting for potential confounding factors.

Conclusion

In conclusion, a few studies suggest that some occupational exposures are associated with increased risks of cancers of the female reproductive system. However, apart from the evidence for asbestos fibers and tetrachloroethylene, the data are rather scarce. As lifestyle habits are known to play a major role in the etiology of these cancers, most published studies did not gather information on occupational history. Given the multifactorial nature of cancers of the female reproductive system, it is of the utmost importance to conduct occupational studies that will gather detailed data on potential individual confounding factors, in particular reproductive history and other factors that influence the body's hormonal environment, together with information on socioeconomic status and lifestyle factors, including physical activity, from multiple sources.

Studies on the mechanisms of carcinogenesis in female reproductive organs are also needed to elucidate the possible role of chemical exposures in the development of these cancers.

References

1. Merritt MA, Cramer DW. Molecular pathogenesis of endometrial and ovarian cancer. Cancer Biomark. 2011;9:287–305.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, cancer incidence and mortality worldwide: IARC Cancer Base No. 10 [Internet]. Lyon: International Agency for Research on Cancer; 2010. Available at http://globocan.iarc.fr. Accessed August 2011
3. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents, Vol VIII. IARC scientific publication no. 155. Lyon: International Agency for Research on Cancer; 2002.
4. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. Vaccine. 2006;24 Suppl 3:S3/11–25.
5. Bosch FX, Cardis E. Cancer incidence correlations: genital, urinary and some tobacco-related cancers. Int J Cancer. 1990;46:178–84.
6. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: the size of the problem. Best Pract Res Clin Obstet Gynaecol. 2006;20:207–25.
7. Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C. Epidemiology and aetiology of gestational trophoblastic diseases. Lancet Oncol. 2003;4:670–8.
8. Andrae B, Andersson TML, Lambert PC, Kemetli L, Silfverdal L, Strander B, et al. Screening and cervical cancer cure: a population-based cohort study. Br Med J. 2012;344:e900.
9. Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. Preventable exposures associated with human cancers. J Natl Cancer Inst. 2011;103:1827–39.
10. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Mod Pathol. 2000;13:295–308.

11. Sherman ME, Sturgeon S, Brinton L, Kurman RJ. Endometrial cancer chemoprevention: implications of diverse pathways of carcinogenesis. J Cell Biochem Suppl. 1995;23:160–4.
12. Basil JB, Goodfellow PJ, Rader JS, Mutch DG, Herzog TJ. Clinical significance of microsatellite instability in endometrial carcinoma. Cancer. 2000;89:1758–64.
13. Faquin WC, Fitzgerald JT, Lin MC, Boynton KA, Muto MG, Mutter GL. Sporadic microsatellite instability is specific to neoplastic and preneoplastic endometrial tissues. Am J Clin Pathol. 2000;113:576–82.
14. Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94:642–6.
15. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol. 1982;6:93–108.
16. Eliassen AH, Hankinson SE. Endogenous hormone levels and risk of breast, endometrial and ovarian cancers: prospective studies. Adv Exp Med Biol. 2008;630:148–65.
17. IARC. Monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens. Part E: personal habits and indoor combustions, vol. 100. Lyon: International Agency for Research on Cancer; 2012.
18. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2007.
19. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009;10:1033–4.
20. McMeekin DS. Sarcoma of the uterus. In: DiSaia PA, Creasman WT, editors. Clinical gynecologic oncology. 7th ed. Philadelphia: Mosby Elsevier; 2007.
21. McCluggage WG. Uterine carcinosarcomas (malignant mixed Mullerian tumors) are metaplastic carcinomas. Int J Gynecol Cancer. 2002;12:687–90.
22. Nordal RR, Thoresen SO. Uterine sarcomas in Norway 1956–1992: incidence, survival and mortality. Eur J Cancer. 1997;33:907–11.
23. Abeler VM, Royne O, Thoresen S, Danielsen HE, Nesland JM, Kristensen GB. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. Histopathology. 2009;54:355–64.
24. Kokawa K, Nishiyama K, Ikeuchi M, Ihara Y, Akamatsu N, Enomoto T, et al. Clinical outcomes of uterine sarcomas: results from 14 years worth of experience in the Kinki district in Japan (1990–2003). Int J Gynecol Cancer. 2006;16:1358–63.
25. Koivisto-Korander R, Butzow R, Koivisto AM, Leminen A. Clinical outcome and prognostic factors in 100 cases of uterine sarcoma: experience in Helsinki University Central Hospital 1990–2001. Gynecol Oncol. 2008;111:74–81.
26. Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989–1999. Gynecol Oncol. 2004;93:204–8.
27. Harlow BL, Weiss NS, Lofton S. The epidemiology of sarcomas of the uterus. J Natl Cancer Inst. 1986;76:399–402.
28. Schwartz SM, Weiss NS, Daling JR, Gammon MD, Liff JM, Watt J, et al. Exogenous sex hormone use, correlates of endogenous hormone levels, and the incidence of histologic types of sarcoma of the uterus. Cancer. 1996;77:717–24.
29. Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino J, Bernstein L, Runowicz CD. Association of tamoxifen and uterine sarcoma. J Clin Oncol. 2002;20:2758–60.
30. Arenas M, Rovirosa A, Hernandez V, Ordi J, Jorcano S, Mellado B, Biete A. Uterine sarcomas in breast cancer patients treated with tamoxifen. Int J Gynecol Cancer. 2006;16:861–5.
31. Permuth-Wey J, Sellers TA. Epidemiology of ovarian cancer. Methods Mol Biol. 2009;472:413–37.
32. Chen VW, Ruiz B, Killeen JL, Cote TR, Wu XC, Correa CN. Pathology and classification of ovarian tumors. Cancer. 2003;97(10 Suppl):2631–42.
33. Averette HE, Nguyen H. Gynecologic cancer. In: Murphy GP, Lawrence I, Lenhard RE, editors. American Cancer Society textbook of clinical oncology. Atlanta: American Cancer Society; 1995. p. 552–79.
34. Iarmarcovai G, Bonassi S, Botta A, Baan RA, Orsiere T. Genetic polymorphisms and micronucleus formation: a review of the literature. Mutat Res. 2008;658:215–33.
35. Tavassoli FA, Devilee P. World Health Organization Classification of Tumours. Pathology and genetics of tumours of the breast and female genital organs. Lyon: International Agency for Research on Cancer; 2003.
36. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med. 1971;284:878–81.
37. Riska A, Leminen A. Determinants of incidence of primary fallopian tube carcinoma (PFTC). Methods Mol Biol. 2009;472:387–96.
38. IARC. Agents classified by the IARC Monographs, volumes 1–102. http://monographs.iarc.fr/ENG/Classification/ClassificationsGroupOrder.pdf. Accessed Aug 2011.
39. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens–part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 2009;10:453–4.
40. IARC. Monographs on the evaluation of carcinogenic risks to humans, Dry cleaning, some chlorinated solvents and other industrial chemicals, vol. 63. Lyon: International Agency for Research on Cancer; 1995.
41. Ruder AM, Ward EM, Brown DP. Cancer mortality in female and male dry-cleaning workers. J Occup Med. 1994;36:867–74.
42. Ruder AM, Ward EM, Brown DP. Mortality in dry-cleaning workers: an update. Am J Ind Med. 2001;39:121–32.
43. Blair A, Stewart PA, Tolbert PE, Grauman D, Moran FX, Vaught J, Rayner J. Cancer and other causes of death among a cohort of dry cleaners. Br J Ind Med. 1990;47:162–8.
44. Blair A, Petralia SA, Stewart PA. Extended mortality follow-up of a cohort of dry cleaners. Ann Epidemiol. 2003;13:50–6.
45. Travier N, Gridley G, De Roos AJ, Plato N, Moradi T, Boffetta P. Cancer incidence of dry cleaning, laundry and ironing workers in Sweden. Scand J Work Environ Health. 2002;28:341–8.
46. Selden AI, Ahlborg Jr G. Cancer morbidity in Swedish dry-cleaners and laundry workers: historically prospective cohort study. Int Arch Occup Environ Health. 2011;84:435–43.
47. Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br J Ind Med. 1982;39:344–8.
48. McDonald JC, Harris JM, Berry G. Sixty years on: the price of assembling military gas masks in 1940. Occup Environ Med. 2006;63:852–5.
49. Vasama-Neuvonen K, Pukkala E, Paakkulainen H, Mutanen P, Weiderpass E, Boffetta P, et al. Ovarian cancer and occupational exposures in Finland. Am J Ind Med. 1999;36:83–9.
50. IARC. Monographs on the evaluation of carcinogenic risks to humans, Ionizing radiation. Part 1: X- and gamma (γ)-radiation, and neutrons, vol. 75. Lyon: International Agency for Research on Cancer; 2000.
51. NTP. Report on carcinogens. 12th ed. Research Triangle Park: US Department of Health and Human Services, Public Health Service, National Toxicology Program; 2011.
52. Kauppinen T, Toikkanen J, Pedersen D, Young R, Ahrens W, Boffetta P, et al. Occupational exposure to carcinogens in the European Union. Occup Environ Med. 2000;57:10–8.

53. ATSDR. Toxicological profile for tetrachloroethylene (PERC). Atlanta: Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention; 1997. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=265&tid=48. Accessed Aug 2011.
54. Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med. 1995;37:797–806.
55. Savitz DA, Andrews KW, Brinton LA. Occupation and cervical cancer. J Occup Environ Med. 1995;37:357–61.
56. Sala M, Dosemeci M, Zahm SH. A death certificate-based study of occupation and mortality from reproductive cancers among women in 24 US states. J Occup Environ Med. 1998;40:632–9.
57. Carpenter L, Roman E. Cancer and occupation in women: identifying associations using routinely collected national data. Environ Health Perspect. 1999;107 Suppl 2:299–303.
58. Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparen P, Tryggvadottir L, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48:646–790.
59. Wesseling C, Ahlbom A, Antich D, Rodriguez AC, Castro R. Cancer in banana plantation workers in Costa Rica. Int J Epidemiol. 1996;25:1125–31.
60. Settimi L, Comba P, Carrieri P, Boffetta P, Magnani C, Terracini B, et al. Cancer risk among female agricultural workers: a multicenter case-control study. Am J Ind Med. 1999;36:135–41.
61. Colt JS, Stallones L, Cameron LL, Dosemeci M, Zahm SH. Proportionate mortality among US migrant and seasonal farm workers in twenty-four states. Am J Ind Med. 2001;40:604–111.
62. Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA. Cancer incidence in Florida professional firefighters, 1981 to 1999. J Occup Environ Med. 2006;48:883–8.
63. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. Scand J Work Environ Health. 2007;33:336–43.
64. Weiderpass E, Pukkala E, Vasama-Neuvonen K, Kauppinen T, Vainio H, Paakkulainen H, et al. Occupational exposures and cancers of the endometrium and cervix uteri in Finland. Am J Ind Med. 2001;39:572–80.
65. Boffetta P, Dosemeci M, Gridley G, Bath H, Moradi T, Silverman D. Occupational exposure to diesel engine emissions and risk of cancer in Swedish men and women. Cancer Causes Control. 2001;12:365–74.
66. Kuzmickiene I, Didziapetris R, Stukonis M. Cancer incidence in the workers cohort of textile manufacturing factory in Alytus, Lithuania. J Occup Environ Med. 2004;46:147–53.
67. Betenia N, Costello S, Eisen EA. Risk of cervical cancer among female autoworkers exposed to metalworking fluids. Scand J Work Environ Health. 2012;38:78–83.
68. Laakkonen A, Verkasalo PK, Nevalainen A, Kauppinen T, Kyyronen P, Pukkala EI. Moulds, bacteria and cancer among Finns: an occupational cohort study. Occup Environ Med. 2008;65:489–93.
69. Petralia SA, Dosemeci M, Adams EE, Zahm SH. Cancer mortality among women employed in health care occupations in 24 U.S. states, 1984–1993. Am J Ind Med. 1999;36:159–65.
70. Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, et al. High breast cancer incidence rates among California teachers: results from the California teachers study (United States). Cancer Causes Control. 2002;13:625–35.
71. MacArthur AC, Le ND, Abanto ZU, Gallagher RP. Occupational female breast and reproductive cancer mortality in British Columbia, Canada, 1950–94. Occup Med (Lond). 2007;57:246–53.
72. Viswanathan AN, Hankinson SE, Schernhammer ES. Night shift work and the risk of endometrial cancer. Cancer Res. 2007;67:10618–22.
73. John EM, Koo J, Horn-Ross PL. Lifetime physical activity and risk of endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2010;19:1276–83.
74. Koivisto-Korander R, Martinsen JI, Weiderpass E, Leminen A, Pukkala E. Incidence of uterine leiomyosarcoma and endometrial stromal sarcoma in Nordic countries: results from NORDCAN and NOCCA data bases. Maturitas. 2012;72:56–60.
75. Concha-Barrientos M, Nelson DI, Driscoll T, Steenland NK, Punnett L, Fingerhut MA, et al. Selected occupational risk factors. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, editors. Comparative quantification of health risks: global and regional burden of diseases attributable to selected major risk factors, vol. 1 & 2. Geneva: World Health Organization; 2004
76. ATSDR. Toxicological profile for asbestos. Atlanta: Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention; 2001. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=30&tid=4. Accessed Aug 2011.
77. Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. Am J Ind Med. 1996;29:435–9.
78. Camargo MC, Stayner LT, Straif K, et al. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. Environ Health Perspect. 2011;119:1211–7.
79. Bulbulyan MA, Ilychova SA, Zahm SH, Astashevsky SV, Zaridze DG. Cancer mortality among women in the Russian printing industry. Am J Ind Med. 1999;36:166–71.
80. IARC. Monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens. Part D: radiation, vol. 100. Lyon: International Agency for Research on Cancer; 2012.
81. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. UNSCEAR 2008 report to the general assembly with scientific annexes, vol. 1. New York: United Nations; 2010.
82. Sigurdson AJ, Doody MM, Rao RS, Freedman DM, Alexander BH, Hauptmann M, et al. Cancer incidence in the US radiologic technologists health study, 1983–1998. Cancer. 2003;97:3080–9.
83. Doody MM, Mandel JS, Lubin JH, Boice Jr JD. Mortality among United States radiologic technologists, 1926–90. Cancer Causes Control. 1998;9:67–75.
84. Wang JX, Zhang LA, Li BX, Zhao YC, Wang ZQ, Zhang JY, Aoyama T. Cancer incidence and risk estimation among medical x-ray workers in China, 1950–1995. Health Phys. 2002;82:455–66.
85. McGeoghegan D, Binks K. The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946–95. J Radiol Prot. 2000;20:111–37.
86. Telle-Lamberton M, Bergot D, Gagneau M, Samson E, Giraud JM, Neron MO, Hubert P. Cancer mortality among French atomic energy commission workers. Am J Ind Med. 2004;45:34–44.
87. Ashmore JP, Krewski D, Zielinski JM, Jiang H, Semenciw R, Band PR. First analysis of mortality and occupational radiation exposure based on the national dose registry of Canada. Am J Epidemiol. 1998;148:564–74.
88. Sont WN, Zielinski JM, Ashmore JP, Jiang H, Krewski D, Fair ME, et al. First analysis of cancer incidence and occupational radiation exposure based on the national dose registry of Canada. Am J Epidemiol. 2001;153:309–18.
89. Shields T, Gridley G, Moradi T, Adami J, Plato N, Dosemeci M. Occupational exposures and the risk of ovarian cancer in Sweden. Am J Ind Med. 2002;42:200–13.
90. IARC. Monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens. Part A: pharmaceuticals, vol. 100. Lyon: International Agency for Research on Cancer; 2011.
91. Heron RJ, Pickering FC. Health effects of exposure to active pharmaceutical ingredients (APIs). Occup Med (Lond). 2003;53:357–62.

92. Edling C, Friis L, Mikoczy Z, Hagmar L, Lindfors P. Cancer incidence among pharmaceutical workers. Scand J Work Environ Health. 1995;21:116–23.
93. Hansen J, Olsen JH. Cancer morbidity among Danish female pharmacy technicians. Scand J Work Environ Health. 1994;20:22–6.
94. Hansen J, Olsen JH, Larsen AI. Cancer morbidity among employees in a Danish pharmaceutical plant. Int J Epidemiol. 1994;23:891–8.
95. Guo J, Kauppinen T, Kyyronen P, Heikkila P, Lindbohm ML, Pukkala E. Risk of esophageal, ovarian, testicular, kidney and bladder cancers and leukemia among finnish workers exposed to diesel or gasoline engine exhaust. Int J Cancer. 2004;111:286–92.
96. Robinson CF, Walker JT. Cancer mortality among women employed in fast-growing U.S. occupations. Am J Ind Med. 1999;36:186–92.
97. Nanni O, Ravaioli A, Bucchi L, Falcini F, Ricci R, Buiatti E, Amadori D. Relative and absolute cancer mortality of women in agriculture in northern Italy. Eur J Cancer Prev. 2005;14:337–44.
98. Koutros S, Alavanja MC, Lubin JH, Sandler DP, Hoppin JA, Lynch CF, et al. An update of cancer incidence in the agricultural health study. J Occup Environ Med. 2010;52:1098–105.
99. IARC. Monographs on the evaluation of carcinogenic risks to humans, Some aromatic amines, organic dyes and related exposures, vol. 99. Lyon: International Agency for Research on Cancer; 2010.
100. Takkouche B, Regueira-Mendez C, Montes-Martinez A. Risk of cancer among hairdressers and related workers: a meta-analysis. Int J Epidemiol. 2009;38:1512–31.
101. Quach T, Doan-Billing PA, Layefsky M, Nelson D, Nguyen KD, Okahara L, et al. Cancer incidence in female cosmetologists and manicurists in California, 1988–2005. Am J Epidemiol. 2010;172:691–9.
102. Czene K, Tiikkaja S, Hemminki K. Cancer risks in hairdressers: assessment of carcinogenicity of hair dyes and gels. Int J Cancer. 2003;105:108–12.
103. Mabuchi K, Bross DS, Kessler II. Epidemiology of cancer of the vulva. A case-control study. Cancer. 1985;55:1843–8.
104. Riska A, Martinsen J, Kjaerheim K, Lynge E, Sparen P, Tryggvadottir L, et al. Occupation and risk of primary fallopian tube carcinoma in Nordic countries. Int J Cancer. 2012;13:186–92.
105. Loukovaara M, Pukkala E, Lehtovirta P, Leminen A. Epidemiology of choriocarcinoma in Finland, 1953 to 1999. Gynecol Oncol. 2004;92:252–5.
106. Reid A, Heyworth J, de Klerk N, Musk AW. Asbestos exposure and gestational trophoblastic disease: a hypothesis. Cancer Epidemiol Biomarkers Prev. 2009;18:2895–8.

Malignant Tumors of the Male Reproductive System

24

Lorenzo Richiardi and Luisa Zuccolo

Keywords
Testicular cancer • Prostate cancer • Occupation • Pesticides • Firefighting

Introduction

The two main cancers of the male reproductive system are prostate cancer and testicular cancer, which have completely different epidemiological behaviors. Prostate cancer is one of the most common cancers in men, with an incidence strongly related with age, making it a cancer that mainly affects older men. Conversely, testicular cancer is quite rare and generally affects young men, with an incidence peak at age 35 years.

One of the features these two types of cancer have in common is that their etiology remains elusive, despite the large number of studies that have been conducted. However, although it cannot be ruled out that a small proportion of cases are occupational cancers, it is not likely that occupational factors play a central role in the etiology of prostate or testicular cancer.

Prostate Cancer

Descriptive Epidemiology

Prostate cancer is the most common cancer among men in several populations and one of the most common causes of cancer death in most developed regions [1]. Its incidence strongly depends on age: about 75 % of all prostate cancer is diagnosed in men aged over 65 years, and about 55 % of all prostate cancer is found in men aged over 75 years [1].

Pathological tumor grade is assigned in prostate cancer cases based on the Gleason score. Tumor grade has a strong prognostic implication and is used to roughly separate highly aggressive tumors (Gleason score ≥8) from other tumors (Gleason score <8).

The introduction of prostate-specific antigen (PSA) testing in the late 1980s has dramatically affected the incidence of prostate cancer worldwide. Already in 1990, 60 % of all newly diagnosed prostate cancers in the United States were detected by PSA testing [2]. This has produced a sharp increase in incidence, particularly of low-grade tumors, which are most commonly discovered in asymptomatic men undergoing opportunistic screening for prostate cancer by PSA testing.

Both for etiological studies and for prognosis, it is thus very relevant to distinguish between latent PSA-detected cases and aggressive PSA- or clinically detected cases.

Nonoccupational Risk Factors

There are a few established risk factors for prostate cancer, all of which are non-modifiable (Table 24.1). Prostate cancer incidence increases dramatically with age, Black-African ethnicity is associated with an increased risk of at least 50 % compared to Caucasians, and the risk of prostate cancer is higher in first-degree relatives of affected individuals (risk ratios of 2–3) compared with the general population [1]. Familial clustering suggests that genetic factors have an important role in this disease, with heritability estimates around 40 % [6]. Recently, genome-wide association studies

L. Richiardi, MD, PhD (✉)
Cancer Epidemiology Unit, Department of Medical Sciences, Univeristy of Turin, and CPO-Piemonte, Via Santena 7, Torino 10126, Italy
e-mail: lorenzo.richiardi@unito.it

L. Zuccolo, MSc, PhD
MRC Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK

Funding This chapter was prepared within the framework of projects funded by the Italian Association for Cancer Research and the Compagnia di San Paolo Foundation.

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_24, © Springer-Verlag London 2014

Table 24.1 Factors associated with prostate cancer risk, by strength of the evidence from published literature

	Risk factors
Established	Old age [3]
	Black-African ethnicity [3]
	Family history of disease [3]
Probable	Circulating IGF-1 [4]
	Diets high in calcium[a, b] [5]

Modified from World Cancer Research Fund, American Institute for Cancer Research [5] and Gronberg [3]
[a]Includes diets that naturally contain calcium and that contain foods fortified with calcium
[b]Effect only apparent at high calcium intakes (around 1.5 g/day or more)

robustly identified 34 common genetic variants associated with prostate cancer, some of which are in or near genes, whereas others are in gene deserts [7–15]. The most studied genomic region to date is on chromosome 8 (8q24). The association of this genomic region with prostate cancer has been consistently replicated in populations of both European and African descent [16].

Among the other probable determinants of prostate cancer, dietary and lifestyle factors may play an important role, as suggested by results from international comparisons showing higher incidence and mortality in countries with a higher gross domestic product and a positive correlation with elements of Western diets [17]. In addition, migrant studies show that low-risk individuals of Chinese and Japanese nationality rapidly acquire Western levels of risk when they move to North America [18, 19].

Consistent evidence indicates that circulating insulin-like growth factor 1 (IGF-1) is a probable risk factor for prostate cancer (Table 24.1). Despite substantial heterogeneity among studies, a recent systematic review and meta-analysis concluded that increased IGF-1 levels increase the risk of prostate cancer, in particular of aggressive disease [4]. Diets high in calcium probably increase prostate cancer risk, as also suggested by some evidence of an increased risk in men with diets rich in milk and dairy products [5].

The evidence of an increased risk of prostate cancer associated with diets rich in processed meat, diets poor in pulses, and foods containing vitamin E and alpha-tocopherol is limited-suggestive [5]. The same is true for tall adult stature, possibly hinting at the importance of childhood environment [20].

Smoking is not a risk factor for prostate cancer [21]. Similarly, vitamin D and sun exposure seem to play almost no role in prostate cancer incidence [22, 23] or progression [24]. For the following factors, the evidence is either currently limited or study results are too heterogeneous and no conclusion can be reached: physical activity, alcoholic beverages, folic acid, foods containing folate and B-group vitamins, circulating IGFBP-3, circulating endogenous sex hormones, lipid profiles, and statins.

Results on obesity are heterogeneous. Higher body mass index is associated with reduced incidence, mostly, of localized, nonaggressive disease, but it is associated with increased incidence of advanced, more aggressive cancer types and increased prostate-cancer-specific mortality [25, 26]. Some other components of metabolic syndrome, in particular high total cholesterol levels [27] and hypertension [28], have been associated with an increased risk of prostate cancer, in particular advanced disease.

Some factors have been associated with a reduced risk of prostate cancer. In terms of diet, there is evidence of a protective effect of foods containing lycopene (found abundantly in tomatoes) and selenium [5]. The drug finasteride has been shown to reduce the incidence of localized prostate cancer in a large randomized clinical trial. However approval from the US Food and Drug Administration to use finasteride as a chemopreventive agent is pending, due to an apparent increase in more aggressive cancers in that same trial [29]. There is strong epidemiological evidence from two meta-analyses that diabetes is associated with a 10–20 % reduction in prostate cancer risk [30, 31]. It is unlikely that these results can be explained by detection bias (namely, an effect of diabetes on PSA level instead of on prostate carcinogenesis), as they were confirmed by a study where all participants received a biopsy irrespective of their PSA levels [25].

Occupational Risk Factors

A number of studies have been conducted on occupational risk factors for prostate cancer, although most of the evidence comes from cohort studies in which prostate cancer was only one of the many investigated outcomes. Overall, evidence points toward a possible increased risk among farmers, which may be associated with exposure to pesticides (further discussed in the next section). Results for other occupational risk factors are much more inconsistent. For example, although prostate cancer is common enough that it can be studied in most occupational cohorts with sufficient power, Siemiatycky and colleagues did not mention prostate cancer in their 2004 review, which summarized the existing knowledge on occupational carcinogens by target organ from the International Agency for Research on Cancer (IARC) Monographs [32].

In a recent large linkage study based on data from the censuses and cancer registries in the Nordic countries, which included about 339,000 prostate cancer patients, the largest observed standardized incidence ratio (SIR) was 1.22 for dentists, followed by an SIR of 1.17 for administrators, and slightly elevated risks for other categories of high socioeconomic status occupations [33]. Thus, there was no evidence of increased occupational risks of prostate cancer and the increased risk among high socioeconomic status occupations was most likely due to more intensive opportunistic screening by PSA testing.

Previous studies have reported an increased risk of prostate cancer in association with some specific occupations,

including high socioeconomic status occupations, power plant worker, metal worker, painter, mechanic, and transport worker, as well as some specific exposures, including metal dust, polyaromatic hydrocarbons, electromagnetic fields, and diesel exhaust, but none of these associations have been consistently replicated [34–50].

Systematic reviews on prostate cancer risk in association with occupations in metal working [51] and the rubber industry [52, 53] concluded that there was no evidence of an association. One recent meta-analysis on miners found an overall decreased relative risk (RR) for prostate cancer of 0.83 (95 % confidence interval [CI]: 0.79–0.87, based on 21 studies) [54], while another recent meta-analysis on driving occupations and prostate cancer risk found heterogeneity between studies and pooled RRs of 0.96 (95 % CI: 0.77–1.21, five studies) for truck drivers and of 1.34 (95 % CI: 0.98–1.82, seven studies) for railroad transport workers [55].

Some reviews and meta-analyses have identified suggestions of an association, but these results should be interpreted with caution due to possible biases introduced by opportunistic prostate cancer screening by PSA testing. In the IARC Monograph on firefighters, the IARC Working Group carried out a random effects meta-analysis of 16 studies published until 2007, which resulted in an estimated 30 % excess risk of prostate cancer (1.30; 95 % CI: 1.12–1.51) in this population [56]. The same monograph also assessed shift work and studies on airline pilots. Pilots were reported to have an excess risk of 65 % (1.65, 95 % CI: 1.19–2.29) in a meta-analysis of cohort studies published in 2000 [57]. Two large cohort studies were published after the 2000 meta-analysis: Pukkala and colleagues found an SIR of prostate cancer of 1.21 (95 % CI: 0.93–1.54) among 10,000 pilots in the Nordic countries, with evidence of an association with increasing number of long-haul flights [58]. Conversely, Blettner and colleagues found a standardized mortality ratio (SMR) of 0.94 (95 % CI: 0.71–1.26) among cockpit workers from nine European countries (including the Nordic countries), with no effect of duration of employment [59].

Many studies have investigated occupational exposure to cadmium compounds and its relationship with prostate cancer, since the first report was published in 1965 [60]. Cadmium may biologically compete and interfere with zinc, which is found in relatively high concentrations in prostate cells. Studies have consistently found increased cadmium (and decreased zinc) concentrations in prostatic tumor tissue [61–63]. In a number of animal experiments, cadmium compounds have been found to induce prostate cancer in rats [64]. Human studies were reviewed in an IARC Monograph published in 1993 [65] and were recently reassessed in the IARC Monograph volume 100. Overall, there is a possible suggestion of an association but also large inconsistencies among studies. In 2005, a meta-analysis of cohort studies of nickel-cadmium battery plant workers identified four studies, with an overall SMR of 1.26 (95 % CI: 0.83–1.84) based on 27 deaths due to prostate cancer [66]. A systematic review published in 2003 concluded that early claims of an increased risk of prostate cancer in men exposed to cadmium compounds could not be confirmed, although data were somewhat scarce [67]. Updates of the follow-up of older cohorts and use of quantitative estimates of cadmium exposure did not lead to sufficient evidence in favor of an association [68]. Results of case-control studies with data on biological measures of cadmium concentrations in toenails, blood, or urine are also inconsistent [69, 70].

Specific Occupational Risk Factors

Farming and Pesticides

Farming and exposure to pesticides are the most debated occupational risk factors for prostate cancer. In addition to several cohorts of farmers that have been repeatedly followed up, farming has also been analyzed as an occupational exposure in several case-control studies on prostate cancer. Overall, however, evidence on prostate cancer risk in farmers is difficult to interpret. Farming involves a wide and heterogeneous variety of occupational exposures, which vary in place and time across different farms and farming operations. Apart from chemicals, mainly different types of pesticides, farmers are also exposed to diesel exhaust, polyaromatic hydrocarbons, fertilizers, sunlight, dust, viruses, etc. In addition, lifestyle is an obvious confounding factor, and overall cancer incidence is typically decreased among farmers [71].

Some meta-analyses of studies on farming and prostate cancer were published in the 1990s and found a modest increased risk of prostate cancer of about 10 %, mainly due to results of case-control and proportion mortality ratio studies (Table 24.2) [72, 78–80]. There was, however, marked heterogeneity among studies.

As summarized in Table 24.2, other meta-analyses and systematic reviews published in the last 10 years attempted to evaluate the role of exposure to pesticides more directly. Increased pooled RRs of prostate cancer of 20–30 % have been found among pesticide applicators and workers employed in the pesticide manufacturing industry. In the meta-analysis of studies on agricultural and nonagricultural occupational exposure to pesticides, applicators had a pooled RR of 1.64 for prostate cancer (95 % CI: 1.13–2.38), while farmers had an RR of 0.97 (0.92–1.03) [73]. The latter RR was higher in North American (RR = 1.26, 95 % CI: 0.83–1.90) than in European (RR = 0.96, 95 % CI: 0.92–1.01) studies. In the meta-analysis on workers employed in the pesticide manufacturing industry, pooled sub-analyses on broad classes of pesticides did not identify any specific group of pesticides that was particularly associated with prostate

Table 24.2 Systematic reviews and meta-analyses on farming, exposure to pesticides, and prostate cancer

Reference	Exposure	Period covered	Number of studies	Effects RR (95 % CI)	Comments
Acquavella et al. (1998)[a] [72]	Farming	Before 1995	Cohort: 11	0.95 (0.93–0.98)	Marked heterogeneity among studies
			Case control: 8	1.21 (1.15–1.28)	PMR estimates biased by a reduced overall mortality among farmers
			PMR: 11	1.11 (1.08–1.18)	Case-control studies with exploratory analyses on occupations were excluded
			Overall: 30	1.07 (1.02–1.13)	
Van Maele-Fabry et al. (2003) [73]	Agricultural and nonagricultural occupational exposure to pesticides	1995–2001	Cohort: 11	1.13 (1.02–1.24)	Marked heterogeneity partly explained by:
			Case control: 7	0.98 (0.71–1.37)	Occupational category → Pesticide applicators: RR = 1.64 (1.13–2.38)
			PMR: 4	Not available	Farmers: RR = 0.97 (0.92–1.03)
			Overall: 22	1.13 (1.04–1.22)	Geographical location → Europe: RR = 0.98 (0.93–1.02)
					United States/Canada: RR = 1.50 (1.08–2.07)
Van Maele-Fabry et al. (2004) [74]	Pesticide users	Before 2004	Cohort: 15	1.27 (1.06–1.52)	PMR studies excluded
			Case control: 7	1.15 (0.77–1.72)	Includes the studies on pesticide applicators included in Van Maele-Fabry et al. [73]
			Overall: 22	1.24 (1.06–1.45)	
Van Maele-Fabry et al. (2006)[b] [75]	Pesticide manufacturing workers	Before 2005	Cohort: 16	1.28 (1.05–1.58)	PMR and case-control studies excluded
					Sub-analyses by classes of pesticide:
					Non-phenoxy herbicides: RR = 1.52 (0.92–2.52)
					Triazines: RR = 1.76 (0.95–3.28)
					Phenoxy herbicides: RR = 1.24 (0.99–1.55)
					Unlikely contaminated: RR = 1.18 (0.83–1.67)
					Contaminated: RR = 1.29 (0.96–1.72)
Mink et al. (2008) [76]	Pesticide exposure in agricultural settings	Before 2007	Cohort: 8	Not available:	Studies with no individual assessment of exposure to pesticides were excluded
			Case control: 5	"No strong consistent associations emerging on specific pesticides"	
Jones et al. (2009)[b] [77]	Crop protection product manufacturing workers	Before 2004	Cohort: 29	1.03 (0.80–1.33)	Sub-analyses on phenoxy herbicide cohorts:
					RR = 1.16 (0.85–1.57)

[a]Other three meta-analyses [78–80] on farmers were published before the paper by Acquavella et al. [72], with similar results but a smaller number of studies

[b]There is some overlap between these two meta-analyses but selection criteria for the studies were different. Mainly the cohorts of the IARC international cohort study [81] were included in Jones et al. [77] but not in Van Maele-Fabry et al. [75] as Jones et al. [77] excluded cohorts of sprayers using the original data

RR relative risk, *CI* confidence interval, *PMR* proportion mortality studies

cancer risk [75]. A similar meta-analysis limited to crop protection product manufacturing workers found no excess risk of prostate cancer and an RR of 1.16 (95 % CI: 0.85–1.57) in an analysis restricted to cohorts of workers exposed to phenoxy herbicide [77].

Heterogeneity was also marked among studies in these meta-analyses on exposure to pesticides, which is to be expected as there are several different types of chemicals involved, and confounding or effect modification from lifestyle factors still apply.

Much of the recent evidence on farming, exposure to pesticides, and prostate cancer comes from the Agricultural Health Study cohort, which includes more than 52,000 licensed private pesticide applicators and about 5,000 licensed commercial applicators all recruited between 1993 and 1997 in Iowa and North Carolina in the United States. Upon enrollment, members of the cohort completed a questionnaire including information on lifestyle factors and occupational exposures. In the latest publications, the cohort had been updated until the end of December 2006 for cancer incidence [82] and until the end of December 2007 for mortality [83]. The Agricultural Health Study cohort reduces some of the issues of heterogeneity described above, as it is a more homogeneous population, with a large sample size and a thorough characterization of the type of exposure.

SIRs of prostate cancer increased by 19 % (95 % CI: 14–25 %; based on 1,719 cases) among private applicators in the Agricultural Health Study cohort and by 28 % (95 % CI: 0–61 %; based on 73 cases) among commercial applicators. Mortality from prostate cancer was not increased (SMR = 0.81, 95 % CI: 0.70–0.95; based on 171 deaths), but SMRs were decreased for almost all cancer sites. When SIRs and SMRs were calculated relative to all cancer sites, the relative SIR was 1.66 (1.57–1.77) and the relative SMR was 1.53 (95 % CI: 1.31–1.78).

A study published in 2003 analyzed the association between exposure to 40 specific types of pesticides and prostate cancer risk in a case-control study nested within the Agricultural Health Study cohort [84]. Difficulties in this analysis included collinearities among exposures to the specific pesticides. In a factor analysis, the factor mainly determined by ever use of some chlorinated insecticides (aldrin, chlordane, dieldrin, DDT, heptachlor, toxaphene) and ever use of two chlorinated phenoxy herbicides (2,4,5-trichlorophenoxyacetic acid and 2,4,5-trichlorophenoxypropionic acid) was positively associated with prostate cancer risk.

In the analyses of individual pesticides, there was a dose-response relationship between exposure to fumigant methyl bromide and prostate cancer risk. Some increased risks were found for a number of pesticides when analyses were confined to patients with a family history of prostate cancer, including, among others, thiocarbamate herbicide butylate, four organophosphate insecticides (cumaphos, fonofos, chlorpyrifos, and phorate), and the insecticide for animal use, permethrin.

Most of the analyses on individual pesticides conducted within the Agricultural Health Study cohort have been recently updated using a cohort approach instead of a nested case-control approach (exceptions include analyses on methyl bromide and phenoxy herbicides, which, to our knowledge, have not yet been updated) [85]. Most of these analyses on individual types of pesticides did not report evidence of an association with prostate cancer [85]. In particular, a paper published in 2007 assessed cancer risk in association with exposure to organochlorine insecticides, which were included, together with chlorinated phenoxy herbicides, in the factor associated with prostate cancer risk in the 2003 analysis [86]. There was no association between exposure to organochlorine insecticides and prostate cancer risk, either in analyses grouping all organochlorine insecticides together or in analyses on specific organochlorine insecticides (aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, and toxaphene). Regarding pesticides associated with prostate cancer among patients with a family history of prostate cancer in the 2003 analysis, (i) the association with fonofos persisted substantially unchanged, from an RR of 1.80 (95 % CI: 1.14–2.84) in 2003 to an RR of 1.67 (95 % CI: 1.35–2.07) for ever exposure, with evidence of a dose-response relationship [87]; (ii) the association with butylate persisted and there was a suggestion of an association also in the analyses that included the whole cohort (with and without family history) [88]; (iii) the association with cumaphos persisted but was considerably attenuated in the updated follow-up, from an RR of 2.07 (95 % CI: 1.19–3.62) to an RR of 1.65 (95 % CI: 1.13–2.38) [89]; (iv) the association with permethrin and pyrethroid products was strongly attenuated, from an RR of 2.38 (95 % CI: 1.34–4.25) to an RR of 1.19 (95 % CI: 0.82–1.3) [90]; and (v) the association with phorate was also attenuated, from an RR of 1.67 (95 % CI: 1.09–2.56) to an RR of 1.53 (95 % CI: 1.10–2.14) [91].

The mechanisms underlying the potential interaction between family history of prostate cancer and exposure to some pesticides remain to be elucidated. A recent article, again nested in the Agricultural Health Study cohort, evaluated the interaction between variants in 8q24, which has been associated with prostate cancer in genome-wide association studies, and exposure to 49 pesticides [92]. In agreement with results based on family history, more than multiplicative effects have been found for variants in 8q24 and exposure to some pesticides, especially fonofos.

Apart from studies on pesticide manufacturing workers included in the meta-analysis carried out by Maele-Fabry and colleagues summarized in Table 24.2 and results from the Agricultural Health Study cohort, a few other studies have investigated the effects of specific pesticides on prostate cancer risk. In a case-control study nested within a cohort of United Farm Workers of America members (a labor union in California), out of 16 pesticides analyzed, there was a significant dose-response relationship for exposure to heptachlor, lindane (organochlorine pesticides), and simazine (a triazine herbicide) and suggestion of a dose-response relationship for methyl bromide and dichlorvos (an organophosphate) [93]. Settimi and colleagues [94] conducted a case-control study on 124 prostate cancer cases in Italy, assessing seven pesticide groups. They reported an RR of 2.5 (95 % CI: 1.4–4.2) for occupational exposure to organochlorine compounds in agricultural settings, but no elevated risks for exposure to carabamates, copper and sulfur compounds, dithiocarbamates, nitrofenoles, organophosphates, and tioftalates. Band and colleagues [95] assessed occupational exposure to a large number ($n = 122$) of pesticides in 1,153 prostate cancer cases compared with cancer controls, all recruited in British Columbia, Canada. Exposures to individual pesticides were strongly correlated. An excess risk of prostate cancer for ever exposure and evidence of a dose-response relationship was found for the fungicides captan, dichlone, dodine, ferbam, maneb, and sulfur and the insecticides 2,4-DB, dinoseb amine, MCPA, simazine, azinophos-methyl, carbaryl, DDT, and malathion. Cockburn and colleagues [96] evaluated environmental exposure to six pesticides in a population-based case-control study of 173 prostate cancer cases recruited in

California's Central Valley, an agriculturally intensive area. The proportion of participation was below 50 % among both cases and controls. The study estimated an increased risk of prostate cancer in association with ever exposure to methyl bromide, organochlorines, and the fungicide captan, with some evidence of a dose-response relationship for the latter two compounds.

Some nonoccupational studies have investigated plasma or adipose tissue levels of organochlorines in association with prostate cancer risk [97–100], with inconsistent results. However, it should be noted that these studies were not conducted in an occupational setting, thus mean exposure levels were low. Moreover, most of the studies had limited sample sizes and used biological samples obtained at the time of cancer diagnosis.

Data on the effect of occupational exposure to pesticides on prostate cancer risk are thus complex to evaluate. Several studies have been conducted, and recent evidence, mainly from the Agricultural Health Study cohort, points toward a possible association with some specific pesticides and, mainly, toward an interaction between exposure to pesticides and family history of prostate cancer. However, these associations are far from being established. A consortium of agricultural cohorts recently launched by the IARC has the potential to provide further evidence on prostate cancer risk associated with farming and exposure to pesticides [101].

A number of potential mechanisms might be involved in the relationship between exposure to pesticides and prostate cancer, reflecting the heterogeneous nature of the chemicals involved. Some pesticides, such as organochlorine insecticides, affect hormonal function either indirectly or directly [102], while others, including methyl bromide [103], may have a genotoxic effect [104]. Oxidative stress is another mechanism that may link cancer incidence to exposure to pesticides [105].

The hormonal effects of pesticides as a potential mechanism leading to increased risk of prostate cancer are part of a broader issue of environmental and occupational exposure to endocrine-disrupting chemicals [106], which have been studied to a larger extent in association with the risk of testicular cancer (see next section). However, at present there are few data on the effects of occupational exposures to endocrine disruptors other than pesticides. Workers exposed to polychlorinated biphenyls (PCBs) are one exception. Prince and colleagues [107] followed up a cohort of 14,458 workers employed in two electrical capacitor plants, one in New York and one in Massachusetts. They found strong evidence of a dose-response relationship between cumulative exposure to PCBs and prostate cancer mortality based on 34 deaths (RR for the highest vs. the lowest exposure level = 6.05, 95 % CI: 2.01–18.2). Charles and colleagues [44] conducted a case-control study of 387 prostate cancer deaths nested in a cohort of workers employed in five United States electric companies and found no evidence of an association with cumulative hours of exposure to PCBs. Other studies on capacitor and transformer manufacturing workers were too small to evaluate prostate cancer mortality with any statistical power [108–110].

Testicular Cancer

Descriptive Epidemiology

Testicular cancer is a rare condition, but it is the most common cancer among young men. Its incidence increases rapidly after puberty, peaks at age 30–35 years, and declines thereafter. Almost no cases are observed between 3 and 15 years of age or after 60 years of age. According to GLOBOCAN 2008, Norway has the highest age-standardized incidence worldwide with a rate of 12.1 cases per 100,000 inhabitants per year [111].

Testicular cancer is one of the most rapidly increasing forms of cancer worldwide, with an increasing trend that began as early as the first decades of the twentieth century [112, 113]. Reasons for this trend, which is observed both in high- and in low-incidence populations, are not known.

Most testicular cancers are of germ-cell origin and can be further classified into two main histological categories: seminomas and nonseminomas. Each category accounts for approximately half of the cases. These two types of germ-cell testicular cancer have different clinical characteristics and age-specific incidence patterns; nonseminomas are more often treated with chemotherapy and the incidence peak occurs 10 years earlier than for seminomas.

Five-year survival after testicular cancer has increased dramatically after the introduction of cis-platinum-based regimes at the end of the 1970s and is currently above 95 %.

Risk Factors for Testicular Cancer

Nonoccupational Risk Factors

The etiology of testicular cancer is largely unknown. Cryptorchidism, family history of testicular cancer, age, and having had a previous contralateral testicular cancer are the only established risk factors (Table 24.3), and they account for only a small proportion of cases.

The occurrence of testicular cancer at young ages, the natural history of the disease, and the molecular similarities between carcinoma in situ of the testis and primordial gonocytes [115] suggest that early exposures acting during fetal life might play a role in the development of testicular cancer. For this reason several studies have investigated indicators of prenatal exposures, with results that are somewhat inconsistent. Overall, recent meta-analyses indicate that low birth

Table 24.3 Risk factors for testicular cancer

	Risk factors
Established	Age
	Contralateral testicular cancer
	Cryptorchidism
	Ethnic group
	Family history
Probable	Low birth order/sibship size
	Low birth weight
	Short gestational duration
	Twinning
	Age at puberty
	Height
	Subfertility

Modified from Richiardi et al. [114]

weight, short gestational duration, being a twin, low birth order, and small sibship size are all associated with testicular cancer risk (Table 24.3) [116, 117].

A possible etiological role of endocrine-disrupting chemicals in testicular cancer has been extensively discussed in the scientific literature [118]. Since the first report at the end of the 1970s, it has been suggested that chemicals with estrogen-like properties (such as diethylstilboestrol [DES], PCBs bisphenol A, organochlorine pesticides) could interfere with gonadal development and function and result in an increased risk of testicular cancer [118, 119]. This hypothesis has been criticized due to empirical inconsistencies, as well as the fact that exogenous estrogens would have to compete with the much more potent maternal endogenous estrogens. Thus the concept has been revised to include substances with antiestrogenic (again DES or some PCBs) and antiandrogenic effects, such as p,p′-DDE, and other pesticides and phthalates [120, 121]. A meta-analysis published in 2008 on studies of prenatal exposure to agents with hormonal effects, including DES, and testicular cancer risk identified nine studies and estimated a pooled RR of 2.14 (95 % CI: 1.48–3.10) [122].

Some authors have suggested that testicular cancer may be part of a proposed new syndrome, testicular dysgenesis syndrome (TDS), which also encompasses poor semen quality, cryptorchidism, and hypospadias and is considered to be the result of environmentally disrupted embryonal programming and gonadal development [123]. The concept of a TDS has been challenged by others, including one of this chapter's authors [124], but it is influential in testicular cancer research.

Postnatal factors have been investigated to a lesser extent than prenatal factors. However, height, age at puberty, and subfertility have been repeatedly and consistently associated with increased testicular cancer risk (Table 24.3), as demonstrated by recent meta-analyses [125, 126].

The associations with postnatal factors include findings of an increased risk of testicular cancer among men who underwent surgery for cryptorchidism after puberty compared to those who underwent the procedure before puberty [127]. These findings may suggest that puberty is a potential window of susceptibility in which environmental exposures can modulate the risk of testicular cancer [128]. This would be consistent with the fact that puberty is a period of high replication of spermatogonia.

Aside from prenatal and postnatal factors, genetic variants have also been recently assessed in genome-wide association studies [129–131]. Testicular cancer risk has been linked with polymorphisms in or near the genes KITLG, SPRY4, BAK1, DMRT1, TERT, and ATF7IP.

Occupational Risk Factors

As testicular cancer occurs at relatively young ages, the role of occupational exposures is thought to be limited. In addition, the hypothesized windows of susceptibility for testicular cancer, i.e., fetal life, the perinatal period, and puberty, occur very early in life. Testicular cancer is also difficult to investigate in occupational cohort studies as it is a rare cancer and, at least as of the end of the 1970s, is associated with very high survival, rendering mortality studies relatively uninformative. In order to provide data on testicular cancer, an occupational cohort should be rather large and be linked to cancer incidence data.

It is not surprising, therefore, that data on occupational risk factors for testicular cancer are scarce, although associations have been repeatedly found with exposure to pesticides and with the occupation of firefighter. These two occupational exposures will be further discussed in the next section.

A number of studies, mainly of a case-control design, have investigated occupational risk factors for testicular cancer, with inconsistent findings. Studies have found increased risks in association with some categories of high socioeconomic status occupations: the occupations of metal worker, welder, printer, electrician, furnace worker, and pulp and paper worker; employment in the industries of glue production, crude petroleum and natural gas extraction, and food processing; and occupational exposure to extreme temperatures, organic solvents, polyvinyl chloride, and textile dust [132–150]. None of these associations, however, have been consistently replicated, and, at present, they can only be considered as topics in need of further study.

A number of studies have focused on testicular cancer in military personnel. Garland and colleagues found an excess risk of testicular cancer among naval automobile mechanics in the US Navy [151]. In a hospital-based case-control study, Tarone and colleagues found an excess risk of testicular cancer associated with service in the Vietnam War [152]. In a study published in 1995, personnel employed in the Royal Air Force were found to have a higher incidence of testicular

cancer when compared with the general population in the United Kingdom [153]. US veterans of the 1990–1991 Gulf War have been repeatedly studied for cancer risk, but no evidence of an increased risk of testicular cancer has been found in comparison with both non-Gulf War veterans and the general population [154–156]. Similar null findings have been reported from the follow-up of Gulf War veterans from the United Kingdom [157]. In a recent study, US military personnel were found to have an incidence of testicular cancer similar to that of the general population [158].

Specific Occupational Risk Factors

Farming and Pesticides

A meta-analysis conducted by Acquavella and colleagues identified 14 studies on testicular cancer in farmers published before 1995 [72]. The overall RR of testicular cancer was 0.97 (95 % CI: 0.87–1.08). As mentioned above, however, only cohort and case-control studies with incidence data are completely informative with regard to testicular cancer, and most of the studies included in the meta-analysis used mortality data. In addition, farmers comprise a heterogeneous group of workers exposed to a wide variety of occupational exposures, which vary in place and time across different farms and farming operations and in most cases have a different lifestyle than the general population.

Studies on specific occupational exposures involved in farming are more informative. Table 24.4 reviews incident cohort studies of pesticide applicators with information on testicular cancer published until the end of August 2011. We found five studies, two from the United States [82, 161], two from Europe [159, 164], and one from Australia [160].

Table 24.4 Cohort studies on pesticide users and testicular cancer incidence

Reference, study location and period	Cohort description	Exposure assessment	Number of observed cases	SIR (95 % CI)	Adjustment for potential confounders	Comments
Frost et al. (2011) United Kingdom [159] 1987–2004	Pesticide Users Health Study (PUHS): 62,960 agricultural pesticide users with certificates of competence	Certified users who gave consent to be included in the cohort	102	1.26 (1.04–1.53)	Age, period, country	
Koutros et al. (2010), Iowa and North Carolina, United States [82] 1993–2006	Agricultural Health Study (AHS) cohort Licensed private (51,035) and commercial (4,712) male pesticide applicators	Questionnaire at recruitment	Private applicators: 32 Commercial applicators: 6	0.97 (0.67–1.37) 1.21 (0.45–2.64)	Age, period, race, country	Individual pesticides have been studied within the AHS cohort but power was too limited for testicular cancer
MacFarlane et al. (2009), New South Wales state, Australia [160] 1983–2002	1,813 pest controllers using pesticides	Workers participating in a pesticide surveillance program offered by the state	6	1.98 (0.89–4.41)	Age, period	
Fleming et al. (1999), Florida, United States [161] 1981–1993	30,155 licensed private, commercial, or public pesticide applicators	Registered licensees	Private applicators: 15 Commercial/ public applicators: 8	2.37 (1.33–3.91) 2.72 (1.17–5.36)	Age, period	
Ditch et al. (1995), Sweden, [162, 163] 1965–1991	20,025 licensed pesticide applicators	Registered licensees 268 applicators interviewed with reference to use of pesticides	21	1.09 (0.68–1.67)	Age, period	Herbicide use: 20 % in the 1950s, 51 % in the 1960s, 68 % in the 1970s Insecticide use: 15 % in the 1950s, 34 % in the 1960s, 46 % in the 1970s Fungicide use: 7 % in the 1950s, 16 % in the 1960s, 31 % in the 1970s

SIR standardized incidence ratio, *CI* confidence interval

With the exception of the Agricultural Health Study [82], all studies found an increased risk of testicular cancer. A random effects meta-analysis rendered a pooled RR of 1.48 for testicular cancer (95 % CI: 1.08–2.01), with some evidence of heterogeneity among studies ($p = 0.06$). The UK study by Frost and colleagues [159] had the largest relative weight, while the study by Fleming and colleagues [165] estimated the highest RR. Exclusion of either of these two studies did not alter the results of the meta-analysis substantially.

We did not include a study of Norwegian orchard and greenhouse workers [166] in the meta-analysis, because it did not include pesticide applicators specifically. However, this study identified an SIR of 1.63 for testicular cancer (95 % CI: 1.01–2.62) based on 20 exposed cases. Similarly, we did not include the Icelandic study by Zhong and colleagues (1996) as only 30 % of the members of the cohort were licensed pesticide applicators [167]. This study reported an SIR of 1.20 for testicular cancer (95 % CI: 0.13–4.32) based on two observed cases. Finally, the recent Australian study conducted by MacFarlane and colleagues [168] on workers exposed to any type of pesticide, including pesticide applicators, was also excluded. That study found an SIR of 0.59 for testicular cancer (95 % CI: 0.32–1.10), based on ten observed cases. Inclusion of these three studies in the meta-analysis would have rendered a pooled RR of 1.36 (95 % CI: 1.03–1.79) and a p value for heterogeneity of 0.02.

A meta-analysis of cohort studies on cancer mortality in workers employed in crop protection product manufacturing estimated a pooled RR of 1.61 (95 % CI: 0.99–2.61) for testicular cancer, based on 20 cohorts [77]. The risk became 1.72 (95 % CI: 0.94–3.16) when the analysis was restricted to the 16 cohorts in which workers were potentially exposed to phenoxy herbicides. Again, these results should be interpreted with caution due to the use of mortality instead of incidence as the outcome.

Few other studies have evaluated the risk of testicular cancer in relation to occupational exposure to pesticides. Guo and colleagues applied the job-exposure matrix FINJEM to a record linkage study between census occupations and cancer incidence in Finland [137]. Out of the many studied agents, they found a significant dose-response relationship for pesticides (in particular, insecticides) solvents (including aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents and other organic solvents), and textile dust. In a case-control study conducted by Swerdlow and colleagues in England, self-reported ever exposure to pesticides (OR = 1.04, 95 % CI: 0.61–1.77) or herbicides (OR = 1.14, 95 % CI: 0.67–1.94) was not associated with an increased risk of testicular cancer [142]. Haughey and colleagues found an OR of 2.08 (95 % CI: 1.1–5.0) for self-reported exposure to phenols in a case-control study on testicular cancer conducted at the end of the 1970s in upstate New York [140]. The study also analyzed exposure to pesticides, the results of which are not reported in the paper but were described therein as nonsignificant.

As recently reviewed Cook et al. [169], four nonoccupational studies have evaluated serum levels of organochlorine compounds, in the context of their function as endocrine-disrupting agents, and their relationship with testicular cancer risk. Overall, results are inconsistent. In a small Swedish study of 58 testicular cancer cases and 61 controls, Hardell and colleagues [170] found an association between testicular cancer risk and diagnostic blood concentrations of cis-nonachlordane, which was one of the nine individual pesticides that were tested for. The ATLAS study, conducted in three counties of Washington State, compared diagnostic blood concentrations of 12 organochlorine pesticides between 246 testicular cancer cases and 630 controls [171]. They found no evidence of an association with any of the included pesticides, with the possible exception of a dose-response relationship with γ (gamma)-hexachlorocyclohexane concentrations. The other two studies used pre-diagnostic blood samples. McGlynn and colleagues [172] studied concentrations of eight pesticides in 739 testicular cancer cases and 915 controls recruited in the United States and found evidence of a dose-response relationship with cis-nonachlor, trans-nonachlor, p,p′-DDE, and total chlordanes. Purdue and colleagues [173] analyzed 12 pesticides in samples obtained on average 10 years before the identification of cases ($n = 49$) and controls ($n = 51$) in Norway. Evidence of a dose-response relationship was found for p,p′-DDE, oxychlordane, and total chlordanes.

When considered together, these occupational and nonoccupational studies suggest that there is a potential role of exposure to pesticides in the etiology of testicular cancer. To confirm this, occupational studies would have to be reanalyzed taking into account the type of pesticide as well as latency and windows of exposure, as early exposures are likely to be more relevant. Indeed, a proportion of farmers with occupational exposure to pesticides might also have been exposed at very young ages, or even during fetal life, through their parents' occupations.

A study conducted by Kristensen and colleagues in Norway among the sons of farmers estimated an SIR of 1.11 for testicular cancer (95 % CI: 0.95–1.30) based on 158 observed cases in the cohort compared with the expected incidence from rural areas in the country [174]. The SIR was higher for boys followed up until the age of 15–19 years (SIR = 1.49, 95 % CI: 0.97–1.96, based on 34 observed cases), and it was particularly high (1.99, 95 % CI: 1.48–21.62, 47 observed cases) among sons of farmers who used fertilizer regimes high in nitrogen and low in phosphorus on their farm. A similar registry-based study conducted by Rodvall and colleagues evaluated cancer incidence in the sons of pesticide applicators in Sweden [175]. Follow-up included both childhood and

early adulthood; they observed two cases of testicular cancer compared with the 1.7 expected. A case-control study on testicular cancer conducted in Denmark did not find a positive association with maternal or paternal occupation in agriculture or with living on a farm during childhood [176]. Similarly, parental farming was not associated with testicular cancer risk in a case-control study conducted in the United States at the end of the 1970s [177].

Firefighting

A recent IARC Monograph classified firefighting as possibly carcinogenic to humans (Group 2B) [56]. The working group judged that there was limited evidence of carcinogenicity in humans, mainly on the basis of results for testicular cancer, prostate cancer, and non-Hodgkin's lymphoma.

Six studies on testicular cancer published between 1993 and 2007 were meta-analyzed by the working group, which estimated an RR for ever- vs. never-employment as a firefighter of 1.47 (95 % CI: 1.21–1.51), with a p value for heterogeneity of 0.56.

Although the finding of the meta-analysis is robust and heterogeneity among studies is limited, there are no clear or convincing hypotheses on the possible mechanisms or chemicals involved in this association.

Conclusion

There are no established occupational risk factors for testicular or prostate cancer, and neither cancer site is more common in men with low socioeconomic status.

Studies on occupational risk factors for these two cancers continue to encounter methodological difficulties. For prostate cancer, detection bias via PSA testing is a major methodological problem, in that it is difficult to distinguish between a carcinogenic effect of an exposure and different opportunistic screening practices among those exposed. Testicular cancer is quite rare and occurs in relatively young men, limiting the possibility to study occupational factors in typical occupational cohorts; moreover, mortality data on testicular cancer are fairly uninformative.

Pesticides are the main occupational exposure of interest for both prostate cancer and testicular cancer. They are often considered in the context of their function as endocrine disruptors. In prostate cancer, the evidence of a carcinogenic effect of exposure to pesticides is conflicting, but there is a possible synergistic effect between family history of prostate cancer and exposure to pesticides, which should be further investigated. For testicular cancer, data are scarce but most of the studies on pesticide applicators report an increased risk of this cancer. In order to further increase our knowledge in this area, future studies will have to focus on specific windows of exposure and specific types of pesticides.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893–917.
2. Jones GW, Mettlin C, Murphy GP, Guinan P, Herr HW, Hussey DH, Chmiel JS, Fremgen AM, Clive RE, Zuber-Ocwieja KE, et al. Patterns of care for carcinoma of the prostate gland: results of a national survey of 1984 and 1990. J Am Coll Surg. 1995; 180:545–54.
3. Gronberg H. Prostate cancer epidemiology. Lancet. 2003;361: 859–64.
4. Rowlands MA, Gunnell D, Harris R, Vatten LJ, Holly JM, Martin RM. Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. Int J Cancer. 2009;124:2416–29.
5. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2007.
6. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343:78–85.
7. Duggan D, Zheng SL, Knowlton M, Benitez D, Dimitrov L, Wiklund F, Robbins C, Isaacs SD, Cheng Y, Li G, Sun J, Chang BL, Marovich L, Wiley KE, Balter K, Stattin P, Adami HO, Gielzak M, Yan G, Sauvageot J, Liu W, Kim JW, Bleecker ER, Meyers DA, Trock BJ, Partin AW, Walsh PC, Isaacs WB, Gronberg H, Xu J, Carpten JD. Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. J Natl Cancer Inst. 2007;99:1836–44.
8. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, Adeyemo A, Chen Y, Zhou J, So WY, Tong PC, Ng MC, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Tres A, Fuertes F, Ruiz-Echarri M, Asin L, Saez B, van Boven E, Klaver S, Swinkels DW, Aben KK, Graif T, Cashy J, Suarez BK, van Vierssen TO, Frigge ML, Ober C, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Palmer CN, Rotimi C, Chan JC, Pedersen O, Sigurdsson G, Benediktsson R, Jonsson E, Einarsson GV, Mayordomo JI, Catalona WJ, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet. 2007;39:977–83.
9. Murabito JM, Rosenberg CL, Finger D, Kreger BE, Levy D, Splansky GL, Antman K, Hwang SJ. A genome-wide association study of breast and prostate cancer in the NHLBI's Framingham heart Study. BMC Med Genet. 2007;8 Suppl 1:S6.
10. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, Staats BJ, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Gelmann EP, Tucker M, Gerhard DS, Fraumeni Jr JF, Hoover R, Hunter DJ, Chanock SJ, Thomas G. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet. 2007;39:645–9.
11. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC,

Dearnaley DP, Muir KR, Smith C, Bagnato M, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM, Jhavar SG, Tymrakiewicz M, Lophatananon A, Bryant SL, Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Fisher C, Jamieson C, Cooper CS, English DR, Hopper JL, Neal DE, Easton DF. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet. 2008;40:316–21.

12. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A, Gudbjartsson D, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Blondal T, Jakobsdottir M, Stacey SN, Kostic J, Kristinsson KT, Birgisdottir B, Ghosh S, Magnusdottir DN, Thorlacius S, Thorleifsson G, Zheng SL, Sun J, Chang BL, Elmore JB, Breyer JP, McReynolds KM, Bradley KM, Yaspan BL, Wiklund F, Stattin P, Lindstrom S, Adami HO, McDonnell SK, Schaid DJ, Cunningham JM, Wang L, Cerhan JR, St Sauver JL, Isaacs SD, Wiley KE, Partin AW, Walsh PC, Polo S, Ruiz-Echarri M, Navarrete S, Fuertes F, Saez B, Godino J, Weijerman PC, Swinkels DW, Aben KK, Witjes JA, Suarez BK, Helfand BT, Frigge ML, Kristjansson K, Ober C, Jonsson E, Einarsson GV, Xu J, Gronberg H, Smith JR, Thibodeau SN, Isaacs WB, Catalona WJ, Mayordomo JI, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Nat Genet. 2008;40:281–3.
13. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cussenot O, Valeri A, Andriole GL, Crawford ED, Tucker M, Gerhard DS, Fraumeni Jr JF, Hoover R, Hayes RB, Hunter DJ, Chanock SJ. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet. 2008;40:310–5.
14. Eeles RA, Kote-Jarai Z, Al Olama AA, Giles GG, Guy M, Severi G, Muir K, Hopper JL, Henderson BE, Haiman CA, Schleutker J, Hamdy FC, Neal DE, Donovan JL, Stanford JL, Ostrander EA, Ingles SA, John EM, Thibodeau SN, Schaid D, Park JY, Spurdle A, Clements J, Dickinson JL, Maier C, Vogel W, Dork T, Rebbeck TR, Cooney KA, Cannon-Albright L, Chappuis PO, Hutter P, Zeegers M, Kaneva R, Zhang HW, Lu YJ, Foulkes WD, English DR, Leongamornlert DA, Tymrakiewicz M, Morrison J, Ardern-Jones AT, Hall AL, O'Brien LT, Wilkinson RA, Saunders EJ, Page EC, Sawyer EJ, Edwards SM, Dearnaley DP, Horwich A, Huddart RA, Khoo VS, Parker CC, Van As N, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Cooper CS, Southey MC, Lophatananon A, Liu JF, Kolonel LN, Le Marchand L, Wahlfors T, Tammela TL, Auvinen A, Lewis SJ, Cox A, FitzGerald LM, Koopmeiners JS, Karyadi DM, Kwon EM, Stern MC, Corral R, Joshi AD, Shahabi A, McDonnell SK, Sellers TA, Pow-Sang J, Chambers S, Aitken J, Gardiner RA, Batra J, Kedda MA, Lose F, Polanowski A, Patterson B, Serth J, Meyer A, Luedeke M, Stefflova K, Ray AM, Lange EM, Farnham J, Khan H, Slavov C, Mitkova A, Cao G, Easton DF. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. Nat Genet. 2009;41:1116–21.
15. Gudmundsson J, Sulem P, Gudbjartsson DF, Blondal T, Gylfason A, Agnarsson BA, Benediktsdottir KR, Magnusdottir DN, Orlygsdottir G, Jakobsdottir M, Stacey SN, Sigurdsson A, Wahlfors T, Tammela T, Breyer JP, McReynolds KM, Bradley KM, Saez B, Godino J, Navarrete S, Fuertes F, Murillo L, Polo E, Aben KK, van Oort IM, Suarez BK, Helfand BT, Kan D, Zanon C, Frigge ML, Kristjansson K, Gulcher JR, Einarsson GV, Jonsson E, Catalona WJ, Mayordomo JI, Kiemeney LA, Smith JR, Schleutker J, Barkardottir RB, Kong A, Thorsteinsdottir U, Rafnar T, Stefansson K. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. Nat Genet. 2009;41:1122–6.
16. Ishak MB, Giri VN. A systematic review of replication studies of prostate cancer susceptibility genetic variants in high-risk men originally identified from genome-wide association studies. Cancer Epidemiol Biomarkers Prev. 2011;20:1599–610.
17. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer. 1975;15:617–31.
18. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br J Cancer. 1991;63:963–6.
19. Luo W, Birkett NJ, Ugnat AM, Mao Y. Cancer incidence patterns among Chinese immigrant populations in Alberta. J Immigr Health. 2004;6:41–8.
20. Zuccolo L, Harris R, Gunnell D, Oliver S, Lane JA, Davis M, Donovan J, Neal D, Hamdy F, Beynon R, Savovic J, Martin RM. Height and prostate cancer risk: a large nested case-control study (ProtecT) and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2008;17:2325–36.
21. IARC. IARC monograph on the evaluation of the carcinogenic risk of chemicals to humans, Tobacco smoke and involuntary smoking, vol. 83. Lyon: IARC Press; 2004.
22. Gilbert R, Martin RM, Beynon R, Harris R, Savovic J, Zuccolo L, Bekkering GE, Fraser WD, Sterne JA, Metcalfe C. Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. Cancer Causes Control. 2011;22:319–40.
23. Gilbert R, Metcalfe C, Oliver SE, Whiteman DC, Bain C, Ness A, Donovan J, Hamdy F, Neal DE, Lane JA, Martin RM. Life course sun exposure and risk of prostate cancer: population-based nested case-control study and meta-analysis. Int J Cancer. 2009;125:1414–23.
24. Chen L, Davey Smith G, Evans DM, Cox A, Lawlor DA, Donovan J, Yuan W, Day IN, Martin RM, Lane A, Rodriguez S, Davis M, Zuccolo L, Collin SM, Hamdy F, Neal D, Lewis SJ. Genetic variants in the vitamin d receptor are associated with advanced prostate cancer at diagnosis: findings from the prostate testing for cancer and treatment study and a systematic review. Cancer Epidemiol Biomarkers Prev. 2009;18:2874–81.
25. Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, Lippman SM, Platz EA, Pollak MN, Thompson IM, Kristal AR. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2006;15:1977–83.
26. Freedland SJ, Platz EA. Obesity and prostate cancer: making sense out of apparently conflicting data. Epidemiol Rev. 2007;29:88–97.
27. Platz EA, Till C, Goodman PJ, Parnes HL, Figg WD, Albanes D, Neuhouser ML, Klein EA, Thompson Jr IM, Kristal AR. Men with low serum cholesterol have a lower risk of high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2009;18:2807–13.
28. Martin RM, Vatten L, Gunnell D, Romundstad P. Blood pressure and risk of prostate cancer: Cohort Norway (CONOR). Cancer Causes Control. 2010;21:463–72.
29. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman Jr CA. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349:215–24.
30. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia. 2004;47:1071–8.
31. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006;15:2056–62.
32. Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, Rousseau MC, Boffetta P. Listing occupational carcinogens. Environ Health Perspect. 2004;112:1447–59.

33. Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparen P, Tryggvadottir L, Weiderpass E, Kjaerheim K. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48:646–790.
34. Pearce NE, Sheppard RA, Fraser J. Case-control study of occupation and cancer of the prostate in New Zealand. J Epidemiol Community Health. 1987;41:130–2.
35. Brownson RC, Chang JC, Davis JR, Bagby Jr JR. Occupational risk of prostate cancer: a cancer registry-based study. J Occup Med. 1988;30:523–6.
36. Elghany NA, Schumacher MC, Slattery ML, West DW, Lee JS. Occupation, cadmium exposure, and prostate cancer. Epidemiology. 1990;1:107–15.
37. Hsing AW, McLaughlin JK, Zheng W, Gao YT, Blot WJ. Occupation, physical activity, and risk of prostate cancer in Shanghai, People's Republic of China. Cancer Causes Control. 1994;5:136–40.
38. van der Gulden JW, Kolk JJ, Verbeek AL. Work environment and prostate cancer risk. Prostate. 1995;27:250–7.
39. Aronson KJ, Siemiatycki J, Dewar R, Gerin M. Occupational risk factors for prostate cancer: results from a case-control study in Montreal, Quebec, Canada. Am J Epidemiol. 1996;143:363–73.
40. Boffetta P, Kogevinas M, Westerholm P, Saracci R. Exposure to occupational carcinogens and social class differences in cancer occurrence. IARC Sci Publ. 1997 (138); 331–41.
41. Krstev S, Baris D, Stewart P, Dosemeci M, Swanson GM, Greenberg RS, Schoenberg JB, Schwartz AG, Liff JM, Hayes RB. Occupational risk factors and prostate cancer in U.S. blacks and whites. Am J Ind Med. 1998;34:421–30.
42. Seidler A, Heiskel H, Bickeboller R, Elsner G. Association between diesel exposure at work and prostate cancer. Scand J Work Environ Health. 1998;24:486–94.
43. Band PR, Le ND, Fang R, Threlfall WJ, Gallagher RP. Identification of occupational cancer risks in British Columbia. Part II: a population-based case-control study of 1516 Prostatic cancer cases. J Occup Environ Med. 1999;41:233–47.
44. Charles LE, Loomis D, Shy CM, Newman B, Millikan R, Nylander-French LA, Couper D. Electromagnetic fields, polychlorinated biphenyls, and prostate cancer mortality in electric utility workers. Am J Epidemiol. 2003;157:683–91.
45. Zeegers MP, Friesema IH, Goldbohm RA, van den Brandt PA. A prospective study of occupation and prostate cancer risk. J Occup Environ Med. 2004;46:271–9.
46. Boers D, Zeegers MP, Swaen GM, Kant I, van den Brandt PA. The influence of occupational exposure to pesticides, polycyclic aromatic hydrocarbons, diesel exhaust, metal dust, metal fumes, and mineral oil on prostate cancer: a prospective cohort study. Occup Environ Med. 2005;62:531–7.
47. Fritschi L, Glass DC, Tabrizi JS, Leavy JE, Ambrosini GL. Occupational risk factors for prostate cancer and benign prostatic hyperplasia: a case-control study in Western Australia. Occup Environ Med. 2007;64:60–5.
48. Sass-Kortsak AM, Purdham JT, Kreiger N, Darlington G, Lightfoot NE. Occupational risk factors for prostate cancer. Am J Ind Med. 2007;50:568–76.
49. Ramanakumar AV, Nadon L, Siemiatycki J. Exposures in painting related occupations and risk of selected cancers: results from a case-control study in Montreal. Am J Ind Med. 2008;51:419–27.
50. IARC. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures, vol. 92. Lyon: IARC; 2010.
51. van der Gulden JW. Metal workers and repairmen at risk for prostate cancer: a review. Prostate. 1997;30:107–16.
52. Stewart RE, Dennis LK, Dawson DV, Resnick MI. A meta-analysis of risk estimates for prostate cancer related to tire and rubber manufacturing operations. J Occup Environ Med. 1999;41: 1079–84.
53. Alder N, Fenty J, Warren F, Sutton AJ, Rushton L, Jones DR, Abrams KR. Meta-analysis of mortality and cancer incidence among workers in the synthetic rubber-producing industry. Am J Epidemiol. 2006;164:405–20.
54. Girschik J, Glass D, Ambrosini GL, Fritschi L. Could mining be protective against prostate cancer? A study and literature review. Occup Environ Med. 2010;67:365–74.
55. Young E, Kreiger N, Purdham J, Sass-Kortsak A. Prostate cancer and driving occupations: could whole body vibration play a role? Int Arch Occup Environ Health. 2009;82:551–6.
56. IARC. IARC monograph on the evaluation of the carcinogenic risk of chemicals to humans, 98, vol. Painting, firefighting, and shiftwork. Lyon: IARC; 2010.
57. Ballard T, Lagorio S, De Angelis G, Verdecchia A. Cancer incidence and mortality among flight personnel: a meta-analysis. Aviat Space Environ Med. 2000;71:216–24.
58. Pukkala E, Aspholm R, Auvinen A, Eliasch H, Gundestrup M, Haldorsen T, Hammar N, Hrafnkelsson J, Kyyronen P, Linnersjo A, Rafnsson V, Storm H, Tveten U. Incidence of cancer among Nordic airline pilots over five decades: occupational cohort study. BMJ. 2002;325:567.
59. Blettner M, Zeeb H, Auvinen A, Ballard TJ, Caldora M, Eliasch H, Gundestrup M, Haldorsen T, Hammar N, Hammer GP, Irvine D, Langner I, Paridou A, Pukkala E, Rafnsson V, Storm H, Tulinius H, Tveten U, Tzonou A. Mortality from cancer and other causes among male airline cockpit crew in Europe. Int J Cancer. 2003;106:946–52.
60. Potts CL. Cadmium proteinuria – the health of battery workers exposed to cadmium oxide dust. Ann Occup Hyg. 1965;8:55–61.
61. Feustel A, Wennrich R, Steiniger D, Klauss P. Zinc and cadmium concentration in prostatic carcinoma of different histological grading in comparison to normal prostate tissue and adenofibromyomatosis (BPH). Urol Res. 1982;10:301–3.
62. Ogunlewe JO, Osegbe DN. Zinc and cadmium concentrations in indigenous blacks with normal, hypertrophic, and malignant prostate. Cancer. 1989;63:1388–92.
63. Brys M, Nawrocka AD, Miekos E, Zydek C, Foksinski M, Barecki A, Krajewska WM. Zinc and cadmium analysis in human prostate neoplasms. Biol Trace Elem Res. 1997;59:145–52.
64. Waalkes MP. Cadmium carcinogenesis. Mutat Res. 2003;533:107–20.
65. IARC. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry, vol. 58. Lyon: IARC; 1993.
66. Sahmoun AE, Case LD, Jackson SA, Schwartz GG. Cadmium and prostate cancer: a critical epidemiologic analysis. Cancer Invest. 2005;23:256–63.
67. Verougstraete V, Lison D, Hotz P. Cadmium, lung and prostate cancer: a systematic review of recent epidemiological data. J Toxicol Environ Health B Crit Rev. 2003;6:227–55.
68. Sorahan T, Esmen NA. Lung cancer mortality in UK nickel-cadmium battery workers, 1947–2000. Occup Environ Med. 2004;61:108–16.
69. Vinceti M, Venturelli M, Sighinolfi C, Trerotoli P, Bonvicini F, Ferrari A, Bianchi G, Serio G, Bergomi M, Vivoli G. Case-control study of toenail cadmium and prostate cancer risk in Italy. Sci Total Environ. 2007;373:77–81.
70. Chen YC, Pu YS, Wu HC, Wu TT, Lai MK, Yang CY, Sung FC. Cadmium burden and the risk and phenotype of prostate cancer. BMC Cancer. 2009;9:429.
71. Blair A, Freeman LB. Epidemiologic studies in agricultural populations: observations and future directions. J Agromedicine. 2009;14:125–31.
72. Acquavella J, Olsen G, Cole P, Ireland B, Kaneene J, Schuman S, Holden L. Cancer among farmers: a meta-analysis. Ann Epidemiol. 1998;8:64–74.

73. Van Maele-Fabry G, Willems JL. Occupation related pesticide exposure and cancer of the prostate: a meta-analysis. Occup Environ Med. 2003;60:634–42.
74. Van Maele-Fabry G, Willems JL. Prostate cancer among pesticide applicators: a meta-analysis. Int Arch Occup Environ Health. 2004;77:559–70.
75. Van Maele-Fabry G, Libotte V, Willems J, Lison D. Review and meta-analysis of risk estimates for prostate cancer in pesticide manufacturing workers. Cancer Causes Control. 2006;17: 353–73.
76. Mink PJ, Adami HO, Trichopoulos D, Britton NL, Mandel JS. Pesticides and prostate cancer: a review of epidemiologic studies with specific agricultural exposure information. Eur J Cancer Prev. 2008;17:97–110.
77. Jones DR, Sutton AJ, Abrams KR, Fenty J, Warren F, Rushton L. Systematic review and meta-analysis of mortality in crop protection product manufacturing workers. Occup Environ Med. 2009;66:7–15.
78. Blair A, Zahm SH, Pearce NE, Heineman EF, Fraumeni Jr JF. Clues to cancer etiology from studies of farmers. Scand J Work Environ Health. 1992;18:209–15.
79. Van Der Gulden JW, Vogelzang PF. Farmers at risk for prostate cancer. Br J Urol. 1996;77:6–14.
80. Keller-Byrne JE, Khuder SA, Schaub EA. Meta-analyses of prostate cancer and farming. Am J Ind Med. 1997;31:580–6.
81. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Saracci R. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epidemiol. 1997;145:1061–75.
82. Koutros S, Alavanja MC, Lubin JH, Sandler DP, Hoppin JA, Lynch CF, Knott C, Blair A, Freeman LE. An update of cancer incidence in the Agricultural Health Study. J Occup Environ Med. 2010;52:1098–105.
83. Waggoner JK, Kullman GJ, Henneberger PK, Umbach DM, Blair A, Alavanja MC, Kamel F, Lynch CF, Knott C, London SJ, Hines CJ, Thomas KW, Sandler DP, Lubin JH, Beane Freeman LE, Hoppin JA. Mortality in the agricultural health study. Am J Epidemiol. 1993–2007;173:71–83.
84. Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, Knott C, Thomas K, Hoppin JA, Barker J, Coble J, Sandler DP, Blair A. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epidemiol. 2003;157:800–14.
85. Weichenthal S, Moase C, Chan P. A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort. Environ Health Perspect. 2010;118:1117–25.
86. Purdue MP, Hoppin JA, Blair A, Dosemeci M, Alavanja MC. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. Int J Cancer. 2007;120:642–9.
87. Mahajan R, Blair A, Lynch CF, Schroeder P, Hoppin JA, Sandler DP, Alavanja MC. Fonofos exposure and cancer incidence in the Agricultural Health Study. Environ Health Perspect. 2006;114:1838–42.
88. Lynch SM, Mahajan R, Beane Freeman LE, Hoppin JA, Alavanja MC. Cancer incidence among pesticide applicators exposed to butylate in the Agricultural Health Study (AHS). Environ Res. 2009;109:860–8.
89. Christensen CH, Platz EA, Andreotti G, Blair A, Hoppin JA, Koutros S, Lynch CF, Sandler DP, Alavanja MC. Coumaphos exposure and incident cancer among male participants in the Agricultural Health Study (AHS). Environ Health Perspect. 2010;118:92–6.
90. Rusiecki JA, Patel R, Koutros S, Beane-Freeman L, Landgren O, Bonner MR, Coble J, Lubin J, Blair A, Hoppin JA, Alavanja MC. Cancer incidence among pesticide applicators exposed to permethrin in the Agricultural Health Study. Environ Health Perspect. 2009;117:581–6.
91. Mahajan R, Bonner MR, Hoppin JA, Alavanja MC. Phorate exposure and incidence of cancer in the Agricultural Health Study. Environ Health Perspect. 2006;114:1205–9.
92. Koutros S, Beane Freeman LE, Berndt SI, Andreotti G, Lubin JH, Sandler DP, Hoppin JA, Yu K, Li Q, Burdette LA, Yuenger J, Yeager M, Alavanja MC. Pesticide use modifies the association between genetic variants on chromosome 8q24 and prostate cancer. Cancer Res. 2010;70:9224–33.
93. Mills PK, Yang R. Prostate cancer risk in California farm workers. J Occup Environ Med. 2003;45:249–58.
94. Settimi L, Masina A, Andrion A, Axelson O. Prostate cancer and exposure to pesticides in agricultural settings. Int J Cancer. 2003;104:458–61.
95. Band PR, Abanto Z, Bert J, Lang B, Fang R, Gallagher RP, Le ND. Prostate cancer risk and exposure to pesticides in British Columbia farmers. Prostate. 2011;71:168–83.
96. Cockburn M, Mills P, Zhang X, Zadnick J, Goldberg D, Ritz B. Prostate cancer and ambient pesticide exposure in agriculturally intensive areas in California. Am J Epidemiol. 2011;173:1280–8.
97. Sawada N, Iwasaki M, Inoue M, Itoh H, Sasazuki S, Yamaji T, Shimazu T, Tsugane S. Plasma organochlorines and subsequent risk of prostate cancer in Japanese men: a nested case-control study. Environ Health Perspect. 2010;118:659–65.
98. Xu X, Dailey AB, Talbott EO, Ilacqua VA, Kearney G, Asal NR. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. Environ Health Perspect. 2010;118:60–6.
99. Ritchie JM, Vial SL, Fuortes LJ, Guo H, Reedy VE, Smith EM. Organochlorines and risk of prostate cancer. J Occup Environ Med. 2003;45:692–702.
100. Hardell L, Andersson SO, Carlberg M, Bohr L, van Bavel B, Lindstrom G, Bjornfoth H, Ginman C. Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. J Occup Environ Med. 2006;48:700–7.
101. Leon ME, Beane Freeman LE, Douwes J, Hoppin JA, Kromhout H, Lebailly P, Nordby KC, Schenker M, Schuz J, Waring SC, Alavanja MC, Annesi-Maesano I, Baldi I, Dalvie MA, Ferro G, Fervers B, Langseth H, London L, Lynch CF, McLaughlin J, Merchant JA, Pahwa P, Sigsgaard T, Stayner L, Wesseling C, Yoo KY, Zahm SH, Straif K, Blair A. AGRICOH: a consortium of agricultural cohorts. Int J Environ Res Public Health. 2011;8: 1341–57.
102. Cocco P. On the rumors about the silent spring. Review of the scientific evidence linking occupational and environmental pesticide exposure to endocrine disruption health effects. Cad Saude Publica. 2002;18:379–402.
103. IARC. Re-evaluation of Some organic chemicals, hydrazine and hydrogen peroxide, vol. 71. Lyon: IARC; 1999.
104. Bolognesi C. Genotoxicity of pesticides: a review of human biomonitoring studies. Mutat Res. 2003;543:251–72.
105. Klaunig JE, Xu Y, Isenberg JS, Bachowski S, Kolaja KL, Jiang J, Stevenson DE, Walborg Jr EF. The role of oxidative stress in chemical carcinogenesis. Environ Health Perspect. 1998;106 Suppl 1:289–95.
106. Prins GS. Endocrine disruptors and prostate cancer risk. Endocr Relat Cancer. 2008;15:649–56.
107. Prince MM, Ruder AM, Hein MJ, Waters MA, Whelan EA, Nilsen N, Ward EM, Schnorr TM, Laber PA, Davis-King KE. Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Environ Health Perspect. 2006;114:1508–14.

108. Gustavsson P, Hogstedt C. A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med. 1997;32:234–9.
109. Yassi A, Tate RB, Routledge M. Cancer incidence and mortality in workers employed at a transformer manufacturing plant: update to a cohort study. Am J Ind Med. 2003;44:58–62.
110. Ruder AM, Hein MJ, Nilsen N, Waters MA, Laber P, Davis-King K, Prince MM, Whelan E. Mortality among workers exposed to polychlorinated biphenyls (PCBs) in an electrical capacitor manufacturing plant in Indiana: an update. Environ Health Perspect. 2006;114:18–23.
111. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, cancer incidence and mortality worldwide: IARC cancer base no. 10 [internet]. Lyon: International Agency for Research on cancer; 2010.
112. Richiardi L, Bellocco R, Adami HO, Torrang A, Barlow L, Hakulinen T, Rahu M, Stengrevics A, Storm H, Tretli S, Kurtinaitis J, Tyczynski JE, Akre O. Testicular cancer incidence in eight northern European countries: secular and recent trends. Cancer Epidemiol Biomarkers Prev. 2004;13:2157–66.
113. Chia VM, Quraishi SM, Devesa SS, Purdue MP, Cook MB, McGlynn KA. International trends in the incidence of testicular cancer, 1973–2002. Cancer Epidemiol Biomarkers Prev. 2010; 19:1151–9.
114. Richiardi L, Tamimi R, Adami HO. Testicular cancer. In: Adami HO, Hunter D, Trichopoulos D, editors. Textbook of cancer epidemiology. 2nd ed. New York: Oxford University Press; 2008. p. 555–72.
115. Sonne SB, Almstrup K, Dalgaard M, Juncker AS, Edsgard D, Ruban L, Harrison NJ, Schwager C, Abdollahi A, Huber PE, Brunak S, Gjerdrum LM, Moore HD, Andrews PW, Skakkebaek NE, Rajpert-De Meyts E, Leffers H. Analysis of gene expression profiles of microdissected cell populations indicates that testicular carcinoma in situ is an arrested gonocyte. Cancer Res. 2009;69:5241–50.
116. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer – experiences of the mother. Int J Epidemiol. 2009;38:1532–42.
117. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer–experiences of the son. Int J Epidemiol. 2010;39:1605–18.
118. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet. 1993;341:1392–5.
119. Henderson BE, Benton B, Jing J, Yu MC, Pike MC. Risk factors for cancer of the testis in young men. Int J Cancer. 1979; 23:598–602.
120. Sharpe RM. The 'oestrogen hypothesis' – where do we stand now? Int J Androl. 2003;26:2–15.
121. Sharpe RM, Skakkebaek NE. Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. Fertil Steril. 2008;89:e33–8.
122. Martin OV, Shialis T, Lester JN, Scrimshaw MD, Boobis AR, Voulvoulis N. Testicular dysgenesis syndrome and the estrogen hypothesis: a quantitative meta-analysis. Environ Health Perspect. 2008;116:149–57.
123. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod. 2001;16:972–8.
124. Akre O, Richiardi L. Does a testicular dysgenesis syndrome exist? Hum Reprod. 2009;24:2053–60.
125. Peng X, Zeng X, Peng S, Deng D, Zhang J. The association risk of male subfertility and testicular cancer: a systematic review. PLoS One. 2009;4:e5591.
126. Lerro CC, McGlynn KA, Cook MB. A systematic review and meta-analysis of the relationship between body size and testicular cancer. Br J Cancer. 2010;103:1467–74.
127. Pettersson A, Richiardi L, Nordenskjold A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med. 2007;356:1835–41.
128. Richiardi L, Pettersson A, Akre O. Genetic and environmental risk factors for testicular cancer. Int J Androl. 2007;30:230–40. discussion 40–1.
129. Turnbull C, Rapley EA, Seal S, Pernet D, Renwick A, Hughes D, Ricketts M, Linger R, Nsengimana J, Deloukas P, Huddart RA, Bishop DT, Easton DF, Stratton MR, Rahman N. Variants near DMRT1, TERT and ATF7IP are associated with testicular germ cell cancer. Nat Genet. 2010;42:604–7.
130. Kanetsky PA, Mitra N, Vardhanabhuti S, Li M, Vaughn DJ, Letrero R, Ciosek SL, Doody DR, Smith LM, Weaver J, Albano A, Chen C, Starr JR, Rader DJ, Godwin AK, Reilly MP, Hakonarson H, Schwartz SM, Nathanson KL. Common variation in KITLG and at 5q31.3 predisposes to testicular germ cell cancer. Nat Genet. 2009;41:811–5.
131. Rapley EA, Turnbull C, Al Olama AA, Dermitzakis ET, Linger R, Huddart RA, Renwick A, Hughes D, Hines S, Seal S, Morrison J, Nsengimana J, Deloukas P, Rahman N, Bishop DT, Easton DF, Stratton MR. A genome-wide association study of testicular germ cell tumor. Nat Genet. 2009;41:807–10.
132. Mills PK, Newell GR, Johnson DE. Testicular cancer associated with employment in agriculture and oil and natural gas extraction. Lancet. 1984;1:207–10.
133. Zhang ZF, Vena JE, Zielezny M, Graham S, Haughey BP, Brasure J, Marshall JR. Occupational exposure to extreme temperature and risk of testicular cancer. Arch Environ Health. 1995;50:13–8.
134. Hardell L, Ohlson CG, Fredrikson M. Occupational exposure to polyvinyl chloride as a risk factor for testicular cancer evaluated in a case-control study. Int J Cancer. 1997;73:828–30.
135. Andersson E, Nilsson R, Toren K. Testicular cancer among Swedish pulp and paper workers. Am J Ind Med. 2003;43:642–6.
136. Hardell L, Malmqvist N, Ohlson CG, Westberg H, Eriksson M. Testicular cancer and occupational exposure to polyvinyl chloride plastics: a case-control study. Int J Cancer. 2004;109:425–9.
137. Guo J, Pukkala E, Kyyronen P, Lindbohm ML, Heikkila P, Kauppinen T. Testicular cancer, occupation and exposure to chemical agents among Finnish men in 1971–1995. Cancer Causes Control. 2005;16:97–103.
138. Langner I, Schmeisser N, Mester B, Behrens T, Gottlieb A, Ahrens W. Case-control study of male germ cell tumors nested in a cohort of car-manufacturing workers: findings from the occupational history. Am J Ind Med. 2010;53:1006–18.
139. Pearce N, Sheppard RA, Howard JK, Fraser J, Lilley BM. Time trends and occupational differences in cancer of the testis in New Zealand. Cancer. 1987;59:1677–82.
140. Haughey BP, Graham S, Brasure J, Zielezny M, Sufrin G, Burnett WS. The epidemiology of testicular cancer in upstate New York. Am J Epidemiol. 1989;130:25–36.
141. Hayes RB, Brown LM, Pottern LM, Gomez M, Kardaun JW, Hoover RN, O'Connell KJ, Sutzman RE, Javadpour N. Occupation and risk for testicular cancer: a case-control study. Int J Epidemiol. 1990;19:825–31.
142. Swerdlow AJ, Douglas AJ, Huttly SR, Smith PG. Cancer of the testis, socioeconomic status, and occupation. Br J Ind Med. 1991;48:670–4.
143. Van den Eeden SK, Weiss NS, Strader CH, Daling JR. Occupation and the occurrence of testicular cancer. Am J Ind Med. 1991; 19:327–37.
144. UK Testicular Cancer Study Group. Social, behavioural and medical factors in the aetiology of testicular cancer: results from the UK study. Br J Cancer. 1994;70:513–20.

145. Rhomberg W, Schmoll HJ, Schneider B. High frequency of metalworkers among patients with seminomatous tumors of the testis: a case-control study. Am J Ind Med. 1995;28:79–87.
146. Knight JA, Marrett LD, Weir HK. Occupation and risk of germ cell testicular cancer by histologic type in Ontario. J Occup Environ Med. 1996;38:884–90.
147. Hobbesland A, Kjuus H, Thelle DS. Study of cancer incidence among 8530 male workers in eight Norwegian plants producing ferrosilicon and silicon metal. Occup Environ Med. 1999;56: 625–31.
148. Pollan M, Gustavsson P, Cano MI. Incidence of testicular cancer and occupation among Swedish men gainfully employed in 1970. Ann Epidemiol. 2001;11:554–62.
149. Whorton MD, Moore DN, Seward JP, Noonan KA, Mendelsohn ML. Cancer incidence rates among Lawrence Livermore National Laboratory (LLNL) employees: 1974–1997. Am J Ind Med. 2004;45:24–33.
150. Walschaerts M, Muller A, Auger J, Bujan L, Guerin JF, Le Lannou D, Clavert A, Spira A, Jouannet P, Thonneau P. Environmental, occupational and familial risks for testicular cancer: a hospital-based case-control study. Int J Androl. 2007;30:222–9.
151. Garland FC, Gorham ED, Garland CF, Ducatman AM. Testicular cancer in US Navy personnel. Am J Epidemiol. 1988;127:411–4.
152. Tarone RE, Hayes HM, Hoover RN, Rosenthal JF, Brown LM, Pottern LM, Javadpour N, O'Connell KJ, Stutzman RE. Service in Vietnam and risk of testicular cancer. J Natl Cancer Inst. 1991;83:1497–9.
153. Foley S, Middleton S, Stitson D, Mahoney M. The incidence of testicular cancer in Royal Air Force personnel. Br J Urol. 1995;76: 495–6.
154. Young HA, Maillard JD, Levine PH, Simmens SJ, Mahan CM, Kang HK. Investigating the risk of cancer in 1990–1991 US Gulf War veterans with the use of state cancer registry data. Ann Epidemiol. 2010;20:265–72 e1.
155. Gray GC, Coate BD, Anderson CM, Kang HK, Berg SW, Wignall FS, Knoke JD, Barrett-Connor E. The postwar hospitalization experience of U.S. veterans of the Persian Gulf War. N Engl J Med. 1996;335:1505–13.
156. Knoke JD, Gray GC, Garland FC. Testicular cancer and Persian Gulf War service. Epidemiology. 1998;9:648–53.
157. Macfarlane GJ, Biggs AM, Maconochie N, Hotopf M, Doyle P, Lunt M. Incidence of cancer among UK Gulf war veterans: cohort study. BMJ. 2003;327:1373.
158. Zhu K, Devesa SS, Wu H, Zahm SH, Jatoi I, Anderson WF, Peoples GE, Maxwell LG, Granger E, Potter JF, McGlynn KA. Cancer incidence in the U.S. military population: comparison with rates from the SEER program. Cancer Epidemiol Biomarkers Prev. 2009;18:1740–5.
159. Frost G, Brown T, Harding AH. Mortality and cancer incidence among British agricultural pesticide users. Occup Med (Lond). 2011;61:303–10.
160. MacFarlane E, Benke G, Del Monaco A, Sim MR. Cancer incidence and mortality in a historical cohort of Australian pest control workers. Occup Environ Med. 2009;66:818–23.
161. Fleming LE, Bean JA, Rudolph M, Hamilton K. Cancer incidence in a cohort of licensed pesticide applicators in Florida. J Occup Environ Med. 1999;41:279–88.
162. Dich J, Wiklund K, Holm LE. Testicular cancer in pesticide applicators in Swedish agriculture. Scand J Work Environ Health. 1996;22:66.
163. Wiklund K, Dich J, Holm LE, Eklund G. Risk of cancer in pesticide applicators in Swedish agriculture. Br J Ind Med. 1989;46:809–14.
164. Wiklund K, Dich J. Cancer risks among male farmers in Sweden. Eur J Cancer Prev. 1995;4:81–90.
165. Fleming LE, Bean JA, Rudolph M, Hamilton K. Mortality in a cohort of licensed pesticide applicators in Florida. Occup Environ Med. 1999;56:14–21.
166. Kristensen P, Andersen A, Irgens LM, Laake P, Bye AS. Incidence and risk factors of cancer among men and women in Norwegian agriculture. Scand J Work Environ Health. 1996;22:14–26.
167. Zhong Y, Rafnsson V. Cancer incidence among Icelandic pesticide users. Int J Epidemiol. 1996;25:1117–24.
168. MacFarlane E, Benke G, Del Monaco A, Sim MR. Causes of death and incidence of cancer in a cohort of Australian pesticide-exposed workers. Ann Epidemiol. 2010;20:273–80.
169. Cook MB, Trabert B, McGlynn KA. Organochlorine compounds and testicular dysgenesis syndrome: human data. Int J Androl. 2011;34:e68–85.
170. Hardell L, van Bavel B, Lindstrom G, Carlberg M, Dreifaldt AC, Wijkstrom H, Starkhammar H, Eriksson M, Hallquist A, Kolmert T. Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. Environ Health Perspect. 2003;111:930–4.
171. Biggs ML, Davis MD, Eaton DL, Weiss NS, Barr DB, Doody DR, Fish S, Needham LL, Chen C, Schwartz SM. Serum organochlorine pesticide residues and risk of testicular germ cell carcinoma: a population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2008;17:2012–8.
172. McGlynn KA, Quraishi SM, Graubard BI, Weber JP, Rubertone MV, Erickson RL. Persistent organochlorine pesticides and risk of testicular germ cell tumors. J Natl Cancer Inst. 2008;100:663–71.
173. Purdue MP, Engel LS, Langseth H, Needham LL, Andersen A, Barr DB, Blair A, Rothman N, McGlynn KA. Prediagnostic serum concentrations of organochlorine compounds and risk of testicular germ cell tumors. Environ Health Perspect. 2009;117:1514–9.
174. Kristensen P, Andersen A, Irgens LM, Bye AS, Vagstad N. Testicular cancer and parental use of fertilizers in agriculture. Cancer Epidemiol Biomarkers Prev. 1996;5:3–9.
175. Rodvall Y, Dich J, Wiklund K. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. Occup Environ Med. 2003;60:798–801.
176. Moller H. Work in agriculture, childhood residence, nitrate exposure, and testicular cancer risk: a case-control study in Denmark. Cancer Epidemiol Biomarkers Prev. 1997;6:141–4.
177. Kardaun JW, Hayes RB, Pottern LM, Brown LM, Hoover RN. Testicular cancer in young men and parental occupational exposure. Am J Ind Med. 1991;20:219–27.

Kidney Cancer

25

Lee E. Moore, Patricia A. Stewart, and Sara Karami

Keywords
Kidney cancer • Occupation • Solvents • Trichloroethylene • Metals • Cadmium • Lead • Pesticides • Diesel auto fumes • Asbestos • Ultraviolet (UV) exposure

Introduction

Malignant tumors of the kidney account for approximately 2 % of all new primary cancer cases diagnosed in the United States (US) and worldwide [1–3]. Renal cell carcinoma (RCC) of the renal parenchyma accounts for over 80 % of all kidney cancers, the majority of which are adenocarcinomas that arise from the renal parenchyma [3]. RCC is divided into distinct histological subtypes, clear cell being the most prevalent (80–85 %) followed by papillary RCC (10 %). Less common subtypes of kidney cancer include oncocytoma and chromophobe tumors [4, 5]. Another histological subtype of kidney cancer is transitional cell carcinoma (TCC) which is most often located in the renal pelvis [6]. Histologically, these tumors are considered more similar to TCC of the bladder [7]. In RCC, the major etiologic risk factors that are thought to explain approximately 50 % of cases include cigarette smoking, obesity (high body mass index or BMI), hypertension, and diabetes [6, 8, 9]. The increasing prevalence of these risk factors may explain temporal variations in renal cancer incidence rates by country/region and within particular subpopulations. While the etiologic factors associated with the remaining 50 % of renal cancer cases are for the most part unexplained, other risk factors that have been described in the literature include analgesic use [3], long-term hemodialysis [10], hormonal/reproductive factors [11], variations in diet [12, 13], family history of renal cancer [14], and genetic factors [15]. Although not generally considered an occupationally related cancer, several studies have pointed towards occupational and environmental exposures [16, 17]; many associations, however, remain inconclusive. The current review will focus upon renal cancer risk associated with exposure to various agents in the workplace that are suspected of being renal carcinogens. Initial studies we present will evaluate historical exposures using job and industry titles, in which exposures to carcinogens were "likely" to be encountered in the workplace. Subsequently, to reduce speculation and exposure misclassification, higher-quality studies that used more sophisticated exposure assessment techniques (i.e., expert-assessed or actual industrial hygiene measurements) will be presented.

Occupations and Industries

Studies of occupational history that classified individuals by job and industry titles provided the first clues to specific exposures as potential risk factors for renal cancer. Industries that have been significantly associated with elevated renal cancer risk include employment in the dry cleaning [18, 19], agricultural and food [20–22], petroleum and gasoline [23–25], iron and steel [23, 25, 26], paper and printing/publishing [6, 18, 25], and automotive [22, 27] industries. Specific job titles have been less consistently associated with kidney

L.E. Moore, PhD, MPH (✉)
Division of Cancer Epidemiology and Genetics,
National Cancer Institute, National Institutes of Health,
9609 Medical Center Drive, Rm 6E614,
Rockville, MD 20850-9771, USA
e-mail: moorele@mail.nih.gov

P.A. Stewart, PhD
Stewart Exposure Assessments, LLC, Arlington, VA, USA

S. Karami, MPH, PhD
Division of Cancer Epidemiology and Genetics,
National Cancer Institute, 9609 Medical Center Drive,
Rockville, MD 20850-9771, USA

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_25,

cancer risk; however, those that have shown significant associations with increased risk include employment as a manager [20, 22, 28], auto or airline mechanic [6, 18, 22, 28], painter [29, 30], firefighter [30, 31], architect [20, 32], engineer [20, 33], truck or bus driver [25, 34, 35], as well as metal [6, 25, 36], railroad [6, 29, 37], and sales [22, 28] workers. Specific agents are identified through studies that used detailed analyses of job and industry reports showing that exposure to solvents [29, 36], pesticides [25, 38], metals (i.e., lead, chromium, cadmium, arsenic, and nickel) [18, 23, 29], asbestos and other fibers/dusts [18, 23, 37], automotive fumes/diesel exhaust [18, 23, 36], polycyclic aromatic hydrocarbons (PAHs) [18, 29], and ultraviolet (UV) radiation [18, 33] could be responsible for the associations observed.

Solvents, Chlorinated Solvents, and Trichloroethylene

Results from occupational studies indicate that the increased kidney cancer rates observed among dry cleaners [39], architects [40], mechanics [41], and aerospace and aircraft maintenance workers [42] could be related to solvent exposures. In particular, chlorinated solvents, a subgroup of organic solvents, have been examined in relation to kidney cancer risk in a number of occupational studies [23, 35, 36, 43–46]; however, significant associations with risk have only been reported in a few case-control studies [23, 36, 45]. Schlehofer and colleagues observed a greater than twofold increase in RCC risk (relative risk (RR) = 2.5, 95 % confidence interval (CI) = 1.2–5.2) among men reporting exposure to chlorinated solvents (N = 27 cases, N = 12 controls) in Germany [36]. In a slightly larger study conducted in the USA, occupational exposure to chlorinated aliphatic hydrocarbons was associated with increased RCC risk (odds ratio (OR) = 2.1, 95 % CI = 1.1–3.9) among women (N = 29) [45]. In a large, internationally based study (the USA, Australia, Sweden, Denmark, and Germany), increased RCC risk was also observed among male (RR = 1.4, 95 % CI = 1.1–1.7) and female (RR = 1.6, 95 % CI = 1.0–2.7) participants who reported ever being occupationally exposed to dry cleaning solvents (N = 245 male cases, N = 223 male controls; number of exposed female subjects not reported); but no clear pattern of association was seen with increasing duration of employment, since the highest level of risk was observed among men in the midrange of exposure [23].

Included within the subgroup of chlorinated organic solvents is trichloroethylene (TCE). In 1997, the International Agency for Research on Cancer (IARC) classified TCE as a Group 2A, "probable" human carcinogen based on limited carcinogenic evidence in humans but sufficient evidence in animals [47]. Recently, the US Environmental Protection Agency (EPA) released its final health assessment for TCE and characterized the chemical as "carcinogenic to humans" based on additional carcinogenic evidence in human epidemiological studies [48]. Subsequently, the IARC working group also elevated TCE's classification to a Group 1 human carcinogen [49]. TCE was a prominent chlorinated solvent used in the 1970s, primarily for degreasing metal parts, but also as an anesthetic, surgical disinfectant, pet food additive, typewriter correction fluid, and extractant of spices in food [50]. Exposure to this solvent is also of concern as it remains a common water contaminant in the USA [51].

TCE has been the most extensively studied of all chlorinated solvents in relation to RCC risk (Table 25.1) [19, 29, 39, 43, 45, 52–67]. In animal studies, TCE exposure has been found to increase nephrotoxicity and nephrocarcinogenicity [68]. At relatively low exposure levels, rats have been shown to develop nonneoplastic kidney lesions, as well as increased incidence of renal adenoma and adenocarcinoma [47, 69]. Findings from animal studies have suggested that kidney tumors result as a consequence of continual cytotoxicity and regeneration [70, 71]. In humans, nephrotoxicity is thought to be a prerequisite for renal cancer development following TCE exposure [70].

Interest regarding TCE exposure as a potential human carcinogen first escalated after publication of two German epidemiological case-control studies that indicated very strong associations between occupational exposure and RCC risk [54, 63], although some have questioned the validity of these two studies due to study design issues such as control selection, potential interview bias, and matching [72, 73]. Since then, accumulating epidemiological evidence from a variety of study designs employing various exposure assessment methodologies has examined the association between occupational TCE exposure and kidney cancer risk, including four meta-analyses published over the past 13 years [72, 73]. The first meta-analysis published on occupational TCE exposure and kidney cancer risk by Wartenberg et al. in 2000 reported a significant summary RR of 1.17 (95 % CI = 1.1–2.7) for incidence cohort studies (N = 5) that assessed TCE exposure using urinary biomarkers, job exposure matrices (JEMs), or job histories. Elevated summary estimates were also reported for other types of study designs though not significantly [73]. In 2007, Kelsh and colleagues observed significant summary estimates for both cohort (N = 16, RR = 1.34, 95 % CI = 1.00–1.81, p-heterogeneity = 0.01) and case-control studies (N = 7, OR = 2.57, 95 % CI = 1.06–2.30, p-heterogeneity = 0.003) that assessed occupational TCE exposure in relation to kidney cancer risk, and estimates remained elevated after excluding outlier studies that introduced heterogeneity to the combined risk estimates [72]. Recently, a US EPA-conducted meta-analysis reported a significant RR with kidney cancer showing a 1.3 increase in risk overall and a 1.6 increase in risk for high exposure groups [74]. A subsequent updated meta-analysis conducted by the US National Cancer Institute (NCI)

Table 25.1 Kidney cancer risk and occupational studies that have examined exposure to trichloroethylene (TCE)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)
Coho9rt studies					
Axelson et al. (1994) [52]	Cohort study of men (N=1,670) from 115 Swedish workforce facilities	Cancer incidence follow-up from 1958 through 1987. Cancer mortality follow-up from 1958 through 1986. Various cancers evaluated including kidney (ICD-7 180; N=6). National incidence rates used to derive expected counts	TCE used in facilities from 1955 to 1975. Workers assessed for exposure to TCE using company urinary biomonitoring measurements (U-TCA). Of the 1,670 total subjects 1,727 were exposed to TCE	Never/ever exposed to TCE	Ever exposed to TCE SIR = 1.16 (0.42–2.52)
Anttila et al. (1995) [53]	Cohort study of 2,050 male and 1,924 female workers from Finland	Cancer incidence follow-up from 1967 through 1992. Various cancers evaluated including kidney (ICD-7 180; N=7). National incidence rates used to derive expected counts	Workers assessed for exposure to TCE using government urinary biomonitoring measurements (U-TCA, B-Per, B-TC). Of the 8,974 total subjects 3,089 were exposed to TCE	Never/ever exposed to TCE. Time in years since first measured for TCE exposure (<10 years, 10+ years)	Ever exposed to TCE SIR = 0.87 (0.32–1.89). Years since measured for exposure to TCE <10 years SIR = 0.53(0.01–2.95), 10+ years SIR = 1.39(0.45–3.24)
Henschler et al. (1995) [54]	Cohort study of 359 male cardboard manufacturing plant workers in Germany	Cancer incidence follow-up from 1956 through 1992. Various cancers evaluated including kidney (ICD-9 189; N=5). National incidence rates from two sources were used to derive expected counts	Exposure to TCE assessed using company work histories, walk-through surveys, interviews, and company records. No actual measurements assessed. Of the 359 total subjects, 169 were assumed to be exposed to TCE	Never/ever exposed to TCE compared to Cancer Registry of the former German Democratic Republic	Ever exposed to TCE SIR = 9.66 (3.14–22.55)
Morgan et al. (1998) [55]	Cohort study of 20,508 aerospace manufacturing workers in Arizona, USA	Cancer mortality follow-up from 1950 through 1993. Various cancers evaluated including kidney (N=32 overall, N=8 in the TCE-exposed subcohort). US mortality rates used as a comparison. Internal comparison analyses also conducted	Exposure to TCE assessed using company work histories, where data for long-term employees was used to develop JEM. Of the 20,508 total subjects, 4,733 assumed to be exposed to TCE	Never/ever exposed to TCE. Never/ever exposed to low levels (<50 % of cumulative exposure score) of TCE. Never/ever exposed to high levels (≥50 % of cumulative exposure score) of TCE	Ever exposed to TCE SMR = 1.32(0.57–2.60). Ever exposed to low levels of TCE SMR = 0.47(0.01–2.62) or high levels of TCE SMR = 1.78(0.72–3.66). Internal comparison – ever exposed to low levels of TCE RR = 0.31(0.04–2.36) or high levels of TCE RR = 1.59(0.68–3.71)
Ritz (1999) [56]	Cohort study of 3,814 male uranium processing workers in Ohio, USA	Cancer mortality follow-up from 1951 through 1989. Various cancers evaluated, including that of the kidney (ICD-8 189; N=5). External US population mortality rates used as comparison as well as internal comparison analyses	Exposure to TCE and other chemicals assessed using company work histories where data for long-term employees used to develop JEM. Of the 3,814 total subjects, 2,971 assumed to be exposed to TCE	Never/ever exposed to TCE	Ever exposed to TCE SMR = 0.65(0.21–1.51)
Boice et al. (1999) [57]	Cohort of 77,965 aircraft manufacturing workers in California, USA	Cancer mortality follow-up from 1960 through 1996. Various cancers evaluated, including that of the kidney (ICD-9 189.0–189.2; N=125 overall, N=7 in TCE-exposed subcohort). General population of white Californian workers used to derive expected counts. Internal comparison analyses also conducted	Exposure to TCE assessed using company work histories, walk-through surveys, interviews, industrial hygiene records which were used to develop JEM. Of the 77,965 total subjects, 2,267 assumed to be routinely exposed to TCE	Never/ever exposed to TCE. Internal comparison to assess years of exposure to TCE (none, <1 year, 1–4 years, 5+ years)	Ever exposed to TCE SMR = 0.99(0.40–2.04). Internal comparison for years of exposure to TCE <1 year RR = 0.97 (0.37–2.50), 1–4 years RR = 0.19(0.02–1.42), 5+ years RR = 0.69(0.22–2.12)

(continued)

Table 25.1 (continued)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)
Hansen et al. (2001) [39]	Cohort of 803 workers from 275 Danish companies	Cancer incidence follow-up from 1968 through 1996. Various cancers evaluated including kidney (ICD-7 180; $N=4$, for males $N=3$ for females $N=1$). National incidence rates used to derive expected counts	Exposure to TCE assessed using urinary biomonitoring (U-TCA) measurements or company air measurements	Never/ever exposed to TCE	Ever exposed to TCE among males SIR = 0.9(0.2–2.6), among females SIR = 2.4(0.03–14.0)
Raaschou-Nielsen et al. (2003) [58]	Cohort of 40,049 Danish blue-collar workers for 347 companies using TCE	Cancer incidence follow-up from 1968 through 1997. Various cancers evaluated, including RCC ($N=76$). National incidence rates used to derive expected counts	Exposure to TCE assessed using pension funding records, government industrial hygiene, and urinary biomonitoring (U-TCA) measurements where a "company exposure matrix" was developed. Of the 40,049 total subjects, 14,360 assumed to be exposed to TCE	Never/ever exposed to TCE. Never/ever exposed to TCE with a lag of 20 years. Duration of employment (none, <1 years, 1–4.9 years, 5+ years). Years since first employed and number of employees in each company also evaluated	Ever exposed to TCE among men SIR = 1.2(0.97–1.48), among women SIR = 1.2(0.55–2.11). A 20 year lag for ever exposure to TCE among males SIR = 1.3(0.8–1.9), among females SIR = 1.3(0.3–3.7). Duration of employment among males <1 year SIR = 0.8(0.5–1.4), 1–4.9 years SIR = 1.2(0.8–1.7), 5+ years SIR = 1.6(1.1–2.3); among females <1 year SIR = 1.1(0.1–3.8), 1–4.9 years SIR = 1.2(0.2–3.4), 5+ years SIR = 1.5(0.3–4.3)
Boice et al. (2006) [59]	Cohort of 41,351 aircraft workers in a rocket engine testing facility in the USA	Cancer mortality follow-up from 1948 through 1999. Various cancers evaluated including kidney (ICD-9 180.0–189.2; $N=17$). External comparison rates used	Exposure to TCE assessed using company work histories, walk-through surveys, and interviews to developed JEM. Of the 41,351 total subjects, 1,111 assumed to be exposed to TCE	Never/ever exposed to TCE. Intra-cohort assessment by years (no, <4 years, 4+ years) of potential TCE exposure among engine flush workers also reported	Ever exposed to TCE SMR = 2.22(0.89–4.57)
Radican et al. (2008) [60]	Cohort of 14,457 aircraft maintenance workers from Utah, USA	Cancer mortality follow-up from 1953 through 2000 and cancer incidence follow-up from 1953 through 1990. Various cancers evaluated including kidney (ICD-8 189; $N=15$). Utah population used as referent group for overall analysis	Exposure to TCE assessed using company work histories, walk-through surveys, interviews, industrial hygiene experts, and other company records to developed JEM. Of the 14,455 total subjects 7,204 assumed to be exposed to TCE	Never/ever exposed to TCE (estimates stratified by sex also reported). Sex-stratified risk estimates for cumulative exposure to TCE (presented in tertiles) also reported	Ever exposed to TCE among all subjects RR = 1.18(0.47–2.94), among males RR = 1.24(0.41–3.72), among females RR = 0.93(0.15–5.76)
Case-control studies					
Asal NR et al. (1988) [19]	US mixed-based (population- and hospital-based) case-control study	Participants included 315 RCC cases and 313 hospital- and 336 population-based controls	Self-reported lifetime occupation/industry collected assessed through questionnaires. Exposure to TCE ($N=29$) assumed in metal degreasing/cleaning industry workers	Never/ever employed in the metal degreasing/ cleaning industry (exposure to TCE assumed) adjusted for age, smoking, and weight	Ever employed in metal degreasing/ cleaning industry OR = 1.7 (0.7–3.8)

Harrington et al. (1989) [61]	Population-based case-control study conducted in the United Kingdom	Participants included 54 RCC cases and 54 population-based controls	Questionnaires and interviews used to collected data on self-reported lifetime occupational histories and exposure to solvents. Data assessed by occupational hygienist for solvent exposure. Exposure to TCE ($N=8$) assumed among metal degreasing/cleaning industry workers	Never/ever exposed to organic solvents (exposure to TCE assumed)	Ever exposed to degreasing solvents OR = 1.0 (0.2–4.9)
Sharpe et al. (1989) [62]	Hospital-based case-control study conducted in Canada from 1982 to 1987	Participants included 164 RCC (ICD-8 189.0) cases and 161 hospital-based controls	Questionnaires used to collected data on self-reported timing and proximity of occupational exposures to various agents. Exposure to TCE ($N=13$) assumed among workers handling degreasing solvents	Never/ever exposed to degreasing solvents (exposure to TCE assumed)	Ever exposed to degreasing solvents OR = 3.42 (0.92–12.66)
Siemiatycki (1991) [67]	Canadian mixed-based (population- and hospital-based) case-control study conducted from 1979 to 1985	Participants included 177 kidney cancer cases and 3,014 mixed-based controls	Self-reported lifetime occupational histories collected using occupation-specific questionnaires and interviews. Occupational data reviewed by an expert (subject-specific) for exposure to TCE ($N=4$ among those with kidney cancer)	Never/ever exposed to TCE	Ever exposed to TCE OR = 0.8(0.4–2.0)
Greenland et al. (1994) [63]	US population-based nested case-control study conducted from 1969 to 1984	Participants included various cancer cases including 12 with kidney cancer and 1,202 population-based controls	Insurance pension records containing work histories of TCE-using transformer assembly plant workers assessed by industrial hygienist. JEM developed for exposure to TCE	Never/ever exposed to TCE	Ever exposed to TCE OR = 0.99(0.30–3.32)
Vamvakas et al. (1998) [64]	German hospital-based case-control study conducted from 1987 to 1992	Participants included 58 RCC cases and 84 hospital-based controls	Questionnaire and interviews used to collected self-reported occupational histories that included hazardous chemicals, insurance, and worker compensation records (appears subject-specific) assessed by occupational hygienist for occupational exposure to TCE ($N=24$)	Never/ever exposed to TCE adjusted for age, sex, smoking, BMI, blood pressure, and use of diuretics	Ever exposed to TCE OR = 10.80(3.36–34.75)
Dosemeci et al. (1999) [45]	US population-based case-control study conducted from 1988 to 1990 in Minnesota, USA	Participants included 438 RCC cases and 687 population-based controls	Questionnaire and interviews used to collected self-reported most recent and usual job and industry with activities, and dates, and duration in 13 industries and 7 jobs. JEM for exposure to TCE exposure ($N=55$) created	Never/ever exposed to TCE adjusted for age, sex, smoking, body mass index, blood pressure, and use of diuretics or antihyper-tension medications	Ever exposed to TCE among all subjects OR = 1.3(0.9–1.9), among males OR = 1.04(0.6 = 1.7), among females OR = 1.96(1.0–4.0)
Pesch et al. (2000) [29]	German population-based case-control study conducted from 1991 to 1995	Participants included 935 RCC cases and 4,298 population-based controls	Questionnaire and interviews used to collected self-reported occupational histories with supplemental questions on tasks with exposures of interest, the exposure and frequency. A job and task exposure matrix applied to examine exposures to chlorinated solvents including TCE ($N=172$)	Exposure to TCE assessed in tertiles (30th, 60th, and 90th percentiles of the distribution of exposure)	Tertiles of exposure to TCE among males: 30th OR = 1.3(1.0–1.8), 60th OR = 1.1(0.8–1.5), 90th OR = 1.3(0.8–2.1) TCE exposure level; among females: 30th OR = 1.3(0.7–2.6), 60th OR = 0.8(0.4–1.9), 90th OR = 1.8(0.6–5.0) TCE exposure level

(continued)

Table 25.1 (continued)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)
Bruning et al. (2003) [76]	German hospital-based case-control study conducted from 1992 to 2000	Participants included 134 RCC cases and 401 hospital-based controls	Questionnaire and interviews used to collected self-reported lifetime occupational histories. A JEM for exposure to TCE ($N=63$) was applied	Never/ever exposed to TCE. Years of exposure to TCE assessed as none, <10 years, 10–<20 years, 20+ years	Ever exposed to TCE OR = 2.47(1.36–4.49). Years of exposure to TCE <10 years OR = 3.78(1.54–9.28), 10–<20 years OR = 1.80(0.67–4.79), 20+ years OR = 2.69(0.84–8.66)
Charbotel et al. (2006) [66]	A French, mixed-based (population- and hospital-based) case-control study conducted from 1993 to 2003	Participants included 86 RCC cases and 316 mixed-based controls	Questionnaire and interviews used to collected self-reported occupational histories. A task-specific JEM was applied. Exposure to TCE assumed among 147 subjects	Never/ever exposed to TCE adjusted for body mass index and smoking	Ever exposed to TCE OR = 1.64(0.95–2.84)
Moore et al. (2010) [43]	Central and Eastern European hospital-based case-control study conducted from 1999 to 2003	Participants included 1,097 RCC cases and 1,476 hospital-based controls	Interviews and occupation-specific questionnaires used to collected self-reported occupational histories which was assessed by occupational health experts (appears subject-specific) for exposure to TCE ($N=88$)	Never/ever exposed to TCE, adjusted for sex, age, and study center. Years (<13.5/13.5+ years), hours (<1,080/1,080+ hours), cumulative exposure (<1.58/1.58+), and average intensity (<0.076/0.076+) of exposure to TCE also examined	Ever exposed to TCE OR = 1.63(1.04–2.54). Years of exposure to TCE <13.5 years OR = 1.44(0.77–2.69), 13.5+ years OR = 1.82(0.99–3.34). Hour of exposure to TCE <1.58 h OR = 1.19(0.61–2.35), 1.58+ hours OR = 2.02(1.14–3.59). Average intensity of exposure to TCE <0.076 OR = 1.38(0.81–2.35), 0.076+ OR = 2.34(1.05–5.21)

RCC renal cell carcinoma, *N* number, *OR* odds ratio, *RR* relative risk, *CI* confidence interval, *ICD-O* international classification of disease for oncology, *US* United States, *JEM* job exposure matrix

observed significantly elevated RRs for cohort studies (RR = 1.26, 95 % CI = 1.02–1.56, *p*-heterogeneity = 0.56), case-control studies (OR = 1.35, 95 % CI = 1.17–1.57, *p*-heterogeneity = 0.41), and both types of studies combined (RR = 1.32, 95 % CI = 1.17–1.50, *p*-heterogeneity = 0.63) after removal of outlier studies, which, incidentally, were those reporting the highest associations between kidney cancer risk and TCE exposure [75]. Nonsignificant elevated summary estimates were observed for studies of workers exposed to the broader classification of chlorinated solvents, but not assessed specifically for TCE.

An important question raised by most critiques surrounds TCE exposure and its mode of action in the kidney. Findings from recent epidemiological studies suggest that the association between TCE exposure and kidney cancer risk may be modified by polymorphisms in genes important in the reductive metabolism of TCE [43, 76]. In particular, evidence from these studies has demonstrated that TCE-associated renal genotoxicity occurs predominantly through glutathione S-transferase (GST) conjugation and subsequent bioactivation by the enzyme renal cysteine beta-lyase (CCBL1) [43, 68, 76]. One early study of RCC and risk modification by *GST* genotypes among workers with long-term occupational exposure to high concentrations of TCE ($N = 45$ cases, $N = 48$ controls) observed positive associations among *GSTT1* active genotypes (OR = 4.2, 95 % CI = 1.16–14.91) [76]; however, findings from a reassessment of the same TCE-exposed kidney cancer cases and additional controls [originating from various sources] did not corroborate the findings [43, 77]. In a large case-control study of 1,097 RCC cases and 1,476 controls conducted in Central and Eastern Europe, job histories were assessed for the likelihood of exposure to organic solvents, chlorinated solvents, and specifically TCE [43]. RCC risk increased for subjects ever (compared to never) exposed to TCE ($N = 48$ cases, $N = 40$ controls), and an exposure–response trend was seen with higher estimated exposure levels. Elevated associations were not observed among individuals exposed to organic or chlorinated solvents. Subsequently, risk modification by *GSTT1* and *CCBL1* genotypes were also evaluated. A significant relationship (OR = 1.88, 95 % CI = 1.06–3.33) was found among likely TCE-exposed subjects with at least one intact *GSTT1* allele (active genotype $N = 32$ cases, $N = 23$ controls), but not among subjects with two deleted alleles (null genotype) [43]. These findings provided the strongest evidence to date that TCE exposure is associated with increased renal cancer risk that was limited to individuals with a particular genotype necessary for the reductive metabolism of TCE. In addition, increased risk was observed among those with an active *GST* genotype that would be able to conjugate and subsequently bioactivate TCE in vivo [43]. This finding adds biological plausibility of the association in humans and provides some understanding of its mechanism of carcinogenicity. Other pathways involved in the metabolism of TCE remain to be evaluated [43, 78].

High-quality exposure assessment and robustness of findings across studies that specifically focused upon TCE exposure raises the likelihood of an association. Weaknesses that exist across all studies conducted to date include potential confounding and exposure misclassification due to possible exposures to other solvents, although both factors would likely reduce risk estimates, rather than increase them. Additional studies, particularly more recently updated meta-analytic studies, are warranted to help support a human health risk assessment between TCE exposure and kidney cancer risk.

Agricultural Work and Exposure to Pesticides, Insecticides, and Herbicides

Increased renal cancer risk has been observed in several studies of agricultural workers and farmers [20, 22, 28, 79, 80]. Updated cancer mortality data among a cohort of US farmers who applied pesticides revealed a significant 62 % increase (95 % CI = 1.28–2.05) in renal cancer mortality [76]. Elevated mortality (standard mortality ratio (SMR) = 2.12) also was observed among a cohort of Italian farmers [80], but a significantly reduced renal cancer incidence was found among Swedish male (standardized incidence ratio (SIR) = 0.88) [28] and female (SIR = 0.81, 95 % CI = 0.68–0.97) [81] farmers. Mixed results have been shown in case-control studies reporting specific agricultural industries, occupations, and job titles [18–20, 22, 36, 82–84]. For example, findings from a recent renal cancer case-control study analyzing job and industry titles reported a significant 43 % (95 % CI = 1.03–2.00) increase in risk for subjects employed as agricultural and animal husbandry workers ($N = 107$ cases, $N = 108$ controls); an overall 35 % (95 % CI = 1.3–1.77) increase for participants in the agricultural, hunting, and related services industries ($N = 132$ cases, $N = 138$ controls); and a more than twofold increase in risk for female general farmers ($N = 16$ cases, $N = 7$ controls, OR = 2.73, 95 % CI = 1.05–7.13). Higher-risk estimates were also observed among those with a longer duration of employment (10+ years) for these jobs/industries [20]. On the other hand, no increase in cancer risk was observed among agricultural livestock workers ($N = 15$ cases, $N = 19$ controls, OR = 1.00) [20]. Additionally, an earlier review of cancer patterns among farmers in developed countries found a significant 8 % reduction in kidney cancer risk (combined RR = 0.92, 95 % CI = 0.86–0.98) (risks ranging from 0.6 to 1.5) based on results from 13 epidemiological studies of various designs [85].

The relationship between evaluation of likely occupational pesticide exposure and RCC risk has been examined in eight epidemiological studies (Table 25.2), and results have

Table 25.2 Renal cancer risk and occupational studies of pesticide, herbicide, and/or insecticide exposures

Reference (year)	Study type and location	Cases	Controls	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)	Adjustment
McCredie and Stewart (1993) [86]	Population-based case-control study of kidney cancer conducted in New South Wales, Australia, from 1989 to 1991	Incident renal parenchyma (ICD-9 189.0; *N* = 489) and renal pelvis (ICD-9 189.1; *N* = 147) cancer cases, 20–79 years old, identified from hospital cancer registries	Population-based controls (*N* = 523) identified from electoral roles	Face-to-face (256 RCC, 71 renal pelvis, 232 controls) and telephone (233 RCC, 76 renal pelvis, 291 controls) interviews conducted. Standardized questionnaires used to collect data on employment in certain industries and occupations and exposure to certain chemicals	Never/ever exposed to herbicides or insecticides/ pesticides	Ever exposed to insecticides/ pesticides RCC RR = 1.39(0.89–2.18). Ever exposed to herbicides RCC OR = 1.45 (0.87–2.40)	Adjusted for age, sex, method of interview, and education
Mellemgaard et al. (1994) [25]	Population-based case-control study of RCC conducted in Denmark from 1989 to 1992	Histologically verified RCC cases (*N* = 365), 20–79 years old, identified from the Danish Cancer Registry and repeat searches in files of all pathology departments in Denmark	Population-based control (*N* = 396) identified from the Central Population Registry and frequency matched to cases on sex and age	In-person interviews conducted to collect data on most recent and longest occupation held. Data pertaining to occupation, industry, and occupational exposures assessed	Never/ever exposed to insecticides or herbicides. Years of exposure to insecticides/herbicides (never, <20 years, 20+ years) among males	Ever exposed to insecticides among males OR = 2.2(0.8–6.3), among females OR = 5.7(0.6–58). Ever exposed to herbicides among males OR = 1.7(0.7–4.3), among females OR = 5.7(0.6–58). Years of exposure to insecticides/herbicides among males <20 years OR = 1.3(0.4–4.1), 20+ years OR = 3.9(1.0–15)	Adjusted for age, BMI, and smoking
Mandel et al. (1995) [23]	Multicenter, international (Australia, Denmark, Germany, Sweden, and USA) population-based case-control study of RCC	Incident RCC (ICD-9 189.0; *N* = 1,732) cases, verified by histology or cytology, 20–79 years old, were identified through active surveillance systems of clinical and pathology departments	Population-based controls (*N* = 2,309) were selected from the same registry areas as cases and identified through population, electoral, residential, and health care financing registries; all were frequency matched to cases on age and sex	Face-to-face interviews conducted to collect data on specific occupations, industries, and exposures of interest	Never/ever exposed to pesticides among males	Ever exposed to pesticides among males RR = 1.2 (0.9–1.5)	Adjusted for age, smoking status, BMI, education, and study center

Schlehofer et al. (1995) [36]	Population-based case-control study of RCC conducted in Germany from 1989 to 1991	Histologically confirmed incident RCC (ICD-9 189.0; *N* = 277) cases, 20–75 years old, identified from ten urology departments within the German Rhein-Neckar-Odenwald area	Population-based controls (*N* = 286) identified from the compulsory population registry of the study area and frequency matched to cases on age and sex	Personal interviews conducted using standardized questionnaires. Life occupational histories evaluated to assess employment in certain industries and occupations and exposure to certain chemicals	Never/ever exposed to pesticides with the referent category being subjects exposed for <5 years	Ever exposed to pesticides among men RR = 0.89 (0.42–1.89)	Adjusted for age and smoking
Hu et al. (2002) [24]	Population-based case-control study of RCC conducted in Canada between 1994 and 1997	Histologically confirmed incident RCC (ICD-O-2 64.9; *N* = 1,279) cases from eight Canadian provinces identified from cancer registries	Population-based controls (*N* = 5,380) included people without cancer selected from a random sample of individuals within a province and frequency matched to cases on age, sex, and province	Mailed questionnaires used to collected information on occupational histories and years of exposure to certain chemicals. Occupational exposures to chemicals evaluated for subjects exposed for at least 1 year	Never/ever exposed to pesticides or herbicides. Years of exposure to herbicides (never, 1–15 years, 16+ years) among men	Ever exposed to pesticide among males OR = 1.8 (1.4–2.3), among females OR = 1.3 (0.9–1.8). Ever exposed to herbicides among males OR = 1.6 (1.3–2.0), among females OR = 0.8 (0.5–1.3). Years of exposure to herbicides among males ≤15 years OR = 1.3 (0.9–1.8), 16+ years OR = 2.0 (1.4–2.7), *p*-trend = 0.001	Adjusted for age, province, education, BMI, pack-years of smoking, alcohol use, and total meat consumption
Buzio et al. (2002) [82]	Hospital-based case-control study of RCC conducted in Northern Italy from 1998 to 2000	Histologically verified RCC cases (*N* = 100) identified from the Parma University Hospital	Hospital-based controls (*N* = 200) identified from outpatient specialty centers at the same university hospital	In-person interviews conducted using a structured questionnaire to collect data on occupational histories and exposures	Duration of exposure to pesticides (never, short (<10 years), long (10+ years)). Never/ever exposed to pesticides with referent being no exposure to any of the major occupational determinants of risk	Duration of exposure to pesticides <10 years OR = 1.1 (0.2–5.9), 10+ years OR = 2.0 (0.8–4.7), *p*-trend = 0.33. Ever exposed to pesticides OR = 2.6 (0.7–9.8)	Adjusted for age
Mattioli et al. (2002) [37]	Hospital-based case-control study of RCC conducted in Northern Italy from 1986 to 1994	Histologically confirmed RCC cases (*N* = 324) were identified from patients registered at the University Hospital of Bologna	Hospital-based controls (*N* = 324) selected from patients from the same hospital as cases and frequency matched to cases on age, sex, and place of birth and residence	Mailed questionnaires (or telephone interviews for non-mail respondents) used to collect information on occupational histories. Job titles assessed by occupational physicians. Occupational exposures assessed by industrial hygienist	Never/ever exposed to pesticides	Ever exposed to pesticides among males OR = 1.24 (0.34–4.57), among females OR = 0.32 (0.01–9.20)	Adjusted for age, sex, birthplace, residence, BMI, smoking, coffee and alcohol consumption, phenacetin/diuretic use, and meat intake

(continued)

Table 25.2 (continued)

Reference (year)	Study type and location	Cases	Controls	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)	Adjustment
Karami et al. (2008) [38]	Hospital-based case-control study of RCC conducted in Central and Eastern Europe from 1999 to 2003	Histologically confirmed incident RCC (ICD-O-2 64; *N* = 1,097) cases, 20–88 years old, identified from local participating hospital centers	Hospital-based controls (*N* = 1,476) selected from patients from the same hospital as cases with conditions unrelated to urological disorders and frequency matched to cases on age, sex, and place of residence	In-person interviews and standardized questionnaires used to collect lifetime occupational data on jobs held for at least 1 year. Job-specific questionnaires also used to collect data on specific occupational exposures. Exposure to pesticides evaluated by occupational health experts	High confidence exposure to pesticides evaluated as never/ever, years (never, ≤8 years, >8 years), hours (never, ≤1,230 h, >1,230 h), cumulative exposure (never, ≤0.86, >0.86), and average exposure (never, ≤0.03, >0.03)	Ever exposed to pesticides OR = 1.82 (1.1–3.00). Years exposed to pesticides ≤8 years OR = 1.0 (0.45–2.21), >8 years OR = 2.66 (1.38–5.12), *p*-trend = 0.01. Hours exposed to pesticides ≤1,230 h OR = 1.43 (0.70–2.93), >1,230 h OR = 2.24 (1.13–4.43), *p*-trend = 0.01. Cumulative exposure to pesticides ≤0.86 OR = 1.60 (0.77–3.32), >0.86 OR = 2.02 (1.04–3.94), *p*-trend = 0.02. Average exposure to pesticides ≤0.03 OR = 2.21 (1.15–4.25), >0.03 OR = 1.37 (0.63–2.96), *p*-trend = 0.06	Adjusted for age, sex, center, and smoking status

RCC renal cell carcinoma, *N* number, *OR* odds ratio, *RR* relative risk, *CI* confidence interval, *ICD-O* international classification of disease for oncology

been inconsistent [23–25, 36–38, 82, 86]. No associations were observed between RCC risk and occupational pesticide exposure in a large international multicenter population-based study of 1,723 cases and 2,309 controls [23] or in three smaller European case-control studies [36, 37, 86]. Nonsignificant increased risks were observed in two European case-control studies [25, 82]. When analyses were restricted to subjects occupationally exposed to pesticides for at least 20 years, one study reported a fourfold increase in risk in males ($N=10$ cases, $N=3$ controls, OR = 3.9, 95 % CI = 1.0–15.0) [25]. A large case-control study conducted in Central and Eastern Europe showed increased RCC risk among subjects whose job histories were assessed for likely pesticide exposure ($N=44$ cases, $N=34$ controls). Elevated risk was observed for ever exposure (OR = 1.60, 95 % CI = 1.00–2.55) and with years (p-trend = 0.01), hours (p-trend = 0.03), and cumulative (p-trend = 0.04) exposures, but no association was observed with average exposure indices (p-trend = 0.09) [38]. Resulting risk estimates from this study were strengthened when analyses were limited to jobs assessed by occupational health experts as having the highest confidence of exposures. Moreover, a significantly elevated RCC risk was reported among males exposed to herbicides ($N=131$ cases, $N=318$ controls, OR = 1.6, 95 % CI = 1.3–2.0) and pesticides ($N=157$ cases, $N=368$ controls, OR = 1.8, 95 % CI = 1.4–2.3) in a large Canadian case-control study of 1,279 cases and 5,370 controls, and risk also increased linearly with increasing years of exposure [24].

Some pesticides are comprised of halogenated compounds, which can be metabolized and subsequently bioactivated through mechanisms similar to chlorinated solvents like TCE [9, 87]. A few studies have examined RCC risk in relation to *GST* genotype [38, 88], with the hypothesis that an active *GST* genotype would result in renal bioactivation of halogenated pesticide compounds. Active genotypes are able to encode GST proteins; therefore, their presence would be required for conjugation and subsequent bioactivation of related metabolites in the kidney [38]. Since *GST* genes are expressed and enzymes are active in the kidney, GST activity associated with functional polymorphisms in the glutathione S-transferase mu (*GSTM1*) and theta (*GSTT1*) genes are hypothesized to modify cancer risk because of the differences in the ability to bioactivate halogenated compounds in the kidney [38, 88]. Although two small earlier studies of GSTs and pesticide exposure did not observe risk modification by *GST* genotype [87, 89], two recent studies have found that RCC risk was increased among likely pesticide-exposed participants with active *GSTM1* or *GSTT1* genotypes [38, 88]. Moreover, the results of both studies were further strengthened among subjects with both active genotypes.

The carcinogenic potential of specific pesticides has been evaluated by the IARC [90]. Most occupational epidemiological studies have not been able to examine cancer risk associated with exposure to specific pesticides given the small number of study participants, the lack of detailed information collected to identify individual classes of pesticides, and misclassification due to exposures to multiple pesticides. However, the carcinogenic risk posed to humans from occupational exposure during the spraying and application of insecticides has been evaluated by the IARC and classified as "probably" carcinogenic to humans (Group 2A) [90]. The need for additional studies is apparent given the limited number of studies that have evaluated occupational pesticide exposure in relation to kidney cancer and the important role of the kidneys in the metabolism of certain classes of pesticides.

Lead

Inorganic lead and lead compounds are classified as "probable" human carcinogens by the IARC [91] and listed as "reasonably anticipated to be human carcinogens" by the National Toxicology Program [92], based on limited evidence of carcinogenicity in humans and sufficient evidence in laboratory animals, particularly for cancers of the stomach and lung. Inconsistent evidence for an association between kidney cancer and exposure to lead or lead compounds has been shown [91–104]. Among lead-exposed workers, high exposure has been reported in lead smelting and lead battery plants, while moderate exposure has been shown for welders of metals containing lead or painted with lead (lead fumes), lead miners, lead glass workers, automobile radiator repair workers, leaded paint manufacture workers, as well as lead typesetting printing workers [93, 94].

Lead has been shown to induce renal cancers in rodents and chronic nephropathy among humans with high occupational exposures [91, 92]. The carcinogenic effect of lead on the kidneys is plausible since urinary elimination is the main route of excretion and the proximal tubules are particularly sensitive to lead given their high reabsorption activity [95]. Moreover, the tubular epithelium of the renal cortex is a major target for the carcinogenicity of inorganic lead salts in animals, although the type of lead used in animal experimentation was different than the type to which humans are occupationally exposed [91, 96].

Exposure to lead has been suspected for the elevated kidney cancer associations observed among welders [18, 28, 29, 86, 97], auto mechanics and technicians [20], painters [29, 30], and lead smelter [98–100] and production [101] workers. However, epidemiological studies examining the association between occupational lead exposure and kidney cancer have been inconsistent [18, 29, 98–100, 102, 103]. Three cohort studies of male lead smelter workers assessed for high lead exposure using air monitoring measurements [98, 99] and industrial hygiene surveys [98–100] observed a

1.4–2-fold increase in kidney cancer mortality risk when compared to national rates. In 1985, Selevan and coauthors reported a borderline significant increase in kidney cancer mortality (SMR = 301, 95 % CI = 98–703) among high-lead-exposed (airborne levels >200 μg/m^3) workers from Idaho (N = 5) [99]. Utilizing updated information from the same cohort, Steenland et al. also found non-statistically elevated risk for kidney cancer mortality among all workers 8 years later, but also a significant increase in risk (SMR = 2.39, 95 % CI = 1.03–4.71) for workers with high lead exposure (N = 8 observed deaths) [98]. Using an internal comparison of workers, Cocco and investigators observed an RR of 10.9 (95 % CI = 1.0–121.0, N = 2 observed cases) among lead smelter workers in Italy who had been employed for at least 21 years [100]. Studies of other lead-exposed occupational cohorts have not found a significant excess in kidney cancer risk [102, 103]. Similarly, a meta-analysis of published epidemiological studies on cancer risk and occupational exposure to lead using measurement of exposure levels or blood levels through the year 2000 (N = 7 studies, N = 40 deaths) did not find an association with kidney cancer (RR = 1.01, 95 % CI = 0.72–1.42) [93]. However, the use of JEMs or occupational experts to estimate likely lead exposures in case-control studies has usually shown an increase in kidney cancer risk [29, 65, 67, 96, 97, 104]. The most recent large-scale case-control study of approximately 1,100 cases and 1,500 controls reported a significant increase in RCC risk (OR = 1.55, 95 % CI = 1.09–2.21) among likely lead-exposed workers (N = 80 cases, N = 71 controls). Although no clear monotonic exposure–response was observed for either duration or cumulative exposure, RCC risk was 2.25 (95 % CI = 1.21–4.19) among subjects in the highest cumulative lead exposure category [96].

Lead is not considered to be directly genotoxic in vitro, and it has been shown to increase the mutagenicity of other carcinogens by acting as a cocarcinogen, possibly through inhibition of DNA repair [93]. One of the most important mechanisms of lead toxicity occurs through its ability to impede key enzymes within the heme biosynthetic pathway [105]. Therefore, previous studies of genetic susceptibility to lead exposure and cancer risk have analyzed risk modification by genetic variants in the δ (delta)-aminolevulinic acid dehydratase (*ALAD*) gene [105–107], the second enzyme in the heme biosynthetic pathway [105]. The gene that encodes *ALAD* exists in two polymorphic forms ($ALAD_1$, $ALAD_2$) [single nucleotide polymorphism (SNP) 1800436], the presence of which may influence an individual's susceptibility to lead poisoning [105, 108]. The substitution of an asparagine for lysine at residue 59 results in an increased affinity for lead by $ALAD_2$ compared to $ALAD_1$ [105, 109]. It is unclear whether other functional variants exist. One recent study found that rs8177796 CT/TT variants were associated with RCC risk overall (OR = 1.35, 95 % CI = 1.05–1.73), compared to the CC major allele. Joint effects of lead exposure and SNP rs2761016 suggested an increased RCC risk for the homozygous wild-type and heterozygous alleles (^{GG}OR = 2.68, 95 % CI = 1.17–6.12; ^{GA}OR = 1.79, 95 % CI = 1.06–3.04) with an interaction approaching significance (p-interaction = 0.06). In contrast, no modification of risk was observed for the functional SNP rs1800435 (K68N) [105], which had previously been associated with brain cancer and susceptibility to lead poisoning [106]. But, due to the limited analytic power (small number of participants) in that study to investigate interaction between *ALAD* and lead exposure in RCC, further investigations are needed to elucidate this relationship.

Results of studies of welders and renal cancer case-control studies of lead exposure may have been subject to confounding by other metal exposures. However, because of the important role of the kidney in metal excretion and reabsorption, and of genetic factors known to influence susceptibility to lead exposures, biological plausibility of the association exists, and additional studies designed to identify susceptible subpopulations are warranted.

Other Metals: Cadmium, Chromium, Nickel, and Arsenic

Cadmium, chromium, nickel, and arsenic are classified by the IARC as group 1, "known" human carcinogens, but this conclusion is based on associations with lung cancer [110]. Findings from studies of cadmium exposure and kidney cancer have for the most part yielded inconclusive results [23, 24, 29, 86, 96, 104, 111, 112]. Cadmium has a long residence time in the renal cortex and nephrotoxic effects associated with occupational and environmental exposures have been observed [113, 114]. Three major sources of cadmium exposure include diet, cigarette smoking, and occupation [115]. One of the earliest studies of cadmium exposure by Kolonel in 1976 reported a positive association between renal cancer risk and occupational cadmium exposure [116]. Three population-based RCC case-control studies, by Mandel et al. [23], Pesch et al. [29], and Hu et al. [24], have since reported significantly elevated cancer risk for self-reported exposure to cadmium and cadmium salts among male workers (N = 25 exposed cases, N = 15 exposed controls, RR = 2.0, 95 % CI = 1.0–3.9; N = 99 exposed cases (number of exposed controls not reported), OR = 1.4, 95 % CI = 1.1–1.8; and N = 19 exposed cases, N = 32 exposed controls, OR = 1.7, 95 % CI = 1.0–3.2, respectively). A significant increase in risk was also reported by Pesch et al. among female workers assessed for high cadmium exposure (OR = 2.5, 95 % CI = 1.2–5.3) [29]. However, further exposure–response analyses revealed no monotonic increase with cancer risk for years [23, 24] or level of exposure [29] in these studies. One of the highest

risk estimates observed with cadmium exposure was reported by Partanen et al., who found a greater than fourfold increase in RCC risk among subjects who were expert-assessed to have likely occupational cadmium exposure (OR = 4.4, 95 % CI = 0.4–43.0), although results were based on only three exposed cases [104]. Most recently, in a European case-control study that collected detailed occupational information and expert exposure assessment, an elevated RCC risk estimate was reported for cadmium exposure (OR = 1.46, 95 % CI = 0.82–2.85). Yet no exposure–response relationship for duration or cumulative exposure was observed, and the number of exposed cases was small (*N* = 25) [96]. Other epidemiological studies have not observed significant associations between occupational cadmium exposure and kidney cancer risk [86, 111].

Studies of occupational exposure to chromium and nickel with kidney cancer risk have been inconsistent [18, 24, 65, 96, 117–120]. To date, significant risk associated with occupational exposure to chromium has only been reported in one small case-control study from Germany that assessed exposure using a JEM in which a greater than twofold increase in risk was seen for both low (*N* = 16 cases, *N* = 28 controls, OR = 2.09, 95 % CI = 1.03–4.22) and high (*N* = 20 cases, *N* = 32 controls, OR = 2.21, 95 % CI = 1.15–4.25) levels of occupational exposure to chromium [65]. Evidence of association between occupational nickel exposure and kidney cancer risk has only been suggested in a large cohort study of nickel alloy plant workers from the USA. Though no increase in kidney cancer mortality risk was observed among all plant workers, a significant twofold increase in risk was reported for white male workers employed in smelting [118]. Arsenic exposure has been associated with kidney cancer mortality in ecologic studies of drinking water contamination [121], but, typically, associations between occupational arsenic exposure and renal cancer risk have not been observed [24, 96, 122].

Given the possibility of exposure misclassification due to the presence of mixed occupational exposures, and limited study power observed in many studies due to the low number of exposed cases, additional well-powered studies that examine the relationship between occupational exposure to each of these metals that are also "known" human carcinogens and kidney cancer are warranted.

Diesel and Automotive Fumes

Interest regarding exposure to diesel and automotive fumes as possible renal carcinogens grew following a study demonstrating RCC among rats chronically exposed to unleaded gasoline fumes [123]. In 1985, McLaughlin and coauthors identified an elevation in RCC risk with duration of employment among gas station attendants [124]. Similar findings in both cohort and case-control studies have since been reported in this group of workers [22, 23, 124–126]. Occupational cohort and case-control studies have also found elevated RCC risk among truck and urban bus drivers [25, 34], railroad workers [29, 37, 127], firefighters [30, 31], and automotive repairers/mechanics [22, 28]. Findings from these and other epidemiological studies further suggest that diesel and gasoline exhaust and fumes may be etiologic risk factors associated with renal cancer risk [18–20, 22, 25, 29, 34, 36, 65, 124, 127, 128].

Diesel exhaust, according to the IARC, is classified as a "probable" human carcinogen because of the limited evidence of carcinogenicity in humans coupled with sufficient evidence of in experimental animals exposed to whole engine exhaust [129]. Epidemiological studies on occupational diesel exhaust and kidney cancer in humans have produced mixed results [128–136]. A small but significant increase in kidney cancer risk (*N* = 2,243, SIR = 1.06, 95 % CI = 1.02–1.11) was shown among men with likely diesel exhaust exposure in a large Swedish occupational cohort study in which exposure was estimated using a JEM [128]. More recently, a similar association between kidney cancer risk and likely exposure to low levels (<2.0 mg/m^3-years) of diesel exhaust (*N* = 465 exposed cases) was observed among men in a cohort of Finnish workers (RR = 1.17, 95 % CI = 1.05–1.30); however, no increase in risk was seen for moderate or high levels of exposure or among female workers [130]. Several early studies of railroad workers reported small increased associations with kidney cancer risk and exposure to diesel [131, 132], but other occupational studies of diesel-exposed workers did not find an elevated risk [133–136].

Occupational gasoline exposure, classified as a Group 2B "possible" human carcinogen by the IARC [129], using both self-reported [23, 36] and JEM-based evaluations [104], has been associated with an elevated RCC risk. A population-based case-control study conducted in Germany found a significantly elevated kidney cancer risk among men reporting occupational exposure to gas exhaust (*N* = 37 cases, *N* = 23 controls, RR = 1.82, 95 % CI = 1.03–3.22) for at least 5 years [36]. A similar result was shown for men in an international study of workers who reported ever having been exposed to gasoline (*N* = 164 cases, 189 controls, OR = 1.6, 95 % CI = 1.2–2.0) [23]. Occupational gasoline exposure, assessed by industrial hygiene experts, was associated with a significant increase in RCC risk among ever versus never exposed workers (*N* = 39 cases, number of exposed controls not reported, OR = 1.72, 95 % CI = 1.03–2.87) and among men with the highest cumulative exposure levels (*N* = 9 cases, number of controls not reported, OR = 4.34, 95 % CI = 1.15–16.4) [104]. Other studies have found no elevation in risk among gasoline-exposed workers [62, 124] or among mechanics, automotive dealers, or service station employees [18, 137].

Limitations in assessing the intensity of exposure based on job title, the geographic differences in gasoline constituents, and the substantial improvements in work practices that have resulted in the decrease in daily exposures to gasoline attendants over time may explain the inconsistent findings between earlier and more recent studies. Moreover, several studies did not adjust for smoking, a known renal cancer risk factor, which may have confounded some of the results observed.

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are a group of chemical compounds found naturally in fossil fuels which are formed as by-products during the incomplete combustion of organic material such as coal, oil, wood, garbage, gas, tobacco, and charbroiled meat [138, 139]. Constituents of diesel and gasoline exhausts also contain PAHs [129]. PAHs comprise over 100 compounds that exist exclusively as complex mixtures [138–140]. PAHs have also been used in the production of plastics, dyes, medicines, aluminum, coke, and pesticides, and they are also present in tars and asphalts [138]. Specific PAHs, such as benzo[a]pyrene and benzo[a]anthracene, are considered known or suspected human carcinogens [138]. The IARC has identified several mixtures containing PAHs, including coal tar, diesel engine exhaust, and soot as carcinogenic or probably carcinogenic to humans [129].

In a few early occupational cohort studies, elevated RCC risk among coke oven and petroleum refinery workers (the latter associated with PAH by-products of the refining process) had generated interest in PAHs as occupational renal carcinogens [23, 141]. However, conflicting results have been reported in studies of employees assessed as highly exposed to PAHs, such as asphalt workers, printers, machinists, and mechanics [18, 25, 28, 86, 142]. Historically, county-level kidney cancer mortality rates in the USA have shown an ecologic correlation with the proportion of the population employed in the petroleum-refining and other petroleum-related industries [143]. Population- and hospital-based case-control studies have reported elevated risks for employment in the oil refinery industry [19, 23, 124]. Two studies have shown a suggestive exposure–response effect with the length of employment [83] and exposure intensity [62] among workers occupationally exposed to various PAHs.

Three European case-control studies that used JEMs to estimate likely PAH intensity did not report a positive association or an exposure–response effect [29, 104, 144]. Studies have also examined *GSTs* [145] and cytochrome p450 (*CYP450*) genotypes [144, 146], and modification of PAH associated risk was observed in one [146], but not both studies [144].

In addition to the duration and level of exposure, the carcinogenicity of PAHs depends on the specific chemical composition of the mixture that can influence toxicodynamics, toxicokinetics, and ultimately their biological effect [144]. Because certain PAHs are recognized as carcinogenic or possibly carcinogenic to humans, additional studies that are well powered for analyses of gene–environment interaction that can identify the unique chemical composition of PAHs are needed.

Asbestos

Exposure to all forms of asbestos, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite, has been classified by the IARC as carcinogenic to humans (Group 1), based on association with respiratory cancers [111]. Asbestos fibers have been shown to induce kidney cancer in animals, and asbestos bodies have been detected in the kidneys of individuals diagnosed with asbestosis [147–149]. Several industry- and occupationally based cohort and case-control studies have reported elevated kidney cancer risk among persons likely exposed to asbestos, including asbestos workers; shipyard, railway, and insulation workers; seafarers; and firefighters [18, 23, 25, 37, 86, 147, 150–153].

Studies that have assessed exposure to asbestos and kidney cancer risk have generally been null [154, 155]. Only two occupational cohort studies to date have reported a significant increase for kidney cancer risk and asbestos exposure [152, 156]. In 1987, Enterline et al. reported a nearly threefold increase in risk for kidney cancer mortality ($N=7$ observed deaths, SMR = 2.76, 95 % CI = 1.11–5.68) among asbestos production and maintenance workers when compared to US national death rates [152]. A few years later, Selikoff and Seidman observed a significant SMR of 1.70 (95 % CI = 1.16–2.39, $N=32$ observed deaths) for kidney cancer among a cohort of asbestos insulator workers from the USA and Canada [156]. Case-control studies utilizing JEMs or occupational health experts to assess likely exposure to asbestos have also shown significantly elevated kidney cancer risks ranging from 1.4 to 1.6 among exposed participants [23, 86]. However, positive trends with increasing intensity [29, 157] or duration [18, 23, 153, 157] of asbestos exposure from case-control studies have not been associated with kidney cancer risk. Moreover, other studies of similar design [24, 83, 104] and two meta-analyses [154, 155] of occupationally exposed cohorts have not corroborated the positive findings.

While animal studies have shown increased kidney cancer risk following exposure, the evidence linking occupational asbestos exposure to kidney cancer risk in humans has been weak. Given the significant findings observed in a few studies, which were mainly based on small case numbers, additional studies would be required to determine if asbestos should be considered a renal carcinogen. Furthermore, the

lack of supporting evidence from incidence cohort studies reduces the plausibility of an association between exposure and kidney cancer risk.

Other Fibers and Dusts

While a positive association between occupational fiber exposures has been observed for cancers of the respiratory system, associations with kidney cancer risk have been found in only a few occupational studies [157–162]. In a large Canadian cohort of 2,557 male fiberglass manufacturing workers, a significantly elevated kidney cancer risk ($N=14$ observed cases, SIR = 192, 95 % CI = 105–321) was observed in comparison to national cancer registry rates [158]. Yet a comparison of US mortality rates revealed no increase in kidney cancer mortality risk ($N=4$ observed cases, SMR = 0.77, 95 % CI = 0.21–1.97) in a cohort of 4,008 female fiberglass manufacturing plant workers [159]. No association with mortality was seen in a US cohort of man-made mineral fiber plant workers exposed to elevated airborne fiber concentrations of mineral wool and fiberglass [160]. However, likely occupational exposure to glass ($N=28$ cases, $N=19$ controls) and mineral wool ($N=22$ cases, $N=14$ controls) fibers (both of which share asbestos-like properties), assessed by industrial hygiene experts through the application of a JEM, was associated with an increase in kidney cancer risk (OR = 2.1, 95 % CI = 1.1–3.9; OR = 2.5, 95 % CI = 1.2–5.1, respectively) in a Central and Eastern European case-control study [157]. Significant trends were also observed with duration and cumulative exposure to glass and mineral wool fibers. However, increased associations between exposure to these fibers and kidney cancer risk have not been shown for all case-control studies [161, 162].

Results from studies on occupational dust exposure and kidney cancer have been mixed [25, 157, 163–169]. In a small group of European bricklayers with suspected brick dust exposure, a nonsignificant elevation in RCC risk was observed [25], and elevated kidney cancer mortality risk was reported in a surveillance study of US construction workers (concrete/terrazzo finishers) [163]. A JEM-based assessment of occupational brick dust exposure among participants in a large European case-control study also reported an increase in RCC risk ($N=72$ exposed cases, $N=80$ exposed controls, OR = 1.5, 95 % CI = 1.0–2.4). Duration and cumulative exposure to brick dust was also significantly associated with risk [157]. A study of female pottery workers, who were also exposed to silica, reported increased kidney cancer mortality [164]. A plausible cause for the relationship observed between brick dust and renal cancer may be related to the silica content of brick [157]. Silica is a Group 1 "known" human carcinogen, according to the IARC, based on sufficient epidemiological evidence from animal studies of lung cancer [165]. Scientific evidence has shown that chronic silica exposure can induce nephrotoxicity and fibrosis, glomerulonephritis, and degenerative changes in the renal tubular epithelium [165, 166, 170–172]. Silica exposure has been associated with cytogenetic damage in both animal and human studies of silica-exposed workers [165]. In 2005, Steenland and colleagues showed that silica exposure was associated with excess risk of end-stage renal disease [166]. A few years earlier, results from cohort studies (including one that assessed exposure using employment histories among silica-exposed taconite miners/millers and duration of employment in specific work areas [167] and a second Norwegian study of ferrosilicon/silicon metal plant workers that used dust measurements as estimates of silica exposure [168]) identified increased kidney cancer risk. Findings from the most recent US cohort study which assessed exposure using six environmental surveys and a JEM showed a significantly elevated threefold increase in kidney cancer mortality among silica-exposed granite workers with at least 15 years of employment [169].

In general, the lack of supporting evidence from cohort studies reduces plausibility of an association between RCC risk with dust and fiber exposures. Although these findings were for the most part negative, the fact that certain fibers are components of mixtures and may induce degenerative changes in renal tissue warrants future larger renal cancer studies with high-quality fiber exposure assessment. Additional studies that take into account silica content of brick dust exposures may help elucidate associations with specific dust subgroups as possible renal carcinogens.

Occupational Ultra Violet (UV) Exposure

Overall, ecologic studies examining the association between cancer risk and UV sunlight exposure have reported inverse associations for kidney cancer mortality and incidence [173–177]. However, results from occupational/industry studies have typically shown that employment as a farmer [20, 22, 28, 79, 80], railway worker [6, 29, 37, 127], gardener [18], or sailor [178], jobs assumed to have the highest UV exposures, is associated with higher kidney cancer risks. A large cohort of over 300,000 Swedish, male, outdoor construction workers observed a 30 % reduction in kidney cancer risk (RR = 0.7, 95 % CI = 0.4–1.0) among those with higher levels of occupational UV exposure ($N=23$ cases) when evaluated by an industrial hygienist from the construction industry [179]. More recently, in a larger European case-control study, JEM-based UV exposure estimates were associated with a significant 24–38 % reduction in RCC risk among males [180]. However, the strongest reduction in RCC risk in that study was observed among men residing at the highest latitudes; subjects suspected to have comparatively the weakest UV exposures may benefit from increased UV exposure overall.

The association between UV exposure and kidney cancer risk is biologically plausible since exposure to solar UV rays accounts for greater than 90 % of 1,25-dihydroxy vitamin D [181], the biologically active form of vitamin D. Moreover, the conversion of vitamin D to its biologically active form occurs within the kidney [181, 182]. Additionally, the kidney is the major organ for vitamin D metabolism, activity, and calcium homeostasis [183–185]. While emerging scientific data suggest that vitamin D has anticarcinogenic properties including inhibition of clonal tumor cell proliferation, induction of immune cell differentiation and apoptosis, and decreased angiogenesis [186, 187], epidemiological evidence in human studies for most cancer sites including kidney have been inconsistent [188–191]. In a recent large pooled cohort consortium study, no significant relationship between serum vitamin D levels and renal cancer risk was observed [188]. While there is general agreement that the serum vitamin D level is the best indicator of current vitamin D status, the short half-life of this biomarker may not reflect long-term exposure levels that are relevant to cancer latency and to lifetime occupational exposure studies [192].

Conclusion

Approximately 50 % of sporadic kidney cancer incidence remains unexplained by established risk factors; therefore, it remains important to investigate relationships with occupational exposures that may also contribute to risk. Although not normally considered an occupational cancer, associations between occupations and industries, as well as specific occupational exposures investigated, using a variety of epidemiological study designs over the past 30 years, have demonstrated some evidence of an occupational contribution to kidney cancer risk. The most consistent association has been observed with the solvent TCE. Elevated risk estimates and exposure–response relationships have been observed in both cohort and case-control studies that were designed to assess risk to TCE specifically, rather than to all chlorinated solvents or organic solvents as a combined group. The biological plausibility of the association appears to be supported by genetic work, but replication is needed. In addition to TCE, employment in farm/agricultural work and evaluation of occupational pesticide exposures have provided some evidence of association, although additional studies that evaluate specific types of pesticide exposures are needed. Similarly, studies of metal exposures, particularly lead and cadmium and other metals associated with nephrotoxicity, are warranted.

This review article covered risk factors for which the strongest associations with kidney cancer risk have been observed. Results from epidemiological studies are limited in their ability to establish causality due to inconsistencies in case definition, misclassification due to imprecise estimates of exposure (i.e., employment length, job title, or exposures to mixed agents), and a lack of control for confounding factors (i.e., smoking, comorbidities, etc.). Studies relying solely on job or industry titles to infer exposure are limited in that exposure may vary considerably among individuals with the same title. Results may also be inconsistent between studies of kidney cancer incidence or mortality, since renal cancer is not always accurately reported as a cause of death. Subsequently, risk estimates may be underestimated in studies of kidney cancer mortality compared to those evaluating incidence [6].

Other limitations of studies conducted to date include recall and selection bias. The application of new biological markers of exposure and internal dose, genotyping/phenotyping of subjects to identify variations in xenobiotic metabolism, as well as inclusion of intermediate biological endpoints that target RCC and related conditions associated with RCC risk could strengthen causal inference and lead to exposure reductions in subpopulations at greatest risk. Future occupational investigations designed to thoroughly address the weaknesses of previous epidemiological studies, identify specific factors influencing individual risk, and to explain the gender variations of kidney cancer risk merit future research.

References

1. Naito S, Tomita Y, Rha SY, et al. Kidney Cancer Working Group report. Jpn J Clin Oncol. 2010;40 Suppl 1:i51–6.
2. Linehan JA, Nguyen MM. Kidney cancer: the new landscape. Curr Opin Urol. 2009;19(2):133–7.
3. Gago-Dominguez M, Yuan JM, Castelao JE, Ross RK, Yu MC. Regular use of analgesics is a risk factor for renal cell carcinoma. Br J Cancer. 1999;81(3):542–8.
4. Moore LE, Wilson RT. Lifestyle factors, exposures, genetic susceptibility, and renal cell cancer risk: a review. Cancer Invest. 2005;23(3):240–52.
5. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol. 2010;7(5):245–57.
6. Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. Cancer J. 2008;14(5):288–301.
7. MedlinePlus Cancer-renal pelvis or ureter. http://www.nlm.nih.gov/medlineplus/ency/article/000525.htm. Accessed 7 Dec 2011.
8. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer. 2004;45 Suppl 2:S3–9.
9. Benichou J, Chow WH, McLaughlin JK, Mandel JS, Fraumeni Jr JF. Population attributable risk of renal cell cancer in Minnesota. Am J Epidemiol. 1998;148:424–30.
10. Hurst FP, Jindal RM, Fletcher JJ, et al. Incidence, predictors and associated outcomes of renal cell carcinoma in long-term dialysis patients. Urology. 2011;77(6):1271–6.
11. Lee JE, Hankinson SE, Cho E. Reproductive factors and risk of renal cell cancer: the Nurses' Health Study. Am J Epidemiol. 2009;169(10):1243–50.
12. Alexander DD, Cushing CA. Quantitative assessment of red meat or processed meat consumption and kidney cancer. Cancer Detect Prev. 2009;32(5–6):340–51.
13. Vainio H, Weiderpass E. Fruit and vegetables in cancer prevention. Nutr Cancer. 2006;54(1):111–42.

14. Karami S, Schwartz K, Purdue MP, et al. Family history of cancer and renal cell cancer risk in Caucasians and African Americans. Br J Cancer. 2010;102(11):1676–80.
15. Linehan WM, Srinivasan R, Schmidt LS. The genetic basis of kidney cancer: a metabolic disease. Nat Rev Urol. 2010;7(5):277–85.
16. Golka K, Wiese A, Assennato G, Bolt HM. Occupational exposure and urological cancer. World J Urol. 2004;21(6):382–91.
17. Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control. 1997;8(3):444–72.
18. Parent ME, Hua Y, Siemiatycki J. Occupational risk factors for renal cell carcinoma in Montreal. Am J Ind Med. 2000;38:609–18.
19. Asal NR, Geyer JR, Risser DR, Lee ET, Kadamani S, Cherng N. Risk factors in renal cell carcinoma. II. Medical history, occupation, multivariate analysis, and conclusions. Cancer Detect Prev. 1988;13:263–79.
20. Heck JE, Charbotel B, Moore LE, et al. Occupation and renal cell cancer in Central and Eastern Europe. Occup Environ Med. 2010;67:47–53.
21. Laakkonen A, Kauppinen T, Pukkala E. Cancer risk among Finnish food industry workers. Int J Cancer. 2006;118(10):2567–71.
22. Zhang Y, Cantor KP, Lynch CF, Zheng T. A population-based case-control study of occupation and renal cell carcinoma risk in Iowa. J Occup Environ Med. 2004;46(3):235–40.
23. Mandel JS, McLaughlin JK, Schlehofer B, et al. International renal-cell cancer study. IV. Occupation. Int J Cancer. 1995;61(5):601–5.
24. Hu J, Mao Y, White K. Renal cell carcinoma and occupational exposure to chemicals in Canada. Occup Med (Lond). 2002;52(3):157–64.
25. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Occupational risk factors for renal-cell carcinoma in Denmark. Scand J Work Environ Health. 1994;20:160–5.
26. Weikert S, Ljungberg B. Contemporary epidemiology of renal cell carcinoma: perspectives of primary prevention. World J Urol. 2010;28:247–52.
27. Vena JE, Sultz HA, Fiedler RC, Barnes RE. Mortality of workers in an automobile engine and parts manufacturing complex. Br J Ind Med. 1985;42(2):85–93.
28. McLaughlin JK, Malker HS, Stone BJ, et al. Occupational risks for renal cancer in Sweden. Br J Ind Med. 1987;44(2):119–23.
29. Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W. Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. Int J Epidemiol. 2000;29(6):1014–24.
30. Delahunt B, Bethwaite PB, Nacey JN. Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand Cancer Registry. Br J Urol. 1995;75(5):578–82.
31. Youakim S. Risk of cancer among firefighters: a quantitative review of selected malignancies. Arch Environ Occup Health. 2006;61(5):223–31.
32. Lowery JT, Peters JM, Deapen D, London SJ. Renal cell carcinoma among architects. Am J Ind Med. 1991;20(1):123–5.
33. Magnani C, Coggon D, Osmond C, Acheson ED. Occupation and five cancers: a case-control study using death certificates. Br J Ind Med. 1987;44(11):769–76.
34. Brownson RC. A case-control study of renal cell carcinoma in relation to occupation, smoking, and alcohol consumption. Arch Environ Health. 1988;43:238–41.
35. Lohi J, Kyyrönen P, Kauppinen T, Kujala V, Pukkala E. Occupational exposure to solvents and gasoline and risk of cancers in the urinary tract among Finnish workers. Am J Ind Med. 2008;51(9):668–72.
36. Schlehofer B, Heuer C, Blettner M, Niehoff D, Wahrendorf J. Occupation, smoking and demographic factors, and renal cell carcinoma in Germany. Int J Epidemiol. 1995;24(1):51–7.
37. Mattioli S, Truffelli D, Baldasseroni A, et al. Occupational risk factors for renal cell cancer: a case-control study in northern Italy. J Occup Environ Med. 2002;44(11):1028–36.
38. Karami S, Boffetta P, Rothman N, et al. Renal cell carcinoma, occupational pesticide exposure and modification by glutathione S-transferase polymorphisms. Carcinogenesis. 2008;29(8):1567–71.
39. Hansen J, Raaschou-Nielsen O, Christensen JM, et al. Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med. 2001;43(2):133–9.
40. Jacob S, Hery M, Protois JC, Rossert J, Stengel B. New insight into solvent-related end stage renal disease: occupations, products and types of solvents at risk. Occup Environ Med. 2007;64(12):843–8.
41. Stewart PA, Lee JS, Marano DE, Spirtas R, Forbes CD, Blair A. Retrospective cohort mortality study of workers at an aircraft maintenance facility. II. Exposures and their assessment. Br J Ind Med. 1991;48(8):531–7.
42. Spirtas R, Stewart PA, Lee JS, et al. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br J Ind Med. 1991;48(8):515–30.
43. Moore LE, Boffetta P, Karami S, et al. Occupational trichloroethylene exposure and renal carcinoma risk: evidence of genetic susceptibility by reductive metabolism gene variants. Cancer Res. 2010;70(16):6527–36.
44. Poole C, Dreyer NA, Satterfield MH, Levin L, Rothman KJ. Kidney cancer and hydrocarbon exposures among petroleum refinery workers. Environ Health Perspect. 1993;101 Suppl 6:53–62.
45. Dosemeci M, Cocco P, Chow WH. Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. Am J Ind Med. 1999;36(1):54–9.
46. McLean D, Pearce N, Langseth H, et al. Cancer mortality in workers exposed to organochlorine compounds in the pulp and paper industry: an international collaborative study. Environ Health Perspect. 2006;114(7):1007–12.
47. IARC (International Agency for Research on Cancer). Trichloroethylene. IARC Monogr Eval Carcinog Risks Hum. 1995;63:75–158.
48. United States Environmental Protection Agency. EPA releases final health assessment for TCE. http://yosemite.epa.gov/opa/admpress.nsf/03dd877d6f1726c285257359004044 43/b8d0e4d8489ad991852579190058d6c3!OpenDocument. Accessed 7 Dec 2011.
49. Guha N, Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Baan R, Mattock H, Straif K, International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of trichloroethylene, tetrachloroethylene, some other chlorinated solvents, and their metabolites. Lancet Oncol. 2012;13(12):1192–3.
50. Agency for Toxic Substances and Disease Registry. Trichloroethylene. 4. Production, import/export, use and disposal. http://www.atsdr.cdc.gov/toxprofiles/tp19-c4.pdf. Accessed 7 Dec 2011.
51. Humphries JA, Ashe AM, Smiley JA, Johnston CG. Microbial community structure and trichloroethylene degradation in groundwater. Can J Microbiol. 2005;51(6):433–9.
52. Axelson O, Seldén A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. J Occup Med. 1994;36(5):556–62.
53. Anttila A, Pukkala E, Sallmén M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med. 1995;37(7):797–806.

54. Henschler D, Vamvakas S, Lammert M, et al. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. Arch Toxicol. 1995;69(5):291–9.
55. Morgan RW, Kelsh MA, Zhao K, Heringer S. Mortality of aerospace workers exposed to trichloroethylene. Epidemiology. 1998;9(4):424–31.
56. Ritz B. Cancer mortality among workers exposed to chemicals during uranium processing. J Occup Environ Med. 1999;41(7): 556–66.
57. Boice Jr JD, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK. Mortality among aircraft manufacturing workers. Occup Environ Med. 1999;56(9):581–97.
58. Raaschou-Nielsen O, Hansen J, McLaughlin JK, et al. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Am J Epidemiol. 2003;158(12):1182–92.
59. Boice Jr JD, Marano DE, Cohen SS, et al. Mortality among Rocketdyne workers who tested rocket engines, 1948–1999. J Occup Environ Med. 2006;48(10):1070–92.
60. Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow up. J Occup Environ Med. 2008;50(11):1306–19.
61. Harrington JM, Whitby H, Gray CN, Reid FJ, Aw TC, Waterhouse JA. Renal disease and occupational exposure to organic solvents: a case referent approach. Br J Ind Med. 1989;46(9):643–50.
62. Sharpe CR, Rochon JE, Adam JM, Suissa S. Case-control study of hydrocarbon exposures in patients with renal cell carcinoma. Can Med Assoc J. 1989;140(11):1309–18.
63. Greenland S, Salvan A, Wegman DH, Hallock MF, Smith TJ. A case-control study of cancer mortality at a transformer-assembly facility. Int Arch Occup Environ Health. 1994;66(1):49–54.
64. Vamvakas S, Brüning T, Thomasson B, et al. Renal cell cancer correlated with occupational exposure to trichloroethene. J Cancer Res Clin Oncol. 1998;124(7):374–82.
65. Brüning T, Pesch B, Wiesenhütter B, et al. Renal cell cancer risk and occupational exposure to trichloroethylene: results of a consecutive case-control study in Arnsberg, Germany. Am J Ind Med. 2003;43(3):274–85.
66. Charbotel B, Fevotte J, Hours M, Martin JL, Bergeret A. Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects. Ann Occup Hyg. 2006;50(8):777–87.
67. Siemiatycki J. Risk factors for cancer in the workplace. Boca Raton: CRC Press; 1991. p. 30–167.
68. Lash LH, Parker JC, Scott CS. Modes of action of trichloroethylene for kidney tumorigenesis. Environ Health Perspect. 2000;108 Suppl 2:225–40.
69. Rudén C. Science and transscience in carcinogen risk assessment – the European Union regulatory process for trichloroethylene. J Toxicol Environ Health B Crit Rev. 2003;6(3):257–77.
70. Brüning T, Bolt HM. Renal toxicity and carcinogenicity of trichloroethylene: key results, mechanisms, and controversies. Crit Rev Toxicol. 2000;30(3):253–85.
71. Nakagawa Y, Kitahori Y, Cho M, et al. Effect of hexachloro-1,3-butadiene on renal carcinogenesis in male rats pretreated with N-ethyl-N-hydroxyethyl-nitrosamine. Toxicol Pathol. 1998;26: 361–6.
72. Kelsh AM, Alexander DD, Mink PJ, Mandel JH. Occupational Trichloroethylene exposure and kidney cancer. Epidemiology. 2010;21:95–102.
73. Wartenberg D, Reyner D, Scott CS. Trichloroethylene and cancer: epidemiologic evidence. Environ Health Perspect. 2000;108 Suppl 2:161–76.
74. Scott CS, Jinot J. Trichloroethylene and cancer: systematic and quantitative review of epidemiologic evidence for identifying hazards. Int J Environ Res Public Health. 2011;8(11):4238–72.
75. Karami S, Lan Q, Rothman N, Stewart PA, Lee KM, Vermeulen R, Moore LE. Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. Occup Environ Med. 2012;69(12):858–67.
76. Bruning T, Lammert M, Kempkes M, Thier R, Golka K, Bolt HM. Influence of polymorphisms of GSTM1 and GSTT1 for risk of renal cell cancer in workers with long-term high occupational exposure to trichloroethylene. Arch Toxicol. 1997;71:596–9.
77. Wiesenhütter B, Selinski S, Golka K, Brüning T, Bolt HM. Re-assessment of the influence of polymorphisms of phase-II metabolic enzymes on renal cell cancer risk of trichloroethylene-exposed workers. Int Arch Occup Environ Health. 2007;81(2): 247–51.
78. Fischer W, Wirkner K, Weber M, et al. Characterization of P2X3, P2Y1 and P2Y4 receptors in cultured HEK293-hP2X3 cells and their inhibition by ethanol and trichloroethanol. J Neurochem. 2003;85(3):779–90.
79. Waggoner JK, Kullman GJ, Henneberger PK, et al. Mortality in the agricultural health study, 1993–2007. Am J Epidemiol. 2011;173(1):71–83.
80. Faustini A, Forastiere F, Di Betta L, Magliola EM, Perucci CA. Cohort study of mortality among farmers and agricultural workers. Med Lav. 1993;84(1):31–41.
81. Wiklund K, Dich J. Cancer risks among female farmers in Sweden. Cancer Causes Control. 1994;5(5):449–57.
82. Buzio L, Tondel M, De Palma G, et al. Occupational risk factors for renal cell cancer. An Italian case-control study. Med Lav. 2002;93(4):303–9.
83. McLaughlin JK, Mandel JS, Blot WJ, Schuman LM, Mehl ES, Fraumeni Jr JF. A population – based case-control study of renal cell carcinoma. J Natl Cancer Inst. 1984;72(2):275–84.
84. Forastiere F, Quercia A, Miceli M, et al. Cancer among farmers in central Italy. Scand J Work Environ Health. 1993;19(6):382–9.
85. Davis DL, Blair A, Hoel DG. Agricultural exposures and cancer trends in developed countries. Environ Health Perspect. 1993;100: 39–44.
86. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales. IV. Occupation. Br J Ind Med. 1993;50(4):349–54.
87. Sweeney C, Farrow DC, Schwartz SM, Eaton DL, Checkoway H, Vaughan TL. Glutathione S-transferase M1, T1, and P1 polymorphisms as risk factors for renal cell carcinoma: a case-control study. Cancer Epidemiol Biomarkers Prev. 2000;9(4):449–54.
88. Buzio L, De Palma G, Mozzoni P, et al. Glutathione S-transferases M1-1 and T1-1 as risk modifiers for renal cell cancer associated with occupational exposure to chemicals. Occup Environ Med. 2003;60(10):789–93.
89. Longuemaux S, Deloménie C, Gallou C, et al. Candidate genetic modifiers of individual susceptibility to renal cell carcinoma: a study of polymorphic human xenobiotic-metabolizing enzymes. Cancer Res. 1999;59(12):2903–8.
90. IARC (International Agency for Research on Cancer). Occupational exposures in insecticide application, and some pesticides. IARC Working Group on the evaluation of carcinogenic risks to humans. IARC Monogr Eval Carcinog Risks Hum. 1991;53:5–586. Lyon, 16–23 October 1990.
91. IARC (International Agency for Research on Cancer). Working Group the evaluation of carcinogenic risks to humans. Inorganic and organic lead compounds. IARC Monogr Eval Carcinog Risks Hum. 2006;87:1–471.
92. National Toxicology Program. Lead and lead compounds. http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/Lead-Public.pdf. Accessed 7 Dec 2011.
93. Steenland K, Boffetta P. Lead and cancer in humans: where are we now? Am J Ind Med. 2000;38(3):295–9.
94. Centers for Disease Control and Prevention. Morbidity and mortality weekly report. Adult blood lead epidemiology and surveillance

– United States, 2005–2007. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5814a3.htm. Accessed 7 Dec 2011.
95. Fowler BA. Mechanisms of kidney cell injury from metals. Environ Health Perspect. 1993;100:57–63.
96. Boffetta P, Fontana L, Stewart P, et al. Occupational exposure to arsenic, cadmium, chromium, lead and nickel, and renal cell carcinoma: a case-control study from Central and Eastern Europe. Occup Environ Med. 2011;68(10):723–8.
97. Simonato L, Fletcher AC, Andersen A, et al. A historical prospective study of European stainless steel, mild steel, and shipyard welders. Br J Ind Med. 1991;48(3):145–54.
98. Steenland K, Selevan S, Landrigan P. The mortality of lead smelter workers: an update. Am J Public Health. 1992;82(12):1641–4.
99. Selevan SG, Landrigan PJ, Stern FB, Jones JH. Mortality of lead smelter workers. Am J Epidemiol. 1985;122(4):673–83.
100. Cocco P, Hua F, Boffetta P, et al. Mortality of Italian lead smelter workers. Scand J Work Environ Health. 1997;23(1):15–23.
101. Cooper WC, Wong O, Kheifets L. Mortality among employees of lead battery plants and lead-producing plants, 1947–1980. Scand J Work Environ Health. 1985;11(5):331–45.
102. Lundström NG, Nordberg G, Englyst V, et al. Cumulative lead exposure in relation to mortality and lung cancer morbidity in a cohort of primary smelter workers. Scand J Work Environ Health. 1997;23(1):24–30.
103. Sankila R, Kajalainen S, Pukkala E, et al. Cancer risk among glass factory workers: an excess of lung cancer? Br J Ind Med. 1990;47:815–8.
104. Partanen T, Heikkilä P, Hernberg S, Kauppinen T, Moneta G, Ojajärvi A. Renal cell cancer and occupational exposure to chemical agents. Scand J Work Environ Health. 1991;17(4):231–9.
105. van Bemmel DM, Boffetta P, Liao LM, et al. Comprehensive analysis of 5-aminolevulinic acid dehydrogenase (ALAD) variants and renal cell carcinoma risk among individuals exposed to lead. PLoS One. 2011;6(7):e20432.
106. Bhatti P, Stewart PA, Linet MS, Blair A, Inskip PD, Rajaraman P. Comparison of occupational exposure assessment methods in a case-control study of lead, genetic susceptibility and risk of adult brain tumours. Occup Environ Med. 2011;68(1):4–9.
107. Rajaraman P, Stewart PA, Samet JM, et al. Lead, genetic susceptibility, and risk of adult brain tumors. Cancer Epidemiol Biomarkers Prev. 2006;15(12):2514–20.
108. Onalaja AO, Claudio L. Genetic susceptibility to lead poisoning. Environ Health Perspect. 2000;108 Suppl 1:23–8.
109. Wetmur JG, Kaya AH, Plewinska M, Desnick RJ. Molecular characterization of the human delta-aminolevulinate dehydratase 2 (ALAD2) allele: implications for molecular screening of individuals for genetic susceptibility to lead poisoning. Am J Hum Genet. 1991;49:757–63.
110. IARC (International Agency for Research on Cancer). Agents classified by the IARC monographs, vols. 1–102. http://monographs.iarc.fr/ENG/Classification/index.php. Accessed 7 Dec 2011.
111. Armstrong BG, Kazantzis G. Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: a case control study. Br J Ind Med. 1985;42(8):540–5.
112. Il'yasova D, Schwartz GG. Cadmium and renal cancer. Toxicol Appl Pharmacol. 2005;207(2):179–86.
113. Satarug S, Moore MR. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ Health Perspect. 2004;112(1099):e103.
114. Bernard A. Renal dysfunction induced by cadmium: biomarkers of critical effects. Biometals. 2004;17(519).
115. Fishbein L. Sources, transport and alterations of metal compounds: an overview. I. Arsenic, beryllium, cadmium, chromium, and nickel. Environ Health Perspect. 1981;40:43–64.
116. Kolonel LN. Association of cadmium with renal cancer. Cancer. 1976;37(4):1782–7.
117. Cole P, Rodu B. Epidemiologic studies of chrome and cancer mortality: a series of meta-analyses. Regul Toxicol Pharmacol. 2005;43(225):e31.
118. Arena VC, Sussman NB, Redmond CK, Costantino JP, Trauth JM. Using alternative comparison populations to assess occupation-related mortality risk. Results for the high nickel alloys workers cohort. J Occup Environ Med. 1998;40(10):907–16.
119. Gerin M, Siemiatycki J, Richardson L, Pellerin J, Lakhani R, Dewar R. Nickel and cancer associations from a multicancer occupation exposure case-referent study: preliminary findings. IARC Sci Publ. 1984;53:105–15.
120. IARC (International Agency for Research on Cancer). Chromium, nickel and welding. IARC Monogr Eval Carcinog Risks Hum. 1990;49:1–648.
121. National Research Council: Subcommittee to Update the 1999 Arsenic in Drinking Water Report. Arsenic in drinking water: 2001 update. Washington, DC: National Academy Press; 2001.
122. Enterline PE, Day R, Marsh GM. Cancers related to exposure to arsenic at a copper smelter. Occup Environ Med. 1995;52(1):28–32.
123. Macfarland HN, Ulrich CE, Holdsworth CE, Kitchen DN, Halliwell NH, Blum SC. A chronic inhalation study with unleaded gasoline. J Am CON Toxicol. 1984;3:23l–48.
124. McLaughlin JK, Blot WJ, Mehl ES, Stewart PA, Venable FS, Fraumeni Jr JF. Petroleum-related employment and renal cell cancer. J Occup Med. 1985;27(9):672–4.
125. Lynge E, Andersen A, Nilsson R, et al. Risk of cancer and exposure to gasoline vapors. Am J Epidemiol. 1997;145(5):449–58.
126. Schnatter AR, Katz AM, Nicolich MJ, Thériault G. A retrospective mortality study among Canadian petroleum marketing and distribution workers. Environ Health Perspect. 1993;101 Suppl 6:85–99.
127. Soll-Johanning H, Bach E, Olsen JH, Tuchsen F. Cancer incidence in urban bus drivers and tramway employees: a retrospective cohort study. Occup Environ Med. 1998;55(9):594–8.
128. Boffetta P, Dosemeci M, Gridley G, Bath H, Moradi T, Silverman D. Occupational exposure to diesel engine emissions and risk of cancer in Swedish men and women. Cancer Causes Control. 2001;12(4):365–74.
129. IARC (International Agency for Research on Cancer). IARC monographs on the evaluation of carcinogenic risks to humans. Diesel and gasoline engine exhausts and some nitroarenes. IARC Monogr Eval Carcinog Risks Hum. 1989;46:1–458.
130. Guo J, Kauppinen T, Kyyrönen P, Heikkilä P, Lindbohm ML, Pukkala E. Risk of esophageal, ovarian, testicular, kidney and bladder cancers and leukemia among Finnish workers exposed to diesel or gasoline engine exhaust. Int J Cancer. 2004;111(2):286–92.
131. Schenker MB, Smith T, Muñoz A, Woskie S, Speizer FE. Diesel exposure and mortality among railway workers: results of a pilot study. Br J Ind Med. 1984;41(3):320–7.
132. Howe GR, Fraser D, Lindsay J, Presnal B, Yu SZ. Cancer mortality (1965–77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. J Natl Cancer Inst. 1983;70(6):1015–9.
133. Siemiatycki J, Gérin M, Stewart P, Nadon L, Dewar R, Richardson L. Associations between several sites of cancer and ten types of exhaust and combustion products. Results from a case-referent study in Montreal. Scand J Work Environ Health. 1988;14(2):79–90.
134. Wong O, Morgan RW, Kheifets L, Larson SR, Whorton MD. Mortality among members of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. Br J Ind Med. 1985;42(7):435–48.
135. Gustavsson P, Reuterwall C. Mortality and incidence of cancer among Swedish gas workers. Br J Ind Med. 1990;47(3):169–74.
136. Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. Am J Ind Med. 1988;14(4):403–15.

137. Wong O, Harris F, Smith TJ. Health effects of gasoline exposure. II. Mortality patterns of distribution workers in the United States. Environ Health Perspect. 1993;101 Suppl 6:63–76.
138. Agency for Toxic Substances and Disease Registry. Toxicological profile for polycyclic aromatic hydrocarbons. http://www.atsdr.cdc.gov/toxpro2.html. Accessed 7 Dec 2011.
139. Jacob J, Seidel A. Biomonitoring of polycyclic aromatic hydrocarbons in human urine. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;778:31–47.
140. IARC (International Agency for Research on Cancer). Polynuclear aromatic compounds, part 1, chemical, environmental and experimental data. IARC Monogr Eval Carcinog Risk Chem Hum. 1983;32:1–453.
141. Redmond CK. Cancer mortality among coke oven workers. Environ Health Perspect. 1983;52:67–73.
142. Bosetti C, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. Ann Oncol. 2007;18:431–46.
143. Mason TJ. Geographic patterns of cancer risk: a means for identifying possible occupational factors. Ann NY Acad Sci. 1976;271:370–6.
144. Karami S, Boffetta P, Brennan P, et al. Renal cancer risk and occupational exposure to polycyclic aromatic hydrocarbons and plastics. J Occup Environ Med. 2011;53(2):218–23.
145. Butkiewicz D, Grzybowska E, Phillips DH, Hemminki K, Chorazy M. Polymorphisms of the GSTP1 and GSTM1 genes and PAH-DNA adducts in human mononuclear white blood cells. Environ Mol Mutagen. 2000;35(2):99–105.
146. Falahatpisheh M, Kerzee J, Metz R, Donnelly K, Ramos K. Inducible cytochrome P450 activities in renal glomerular mesangial cells: biochemical basis for antagonistic interactions among nephrocarcinogenic polycyclic aromatic hydrocarbons. J Carcinog. 2004;3(1):12.
147. Smith AH, Shearn VI, Wood R. Asbestos and kidney cancer: the evidence supports a causal association. Am J Ind Med. 1989;16(2):159–66.
148. Patel-Mandlik KJ. Asbestos fibers in normal and cancerous human kidneys. Arch Environ Contam Toxicol. 1981;10(1):47–54.
149. Huang J, Hisanaga N, Sakai K, et al. Asbestos fibers in human pulmonary and extrapulmonary tissues. Am J Ind Med. 1988;14(3):331–9.
150. Selikoff IJ, Lilis R, Nicholson WJ. Asbestos disease in United States shipyards. Ann N Y Acad Sci. 1979;330:295–311.
151. Maclure M. Asbestos and renal adenocarcinoma: a case-control study. Environ Res. 1987;42(2):353–61.
152. Enterline PE, Hartley J, Henderson V. Asbestos and cancer: a cohort followed up to death. Br J Ind Med. 1987;44(6):396–401.
153. Saarni H, Pentti J, Pukkala E. Cancer at sea: a case-control study among male Finnish seafarers. Occup Environ Med. 2002;59(9):613–9.
154. Sali D, Boffetta P. Kidney cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies. Cancer Causes Control. 2000;11(1):37–47.
155. Goodman M, Morgan RW, Ray R, Malloy CD, Zhao K. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. Cancer Causes Control. 1999;10(5):453–65.
156. Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987. Ann N Y Acad Sci. 1991;643:1–14.
157. Karami S, Boffetta P, Stewart PS, et al. Occupational exposure to dusts and risk of renal cell carcinoma. Br J Cancer. 2011;104(11):1797–803.
158. Shannon H, Muir A, Haines T, Verma D. Mortality and cancer incidence in Ontario glass fiber workers. Occup Med (Lond). 2005;55(7):528–34.
159. Stone RA, Youk AO, Marsh GM, Buchanich JM, Smith TJ. Historical cohort study of U.S. man-made vitreous fiber production workers IX: summary of 1992 mortality follow up and analysis of respiratory system cancer among female workers. J Occup Environ Med. 2004;46(1):55–67.
160. Marsh GM, Enterline PE, Stone RA, Henderson VL. Mortality among a cohort of US man-made mineral fiber workers: 1985 follow-up. J Occup Med. 1990;32(7):594–604.
161. Olsen JH, Jensen OM. Cancer incidence among employees in one mineral wool production plant in Denmark. Scand J Work Environ Health. 1984;10(1):17–24.
162. Siemiatycki J, Richardson L, Gérin M, et al. Associations between several sites of cancer and nine organic dusts: results from an hypothesis-generating case-control study in Montreal, 1979–1983. Am J Epidemiol. 1986;123(2):235–49.
163. Robinson C, Stern F, Halperin W, et al. Assessment of mortality in the construction industry in the United States, 1984–1986. Am J Ind Med. 1995;28(1):49–70.
164. Burnett CA, Dosemeci M. Using occupational mortality data for surveillance of work-related diseases of women. J Occup Med. 1994;36(11):1199–203.
165. IARC (International Agency for Research on Cancer). IARC monographs on the evaluation of carcinogenic risks to humans. Silica, some silicates, coal dust and para-aramid fibrils. IARC Monogr Eval Carcinog Risk Chem Hum. 1997;68:1–475.
166. Steenland K. One agent, many diseases: exposure-response data and comparative risks of different outcomes following silica exposure. Am J Ind Med. 2005;48(1):16–23.
167. Cooper WC, Wong O, Trent LS, Harris F. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. J Occup Med. 1992;34(12):1173–80.
168. Hobbesland A, Kjuus H, Thelle DS. Study of cancer incidence among 8530 male workers in eight Norwegian plants producing ferrosilicon and silicon metal. Occup Environ Med. 1999;56(9):625–31.
169. Attfield MD, Costello J. Quantitative exposure-response for silica dust and lung cancer in Vermont granite workers. Am J Ind Med. 2004;45(2):129–38.
170. Kolev K, Doitschinov D, Todorov D. Morphologic alterations in the kidneys by silicosis. Med Lav. 1970;61(4):205–10.
171. BL M ć, Arambasić MD. Experimental chronic interstitial nephritis compared with endemic human nephropathy. J Pathol. 1971;103(1):35–40.
172. EL-Safty IA, Gadallah M, Shouman AE, Nessim DE. Subclinical nephrotoxicity caused by smoking and occupational silica exposure among Egyptian industrial workers. Arch Med Res. 2003;34(5):415–21.
173. Boscoe FP, Schymura MJ. Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993–2002. BMC Cancer. 2006;6:264.
174. Grant WB. The effect of solar UVB doses and vitamin D production, skin cancer action spectra, and smoking in explaining links between skin cancers and solid tumours. Eur J Cancer. 2008;44:12–5.
175. Grant WB, Garland CF. Evidence supporting the role of vitamin D in reducing the risk of cancer. J Intern Med. 2002;252:178–9.
176. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer. 2002;94:1867–75.
177. Mohr SB, Gorham ED, Garland CF, Grant WB, Garland FC. Are low ultraviolet B and high animal protein intake associated with risk of renal cancer? Int J Cancer. 2006;119:2705–9.
178. Rafnsson V, Gunnarsdóttir H. Mortality among Icelandic seamen. Int J Epidemiol. 1994;23(4):730–6.
179. Hakansson N, Floderus B, Gustavsson P, Feychting M, Hallin N. Occupational sunlight exposure and cancer incidence among Swedish construction workers. Epidemiology. 2001;12:552–7.

180. Karami S, Boffetta P, Stewart P, et al. Occupational sunlight exposure and risk of renal cell carcinoma. Cancer. 2010;116(8): 2001–10.
181. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. J Nutr. 2005;135:310–6.
182. John EM, Schwartz GG, Koo J, Wang W, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and breast cancer risk in a multiethnic population. Am J Epidemiol. 2007;166: 1409–19.
183. Norman AW. Sunlight, season, skin pigmentation, vitamin D, and 25-hydroxyvitamin D: integral components of the vitamin D endocrine system. Am J Clin Nutr. 1998;67:1108–10.
184. Matsuoka LY, Wortsman J, Haddad JG, Kolm P, Hollis BW. Racial pigmentation and the cutaneous synthesis of vitamin D. Arch Dermatol. 1991;127:536–8.
185. Deeb KK, Trump DL, Johnson CS. Vitamin D signaling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer. 2007;7:684–700.
186. Ordonez-Moran P, Larriba MJ, Pendas-Franco N, Aguilera O, Gonzalez-Sancho JM, Munoz A. Vitamin D and cancer: an update of in vitro and in vivo data. Front Biosci. 2005;10:2723–49.
187. Trump DL, Hershberger PA, Bernardi RJ, et al. Anti-tumor activity of calcitriol: pre-clinical and clinical studies. J Steroid Biochem Mol Biol. 2004;89–90:519–26.
188. Gallicchio L, Moore LE, Stevens VL, et al. Circulating 25-hydroxyvitamin D and risk of kidney cancer: cohort consortium vitamin D pooling project of rarer cancers. Am J Epidemiol. 2010;172(1):47–57.
189. Zheng W, Danforth KN, Tworoger SS, et al. Circulating 25-hydroxyvitamin D and risk of epithelial ovarian cancer: cohort consortium vitamin D pooling project of rarer cancers. Am J Epidemiol. 2010;172(1):70–80.
190. Zeleniuch-Jacquotte A, Gallicchio L, Hartmuller V, et al. Circulating 25-hydroxyvitamin D and risk of endometrial cancer: cohort consortium vitamin D pooling project of rarer cancers. Am J Epidemiol. 2010;172(1):36–46.
191. Abnet CC, Chen Y, Chow WH, et al. Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: cohort consortium vitamin D pooling project of rarer cancers. Am J Epidemiol. 2010;172(1):94–106.
192. Holick MF, Vitamin D. Status: measurement, interpretation, and clinical application. Ann Epidemiol. 2009;19(2):73–8.

Bladder Cancer

26

Manolis Kogevinas and Montserrat Garcia-Closas

Keywords
Bladder cancer • Occupational bladder cancer • Aromatic amines • 4-Aminobiphenyl • Benzidine • Polycyclic aromatic hydrocarbons (PAHs) • Diesel engine exhaust • Occupational exposure assessment

Introduction

Tumors of the urinary bladder contribute significantly to the overall human cancer burden with approximately 380,000 new cases per year worldwide [1]. Of those, around 290,000 occur in men, and about two thirds occur in more developed regions. Occupation has been identified, after smoking, as the second important risk factor for bladder cancer. Several exposures, occupations, and industries have been associated with increased bladder cancer risk. Aromatic amines (benzidine, 4-aminobiphenyl, b-naphthylamine, 4-chloro-*ortho*-toluidine) in dyestuff manufacture and in the rubber and other industries are the only specific agents in the workplace which have been unequivocally associated with bladder cancer in humans. Excess risks have been observed among aluminum process painters, machinists and other metal workers, workers in the textile industry, leather workers and shoemakers, printers, hairdressers, dry cleaners, and transport workers. Exposures associated with the increased risk in these occupations/industries include polycyclic aromatic hydrocarbons (PAHs), diesel engine exhaust, paints, dyes, chlorinated hydrocarbons, and other solvents, metals, and industrial oils/cutting fluids.

M. Kogevinas, MD, PhD (✉)
Centre for Research in Environmental Epidemiology (CREAL), 88 Dr Aiguader Rd, Barcelona 08003, Spain
e-mail: kogevinas@creal.cat

M. Garcia-Closas, MD, DrPH
Division of Genetics and Epidemiology, Institute of Cancer Research, Sutton, UK

Exposures, Occupations, and Industries Associated with High Bladder Cancer Risk

A review of the epidemiological evidence on the main exposures, occupations, and industries associated with bladder cancer, together with recent evidence on occupational exposures and bladder cancer in men and women, is discussed in the following section. The exposures, occupations, or industries evaluated by the International Agency for Research on Cancer (IARC) as having sufficient or limited epidemiological evidence regarding bladder cancer risk are listed in Table 26.1.

Aromatic Amines, the Dye and the Rubber Industry

The synthetic aromatic amine in the dye industry started in the 1870s in Germany, while previously all dyes were natural. The first reported case of bladder cancer in fuchsin dye manufacturing workers in Germany was done in 1895 by Ludwig Rehn. The production of synthetic aromatic amines started later in other countries, and in the 1930s and 1940s several reports were associated with bladder cancer cases with exposure to aromatic amines from dye manufacturers and other industries in the USA and the UK [31]. The manufacture of benzidine, an aromatic amine, begun in the 1950s in industries established in developing countries, and around 40 years later the reports of bladder cancer cases among workers in countries such as China emerged.

The first large epidemiological study examining aromatic amines was conducted by Case and Pearson [8, 32] in the UK dyestuff manufacturing workers. Exposure to

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_26, © Springer-Verlag London 2014

Table 26.1 Exposures, occupations, and industries evaluated by the International Agency for Research on Cancer (IARC) as having sufficient or limited epidemiological evidence regarding bladder cancer risk

Chemical, industry, or occupation	IARC monograph	Main epidemiological evidence
Sufficient evidence in humans		
Aluminum production	92 (2010); 100 F (2012)	Workers in aluminum production are primarily exposed to polycyclic aromatic hydrocarbons (PAHs) although they are also exposed to a multitude of other chemicals. High risks have been observed among workers in the Söderberg process of aluminum production where exposure to PAHs has been very high. Cohort studies have been conducted in several countries including two each from Canada, Italy, and France and one each from the USA, Norway, Sweden, and Australia. Furthermore, several case-control or case-cohort studies were conducted in Canada, for example [2], focusing on exposures among workers in the Söderberg process. Nearly all studies identified an increased risk for bladder cancer although some of the most recent ones that had relatively short follow-up did not. A meta-analysis of cohort studies [3] among aluminum production workers identified a meta-RR of 1.29 (95 % CI 1.12–1.49). A meta-analysis evaluating cumulative exposure in this industry to benzo[a]pyrene (BaP) identified an RR of 1.42, 95 % CI, 1.2–1.7, based on six studies [4]
4-Aminobiphenyl	99 (2010); 100 F (2012)	Initial case reports in the 1960s identified a high proportion of bladder cancer cases among workers exposed to 4-aminobiphenyl (4-ABP). Cohort studies in a chemical plant producing several chemicals in the USA identified a tenfold increased mortality among 4-ABP exposed workers; in a subsequent mortality follow-up through 1987, there were 11 deaths among exposed workers with 0.54 expected [5]
Auramine production	99 (2010); 100 F (2012)	Three studies of workers in auramine production in the UK, Germany, and Switzerland, mostly involving workers employed before 1960, found increased mortality from bladder cancer. SMRs ranged from 2.6 to 13.3. Auramine production has been discontinued in western Europe and North America and takes place mainly in India and China
Benzidine	99 (2010); 100 F (2012)	Case reports and epidemiological studies from several countries show very strong associations between benzidine exposure and risk for bladder cancer. Starting from the first study by Case in the UK in 1954, there are 16 cohort studies, 4 each in the USA and China, 3 in Japan, 2 in Poland, and one each in the UK, Italy, and Russia. Several of these have been updated [6]. Several studies have found dose–response relationships with duration of exposure or other exposure indices. In one of the recent follow-ups of a large study of Chinese workers in benzidine production and similar facilities, the odds ratios (OR) for bladder cancer were 2.7 (1.1–6.3) for medium cumulative exposure to benzidine and 4.4 (1.8–10.8) for high exposure after adjustment for lifetime cigarette smoking [7]
Magenta production	99 (2010); 100 F (2012)	Two cohort studies of workers exposed to magenta mostly involved workers employed before the 1950s and identified very high risks for bladder cancer among workers who were not exposed to b-naphthylamine or benzidine. In the UK study [8] the SMR was 23 (95 % CI 5–67), and in the Italian study [9] it was 63 (95 % CI 20–146). Both studies were small and there were a total of five deaths from bladder cancer
2-Naphthylamine	99 (2010); 100 F (2012)	Case series have repeatedly reported bladder cancer in workers exposed to 2-naphthylamine. All 11 cohort studies (four in the USA, two in the UK, two in Japan, and one each in Poland, the Russian Federation, and Italy) that examined bladder cancer risk in workers exposed to 2-naphthylamine found markedly elevated bladder cancer risks associated with the manufacture and use of 2-naphthylamine. In only few of these studies could simultaneous exposure to benzidine be taken into account. The early study by Case et al. [8] reported 26 bladder cancer deaths, with 0.3 expected [SMR = 87, 95 % CI 57–127], in British dyestuff-industry workers exposed to 2-naphthylamine. The study by Veys [10], initial study published in the 1950s in a British rubber industry, showed excess risk of bladder cancer in workers employed between 1946 and 1949 when 2-naphthylamine-contaminated antioxidants were used (58 cases, SIR = 1.7, 95 % CI 1.3–2.2), while no excess risk was observed in workers employed after 2-naphthylamine was removed (39 cases, SIR = 1.02, 95 % CI 0.7–1.4)
Painting	98 (2010); 100 F (2012)	About 40 epidemiological studies have evaluated bladder cancer risk among painters. Two recent meta-analyses [11, 12] provided similar conclusions. The meta-analysis by Guha included 41 independent studies (11 cohort and record linkage studies and 30 case-control studies) and showed a meta-relative risk of 1.25 (95 % CI 1.16–1.34). This association did not change significantly when the analysis was restricted to population-based studies or studies that adjusted for smoking and other potentially confounding occupational exposures. Risk increased with duration of employment with those exposed less than 10 years having a meta-RR of 1.41 (95 % CI 1.00–2.01) and those exposed more than 10 years a meta-RR of 1.81 (95 % CI 1.20–2.75)

Table 26.1 (continued)

Chemical, industry, or occupation	IARC monograph	Main epidemiological evidence
Rubber production industry	Suppl 7 (1987); 100 F (2012)	Workers in the rubber-manufacturing industry are exposed to dusts and fumes from rubber-making and vulcanization processes and potential carcinogenic exposures including N-nitrosamines, polycyclic aromatic hydrocarbons, solvents, and phthalates. The first evidence of an increased risk of bladder cancer was observed among rubber workers in the UK [8]. The IARC evaluated the evidence in 1982 and concluded that there was sufficient evidence for an increased bladder cancer risk. A systematic review of epidemiological studies on cancer in the rubber-manufacturing industry included cohort and case-control studies published after the IARC evaluation in 1982 [13]. Moderately increased risks for bladder cancer were reported in 6 of 8 cohort studies of workers employed in the rubber-manufacturing industry in different regions of the world. A generally increased risk was also observed in most case-control studies. In four cohort studies that reported results by calendar period, the risk was highest among workers employed before 1950. Subsequent follow-up of some of these studies identified only moderate increased risks
Ortho-toluidine	99 (2010); 100 F (2012)	Overall, the epidemiological studies show consistent associations between exposure to ortho-toluidine and bladder cancer. Six cohort studies have been conducted among workers potentially exposed to ortho-toluidine (two in the UK, two in the USA, and one each in Italy and Germany). Exposure to other potential bladder carcinogens in the workplace occurred in some of the studies, and some of the studies were small. The two most recent studies [14] updated by [15–17] reported an excess risk in bladder cancer. In the US study of workers employed in the production of rubber additives from ortho-toluidine and aniline, risks were greatest for workers with the strongest likelihood of exposure (11 cases, SIR = 5.8, 95 % CI 2.9–10.5) and for those exposed more than 10 years (9 cases, SIR = 11, 95 % CI 5.1–21.1). Sorahan et al. [16, 17] reported an excess in bladder cancer risk in workers exposed to ortho-toluidine in the UK. Sorahan [16] found increased risks with longer duration of employment in departments where ortho-toluidine was processed (0.1–4.9 years exposure, 4 cases, RR = 3.72, 1.21–11.4; ≥5.0 years exposure, 2 cases, RR = 3.38, 0.67–17.0), after adjusting for exposure to other bladder carcinogens in the factory
X- and gamma radiation	75 (2000); 100D (2012)	The Life Span Study (LSS) of atomic bomb survivors and 3 more medical radiation cohorts have identified increased risk for bladder cancer. The excess RR in the most recent analysis of cancer incidence of the LSS was ERR/Sv = 1.23; 90 % CI 0.59–2.1 [18]. No significant excess was observed in the occupational studies, e.g., the IARC 15-country study or the UK National Registry for Radiation Workers (NRRW)
Limited evidence in humans		
4-Chloro-*ortho*-toluidine	99 (2010)	There are three small cohort studies of workers exposed to 4-chloro-ortho-toluidine, one among dye production workers in the USA and two of 4-chloro-ortho-toluidine production workers in Germany. No excess mortality was observed in the US study. The two German studies showed high relative risks of bladder cancer incidence. Co-exposure to ortho-toluidine could not be excluded as the cause of the excess risk in the 4-chloro-ortho-toluidine production workers. An excess of bladder cancer incidence was observed in the study by Stasik et al. [19] with eight cases reported (SIR, 72.7; 95 % CI, 31.4–143.3). No quantitative measure of exposure to 4-chloro-ortho-toluidine was available. An excess risk of bladder cancer was observed in the study by Popp et al. [20], with seven observed cases (SIR, 53.8; 95 % CI, 21.7–110.9), all occurring in workers exposed before 1976, when working conditions were improved. Exposure to other amines was present
Coal-tar pitch	92 (2010); 100 F (2012)	Coal-tar pitch is used in electrode manufacture, roofing, and paving. In the largest study with extensive exposure assessment, the overall mortality of bladder cancer in European bitumen workers was similar to that expected (SMR 1.05; 0.77–1.41[21]). Bladder cancer incidence by estimated average and cumulative benzo[a]pyrene exposure levels was evaluated in paving cohorts from Denmark, Finland, Israel, and Norway. An internal comparison showed a slightly increasing risk with average exposure to benzo[a]pyrene (RR = 1.36, 0.54–3.44 for more than 198 ng benzo[a]pyrene/m^3) but the trend was not significant (p-trend = 0.4) [22]
Dry cleaning	63 (1995)	Two US cohorts [23, 24] found an increased risk of 1.81 (0.87–3.33) and 1.3 (0.7–2.4). A recent large prospective record linkage study in the Nordic countries did not identify a clear increase in risk among launderers and dry-cleaning workers in men (RR = 1.10, 0.95–1.27) or women (RR = 1.07, 0.95–1.22) [25]. Several case-control studies have evaluated dry cleaning, and most have found an excess risk ranging from 1.3 to 2.8, although statistically significant excess was observed in only one study [26]. A European pooled analysis of 11 case-control studies [27] found an OR of 1.24 (95 % CI 0.67–2.31) for launderers, dry cleaners, and pressers

(continued)

Table 26.1 (continued)

Chemical, industry, or occupation	IARC monograph	Main epidemiological evidence
Diesel engine exhaust	105 (in press)	Numerous case-control and cohort studies have evaluated diesel engine exhaust. Most studies have used fairly crude exposure assessment methods or only examined employment at occupations associated with exposure to diesel exhaust such as miners or truck drivers. In a large pooled analysis in Europe, the highest exposure group (top tertile of exposure based on a JEM, 463 exposed cases, 939 exposed controls) had around 20 % increased risk compared to the lowest tertile of exposure (OR = 1,19, 95 % CI 1,04–1,36). A large recent study of miners in the USA that identified an increase in lung cancer associated with diesel exhaust did not find an increase for bladder cancer [28]
Hairdressers and barbers (occupational exposure)	99 (2010)	There are numerous cohort and case-control studies in hairdressers and barbers. A recent record linkage study in the Nordic countries identified significant increased risks in both men (OR = 1.31, 95 % CI 1.18–1.45) and women (RR = 1.24, 95 % CI 1.08–1.43) hairdressers [25]. A pooled analysis of 11 case-control studies conducted in six European countries including around 10,000 cases and controls [27, 29] did not find increases in risk among male (1.09) (95 % CI 0.70–1.70) or female hairdressers (0.8) (95 % CI, 04.–1.7). Overall, risks appeared generally lower for women than for men, and there was no clear pattern with duration of employment
Printing processes	65 (1996)	Among the seven cohort studies evaluated by the IARC in 1995, two found a 40–50 % excess risk for workers in the printing industry, while risks in the remaining studies were lower than 1.1. A recent large prospective record linkage study in the Nordic countries identified an increased risk among printers in men (RR = 1.19 1.12–1.27) and women (RR = 1.46, 1.22–1.74) [25]. In a large pooled analysis of European case-control studies [27], an increased OR was found for printers and related workers in men (OR = 1.45, 1.07–1.97)
Textile manufacturing	48 (1990)	The most consistent results for an increased risk of bladder cancer when the IARC evaluated the evidence were workers using dyes and possibly for weavers, with several studies reporting twofold or higher risks. In recent case-control study conducted in Spain that used an extensive evaluation of exposures, no increased risk of bladder cancer was found for textile workers overall, but increased risks were observed for specific work categories including weavers (OR = 1.82, 95 % CI 0.95–3.47). A large study in Shanghai, China, examined cancer incidence in a cohort of 267,400 women textile workers [30] and found a lower risk for bladder cancer (SIR = 0.63, 95 % CI = 0.46–0.85). A recent large prospective record linkage study in the Nordic countries did not identify an increased risk among textile workers in men (RR = 1.05 0.99–1.12), while slightly higher risk although statistically significant was observed in women (RR = 1.07 1.01–1.14) [25]

The table is based on recent summaries of the evidence in the indicated IARC monographs. Dyes metabolized to benzidine were classified as group 1 carcinogens based on sufficient evidence in animals, inadequate evidence in humans, and strong mechanistic evidence. The evaluation was based on the following considerations: (1) there is sufficient evidence in humans and in experimental animals for the carcinogenicity of benzidine and (2) the metabolism of benzidine-based dye results in the release of free benzidine and the induction of chromosomal aberrations in humans and in all experimental animal species studied

b-naphthylamine was associated with a 90-fold excess risk and to benzidine with a 14-fold risk. Excess risks were also observed for aniline and 1-naphthylamine, but these were most likely due to contamination with b-naphthylamine. Exposure to 4-ortho-toluidine has been associated with very high risks of bladder cancer [6]. Numerous other studies in dyestuff manufacture including auramine and magenta production have confirmed these findings [31] and provided, for example, exposure–response analyses [33]. In exceptional situations extremely high risks were described, with all 15 workers in a plant distilling b-naphthylamine developing bladder cancer [8]. Very high risks ranging from 6 to 70 have also been found for workers manufacturing aromatic amines including b-naphthylamine, benzidine, 4-aminobiphenyl, and 4-o-toluidine [14, 19, 34, 35]. Findings for users of dyes are less consistent [26, 36, 37].

An excess bladder cancer risk was identified since the early 1950s in the rubber industry and was associated with the use of b-naphthylamine containing antioxidant [38]. Figure 26.1 shows a spot map of cases of bladder cancer occurring in a tire factory in England in the late 1940s to early 1950s where the association with exposure to 2-naphthylamine was shown [10]. All cases of bladder cancer occurred in sectors of the plant where 2-naphthylamine had been used, and a simple visual inspection gave strong clues for etiology. Studies in Europe have identified higher risks compared to those in North America [39, 40] probably because of the more limited use of b-naphthylamine in the USA. Withdrawal of this compound in the rubber industry in the early 1950s led to a clear reduction of bladder cancer risk among rubber workers. A small excess of bladder cancer risk of the order of 50 % has, however, been consistently observed even in more recent

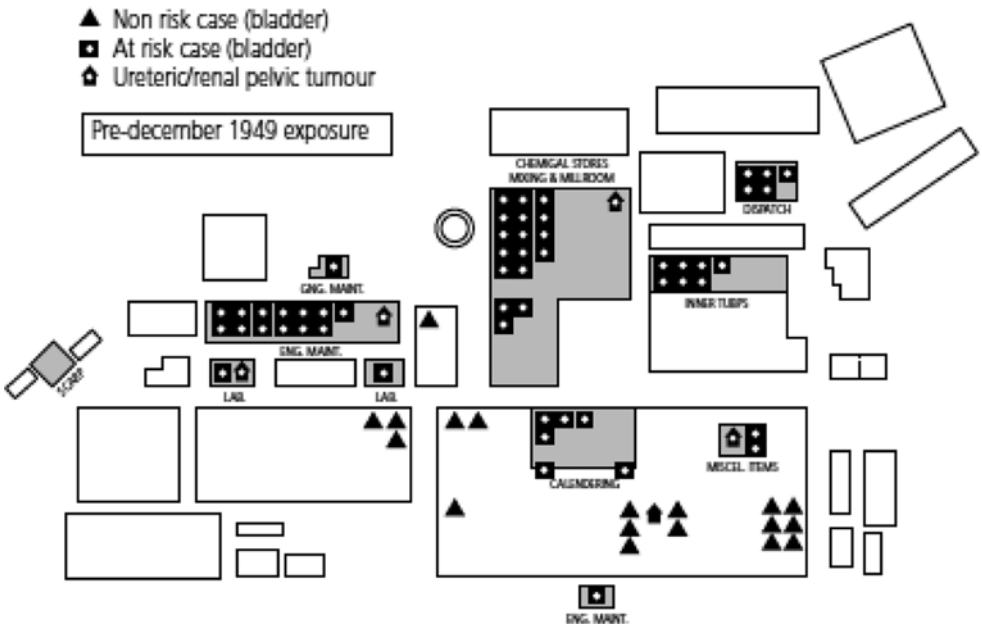


Fig. 26.1 Map of rubber tire production in a factory in England and deaths from bladder cancer (*squares*) for men employed before December 1949. *Shaded areas* indicate departments of the plant where 2-naphthylamine exposure occurred (From Veys [10], by permission of Oxford University Press)

studies of rubber workers published in the 1980s and 1990s (Fig. 26.2) [13]. A large very recent study conducted in Germany did not observe an increased risk of bladder cancer; this cohort, however, had a relatively short follow-up and included workers of fairly young ages [42].

Aromatic amines are present in lower quantities in many other occupational settings including shoemaking and printshops and in painters and hairdressers. The extent to which aromatic amines contribute to the excess risk observed in these occupations has been little examined [43].

The IARC has evaluated that there is strong mechanistic evidence on the carcinogenicity in humans of several aromatic amines including 4-aminobiphenyl and benzidine. The genotoxic mechanisms of action of these chemicals "involves metabolic activation, formation of DNA adducts, and induction of mutagenic and clastogenic effects" [44]. There are multiple metabolic pathways implicated in the activation of aromatic amines to DNA-reactive intermediates involving *N*-oxidation by cytochrome P-450 enzymes and *N*-acetylation by *N*-acetyltransferase 2 (NAT2). O-acetylation that is mediated by *N*-acetyltransferase 1 (NAT1) takes place in the bladder urothelium and represents the final activation step of *N*-hydroxyarylamines. The importance of several of these pathways may differ depending on the specific compound.

Polycyclic Aromatic Hydrocarbons (PAHs), Aluminum Production, Coal Gasification, Asphalt Workers, and Other Industries

High occupational exposure to PAHs occurs in several industries and occupations including the Söderberg potrooms in aluminum production, coal gasification, coke production and coke ovens, coal-tar distillation, roofing and road paving with coal tar, wood impregnation with creosote, carbon-electrode manufacture, chimney sweeping, power plants, and the transport industry (the latter is discussed in the section on diesel engine exhaust). The highest levels of exposure to PAHs have been observed in aluminum production (Söderberg process) with midrange levels observed in roofing and paving [6]. Early studies in the aluminum industry in Canada have associated exposure to PAHs with bladder cancer [2]. Several reviews and meta-analyses have been published on PAH exposure and bladder cancer [3, 4, 45], and the IARC evaluated the evidence in 2005 published at [46] and again in 2009 published at [44]. The IARC classifies *sufficient evidence* in humans for the carcinogenicity of occupational exposures during coal gasification, manufactured gas plant residues, coke production, coal-tar distillation, solvent-refined coal distillates, chimney sweep, paving and roofing with coal-tar pitch, and aluminum production. Although increased risks for bladder cancer were observed in several industries, with the exception of aluminum production for which the epidemiological evidence for bladder cancer was classified as sufficient, the strongest evidence for most other industries was for lung cancer.

In a review of asphalt workers and roofers exposed to bitumen and in earlier periods also coal-tar fumes, Partanen and Boffetta [47] examined the evidence from cohort and case-control studies. The meta-analysis included studies evaluated to have adequate occupational information. The pooled relative risk in cohort studies were 1.38 (95 % CI, 1.06–1.78; based on 60 cases) for all asphalt workers, 1.68 (95 % CI, 0.90–2.88; based on study) for roofers, and 1.20

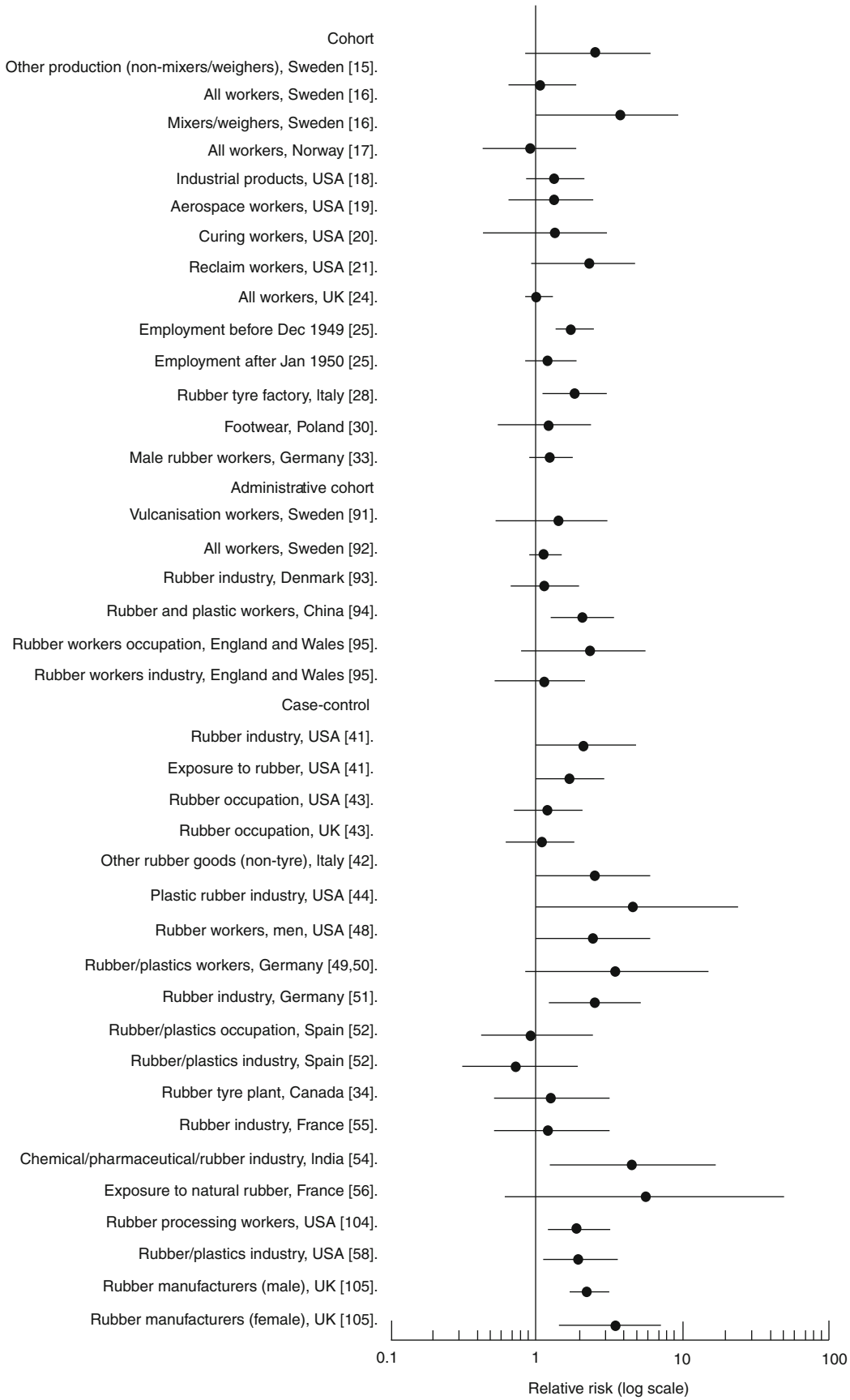


Fig. 26.2 Bladder cancer risk in workers employed in the rubber industry. Odds ratios (95 % CIs) for studies including >5 exposed cases (Reproduced from Kogevinas et al. [41], © 1998, with permission from BMJ Publishing Group Ltd)

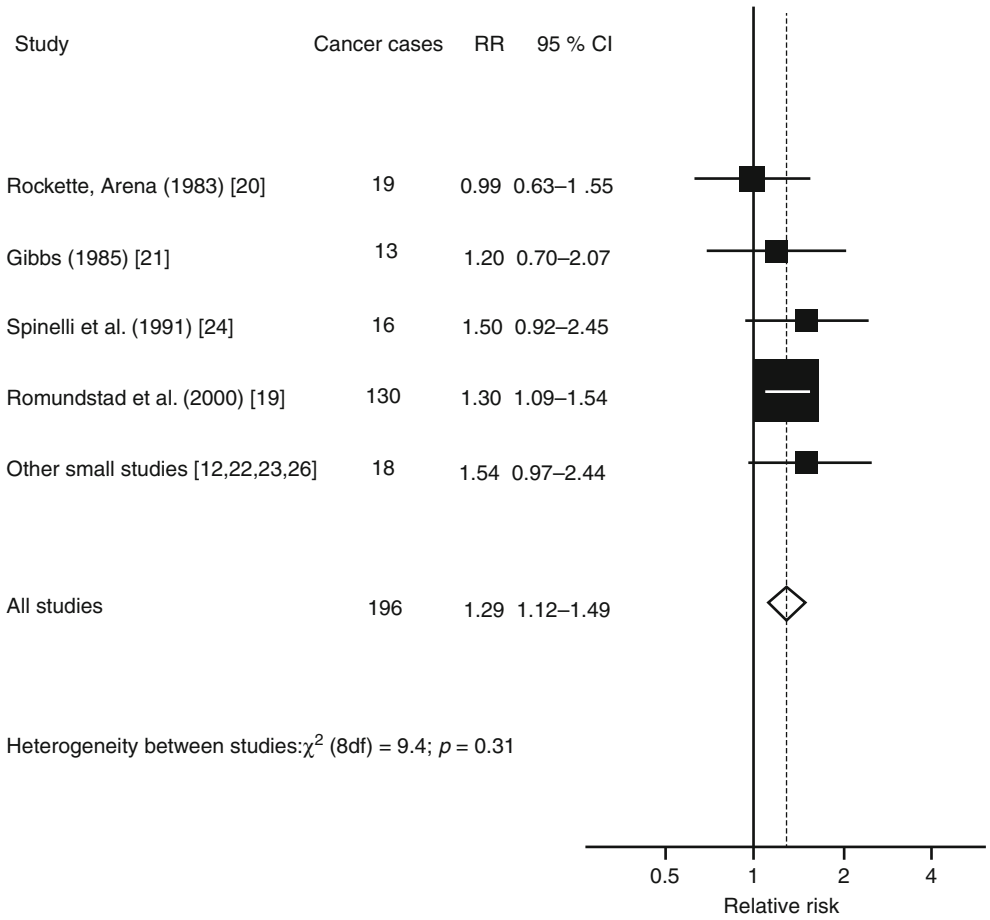


Fig. 26.3 Relative risks (*RR*) of bladder cancer among aluminum production workers and corresponding confidence intervals (*CI*), by study and overall. Meta-analysis of cohort studies (From Bosetti et al. [3], by permission of Oxford University Press)

(95 % CI, 0.74–1.83; based on two studies) for pavers and highway maintenance workers.

In a meta-analysis of urinary bladder cancer [4], 27 eligible cohorts were identified. Cumulative exposure to benzo[*a*]pyrene (BaP) was estimated. A statistically significant increased relative risk was observed for the aluminum industry (RR = 1.42, 95 % CI, 1.2–1.7; based on six studies. No increase was observed for exposures in coke ovens (RR = 1.04, 95 % CI, 0.79–1.37; based on six studies). Estimates for other industries were based on fewer studies, and relative risks were 8.80 (95 % CI, 0.08–967) for gas workers, 4.40 (95 % CI, 0.3–71) for asphalt workers, and RR >1,000 (95 % CI, 0.04–>1,000) for tar distillery workers.

A more recent meta-analysis of cohort studies [3] included more studies than Armstrong 2002. A consistent increased risk for cancer of the bladder was observed for workers in aluminum production (meta-RR of 1.29, 95 % CI 1.12–1.49) (Fig. 26.3), coal gasification (meta-RR = 2.39, 95 % CI 1.36–4.21), and iron and steel foundries (meta-RR = 1.29, 95 % CI 1.06–1.57).

Diesel Engine Exhaust

The IARC classified recently diesel engine exhaust as a human carcinogen [44] based mainly on evidence for lung cancer, while it was noted that a positive association has been observed between exposure to diesel exhaust and cancer of the urinary bladder. Exposure to diesel engine exhaust occurs in many occupational settings including the mining, railroad, transportation, and construction industries. The determinants of exposure include the size and number of diesel engines, the amount of ventilation, and whether exposure occurs indoor or outdoor. Diesel engine exhaust consists of a complex and varying mixture of gases, particles, volatile organic compounds (such as benzene) polycyclic aromatic hydrocarbons (PAHs) including nitrated PAH derivates. Diesel engine exhaust contains more particulate matter and lower levels of some gases compared to gasoline engines [44].

Several case-control, mortality, and registry-based studies evaluated diesel engine exhaust and bladder cancer. Many of the early case-control studies provided evidence of an excess

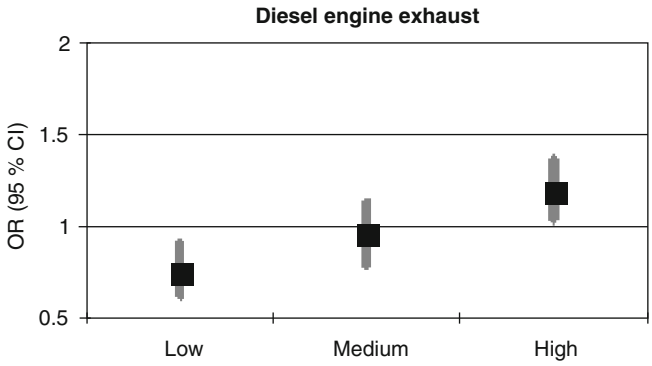


Fig. 26.4 Odds ratios for bladder cancer in European men by exposure to diesel engine exhaust, using a job-exposure matrix. Exposure was evaluated for different time periods as the product of the prevalence of exposure times the average exposure level in each occupation. Exposed subjects are classified in tertiles of maximum achieved exposure during their job history. Non-exposed subjects are the reference group (With kind permission from Springer Science + Business Media: Kogevinas et al. [41])

risk among transport workers exposed to engine exhausts including diesel [26, 48–52] even when adjusting for aromatic amine exposure [53, 54]. Most studies did not evaluate specifically diesel engine exhaust but rather examined employment at occupations associated with exposure to diesel exhaust. Very few studies examined dose–response. An evaluation specifically of exposure to diesel exhaust was done in the pooled analysis of European case-control studies [27] and four more studies in Canada, Belgium, and Sweden [52, 55–57]. Although overall there was only a modest increase in risk, all five studies identified the highest risk among those with highest exposures. The trend by diesel exhaust assessed on lifetime occupational history and a job-exposure matrix (JEM) from the European study is shown in Fig. 26.4. Only the study in British Columbia found a statistically significant association with cumulative exposure. A large recent study in miners in the USA that identified an increase in lung cancer associated with diesel exhaust did not find an increase for bladder cancer. A statistically nonsignificant increase in mortality was observed for surface-only mine workers, who had however much lower exposure to diesel exhaust than underground miners for whom no increase was observed [28].

Painters

The IARC has recently evaluated that occupational exposure as a painter is *carcinogenic to humans* [58]. This was based on *sufficient evidence* in humans for the carcinogenicity of occupational exposure as a painter for cancers of the lung and of the urinary bladder. The IARC evaluated 11 cohort and linkage studies of painters. These studies showed consistent excesses of mortality of around 20 % from urinary bladder cancer. These excesses are consistent with findings of case-control studies of painters that controlled for smoking. Most of the studies evaluated showed odds ratios above one. A meta-analysis [11] included around 2,900 incident cases or deaths from bladder cancer among painters from 41 cohort studies (Fig. 26.5). The relative risk (meta-RR, random effects) in painters was 1.25 (95 % CI 1.16–1.34; 41 studies). The meta-RR when including only the 27 studies that adjusted for smoking was 1.28 (95 % CI 1.15–1.43). A similar risk was observed in the four studies that adjusted for other occupational exposures (meta-RR 1.27; 95 % CI 0.99–1.63). Painters are exposed to solvents and other paint components through inhalation and dermal contact. They are also exposed to a variety of agents used by them or their coworkers such as asbestos, silica, metals, and epoxy resins although these exposures are not known to be associated with bladder cancer. Thousands of chemical compounds are used in paint products as pigments, extenders, binders, solvents, and additives. The main organic solvents used are toluene, xylene, aliphatic compounds, ketones, alcohols, esters, and glycol ethers. During the application of paint, workers are exposed primarily to solvents, whereas the mechanical removal of paint leads mainly to exposure to pigments and fillers. Several hazardous chemicals including benzene have been reduced or replaced in paint, although they are still used in some countries. The increasing use of water-based paints and powder coatings has promoted this trend. Biomonitoring of exposure to paint products reveals elevated levels of paint compounds or their metabolites in blood and urine [58].

Hairdressers and Barbers

In 2008, an IARC working group that evaluated the evidence on occupational exposure of hairdressers and barbers concluded that there was limited evidence of an increased risk for bladder cancer in hairdressers [6]. The evidence evaluated in 2008 was mainly concerned with exposures that occurred before 1980.

There are numerous cohort studies although most data from these studies derive from linkage between census data and cancer registries in Scandinavian countries. These cohort studies although large have limited potential to adjust for potential confounding by lifestyle factors. The cohort studies indicated an increased risk for cancer of the urinary bladder among male hairdressers, but not among female hairdressers. In a large Scandinavian cohort of hairdressers, barbers, beauticians, and other related workers identified in the 1970 census and followed up for 20 years, there was a significant 50 % increase in risk for bladder cancer in men and a nonsignificant 10 % decrease in risk in women. These studies did not evaluate the potential

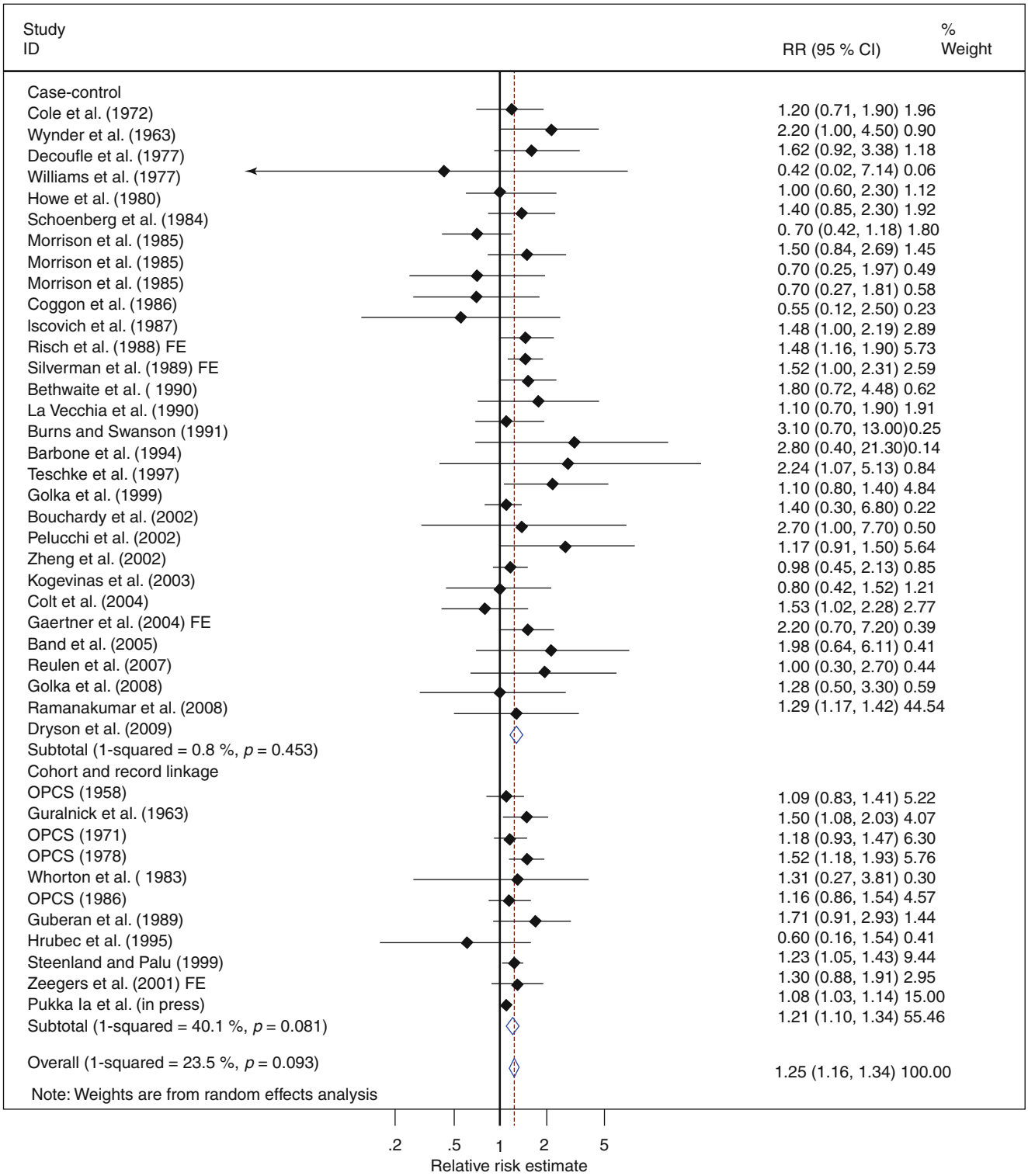


Fig. 26.5 Meta-analysis of all studies assessing bladder cancer among persons with occupation as a painter, stratified by study design. If only subgroup results (e.g., by gender, race, or duration of exposure) were reported, fixed effects (*FEs*) models were used to combine stratum-specific data into one summary estimate (Reproduced from Guha et al. [11], with permission from BMJ Publishing Group Ltd)

confounding effect of smoking, but the lack of a clear increase for lung cancer suggests that exposure to tobacco in hairdressers could not totally account for the bladder cancer excess. In an earlier meta-analysis of seven cohort studies on hairdressers and barbers [59], the relative risk estimate was 1.4 (183 observed vs. 129 expected). A recent

large prospective record linkage study in the Nordic countries identified significant increased risks in both men (OR = 1.31, 95 % CI 1.18–1.45) and women (RR = 1.24, 95 % CI 1.08–1.43) hairdressers [25]. There are more than 20 case-control studies evaluating exposures of hairdressers in males and females. Most of these studies found increased risks in the range of 1.3–1.7 in male hairdressers. A pooled analysis of 11 case-control studies conducted in six European countries including around 10,000 cases and controls [27, 29] did not find increases in risk among male (1.09) (95 % CI 0.70–1.70) or female hairdressers (0.8) (95 % CI, 04.–1.7). Overall, risks appeared generally lower for women than for men, and there were no clear pattern with duration of employment. The studies mostly evaluated employment as a hairdresser or barber rather than specific exposures. Hairdressers are exposed to hair dyes mostly through skin absorption rather than inhalation. Numerous individual chemicals have been used in hair dyes and in brilliantine including aromatic amines. Hairdressers are exposed also to many other compounds such as volatile solvents, propellants, and aerosols.

Dry Cleaning

Several million people are employed in dry cleaning worldwide. The predominant route of exposure to the solvents used in dry cleaning is by inhalation, although skin absorption and ingestion may also occur. Tetrachloroethylene has been the main solvent used in this industry since the 1950s although its use has been reduced in recent decades in several countries. A wide range of other chemicals have been also used including chlorinated solvents, amyl acetate, bleaching agents, acetic acid, aqueous ammonia, oxalic acid, hydrogen peroxide, and dilute hydrogen fluoride solutions [60]. The epidemiological evidence on occupational exposures in dry cleaning has been evaluated by the IARC [60] as limited. At that time the main evidence evaluated included two cohort studies in the USA that found an approximately twofold excess risk for dry cleaners [60], while no excess risk was observed in two large record linkage studies in Sweden and Denmark. Two US cohorts and the study in Sweden and Denmark expanded to include four Nordic countries have been updated [23, 24, 61]. All three cohorts found an increased risk of bladder cancer with relative risks of 1.44 (95 % CI, 1.07–1.93) for the Nordic study and RR of 1.81 (0.87–3.33) and 1.3 (0.7–2.4) for the two studies in the USA. None of the cohort studies reported notable exposure–response relationship, for the study by Calvert among workers exposed for more than 5 years and first exposed more than 20 years previously (standardized mortality ratio 4.08, 95 % CI 2·13–7·12). A recent large prospective record linkage study in the Nordic countries did not identify a clear increase in risk among launderers and dry-cleaning workers in men (RR = 1.10, 0.95–1.27) or women (RR = 1.07, 0.95–1.22) [25]. Several case-control studies have evaluated dry cleaning, and most have found an excess risk ranging from 1.3 to 2.8, although statistically significant excess was observed in only one study [26]. A European pooled analysis of 11 case-control studies [27] found an OR of 1.24 (95 % CI 0.67–2.31) for launderers, dry cleaners, and pressers. The epidemiological evidence on tetrachloroethylene was recently [44] evaluated by the IARC and was classified as limited. In most studies available in 2012, the indicator of exposure to tetrachloroethylene was, however, employment in dry cleaning [62]. Overall, taking into account also animal and mechanistic data, tetrachloroethylene was classified as probable human carcinogen (Group 2A).

Printers

During the manufacture of printing inks, exposure to pigments, vehicles, and additives can occur through inhalation or skin contact during mixing and dispersion and during cleanup of mixers. In the past, the major exposure in newspaper printing by letterpress or lithography was to ink mist. Historically, workers in ink manufacture and printing could be exposed to high levels of lead, PAHs and benzene. However, in recent decades, modern technologies have made possible a drastic reduction of exposure to solvents, ink mist, and other chemicals. Printers have been found more frequently than not with a modest excess bladder cancer risk. In 1995, the IARC evaluated that there was limited evidence that occupational exposures in printing processes are carcinogenic. Among the seven cohort studies evaluated by the IARC in 1995, two found a 40–50 % excess risk for workers in the printing industry, while risks in the remaining studies were lower than 1.1. The available studies in this industry have not examined specific exposures potentially associated with the bladder cancer risk. A recent large prospective record linkage study in the Nordic countries identified an increased risk among printers in men (RR = 1.19 1.12–1.27) and women (RR = 1.46, 1.22–1.74) [25]. At the time of the IARC evaluation, around 25 case-control studies reported results of bladder cancer risk among workers employed in the printing industry [63], and, of those, 20 found excess risks ranging from 1.1 to fivefold either in the whole study group or in subgroups. In the more recent pooled analysis of European case-control studies [27], an increased OR was found for printers and related workers 1.45 (1.07–1.97), while a higher OR was found in a more recent study in Spain (Samanic et al. 2008) with an OR of 2.81 (1.28–6.17) that was slightly higher among workers employed in this industry for more than

10 years (OR = 3.11, 95 % CI1.02–9.47). Overall, in only few of the studies were the results statistically significant, and the occupational groups examined were heterogeneous and usually included broad categories such as "the printing industry."

Textile Industry

The epidemiological evidence on occupational exposures in the textile industry has been evaluated by the IARC [65] as limited. This evaluation was based mainly on findings on bladder cancer among dyers and among weavers possibly due to exposure to dusts from fibers and yarns. Evidence on the risk associated with occupation in the textile industry comes mainly from case-control studies. More than 20 studies have reported risks for workers in the textile industry or for subgroups. The most consistent results are for workers using dyes and possibly for weavers, with several studies reporting twofold or higher risks. Studies in European countries (e.g., [66–69]) tend to identify higher risks than those conducted in, for example, North America [70–72], although this pattern is not entirely consistent [43]. A recent study conducted in Spain including around 1,200 cases and an equal number of controls is among the studies with more extensive exposure assessment [73]. Lifetime occupational history was obtained using a computer-assisted personal interview, and occupations, locations, and materials used in the textile industry were assessed by a detailed questionnaire and expert assessment. No increased risk of bladder cancer was found for textile workers overall, but increased risks were observed for specific work categories including weavers (OR = 1.82, 95 % CI 0.95–3.47). A large study in Shanghai, China, examined cancer incidence in a cohort of 267,400 women textile workers [30]. There was a decrease in cancer incidence overall for the cohort compared with urban Shanghai women and a lower risk for bladder cancer (SIR = 0.63, 95 % CI = 0.46–0.85). A recent large prospective record linkage study in the Nordic countries did not identify an increased risk among textile workers in men (RR = 1.05 0.99–1.12), while slightly higher risk although statistically significant was observed in women (RR = 1.07 1.01–1.14) [25].

Leather Workers

Leather workers have been found to have an up to twofold excess risk in many studies [36, 69, 71, 74–76]. Results have been equivocal in some studies [26, 77], while several studies have not found any excess risk [43, 49, 67, 68]. The definition of leather workers differs between studies and includes occasionally tanners, shoemakers, or/and other leather workers. Within the wide category of leather workers, a variety of exposures may occur including leather dust, aniline and azo dyes, arsenic, chromium, formaldehyde, mercury compounds, and organic solvents.

Machinists and Metal Workers

Elevated risk for bladder cancer has frequently been found in occupations within the metal sector including machinists, blacksmiths, furnace operators, foundry workers, welders, aluminum smelter workers [26, 27, 29, 43, 67, 70, 72, 78] and others. In many of these studies, higher than twofold risks were observed. No excess risks were found in some studies [39, 49, 79]. This group of occupations is heterogeneous, and exposures of these workers vary and include cuttings oils (a category referring to numerous diverse agents), PAHs, metal fumes and dusts, and combustion gases and vapors. In recent studies, excess risks found for machinists and other metal workers although only moderately high appear among the most consistent findings. At present in European Union countries, metal workers appear as the largest occupational group associated with bladder cancer risk [27].

Recent Evidence from International Studies

Table 26.2 shows odds ratios for industries in Europe with increased risk for bladder cancer from a large international study. The highest risk was seen for workers in salt mining (OR 4.41), while the other industries included manufacture of paints, varnishes, and lacquers and industries in textile and clothing. Among the occupations identified with statistically significant high risks in this European study (Table 26.3) were metal workers, textile workers, electrical workers and painters, miners, transport operators, excavating-machine operators, and also nonindustrial workers such as concierges and janitors [27]. A recent analysis of census data from Denmark, Finland, Iceland, Norway, and Sweden evaluated up to 45 years of cancer incidence data (2.8 million incident cancer cases from 1960 to 2005) by occupational category for these Nordic populations. Bladder cancer was considered as one of the cancer types most likely to be related to occupational carcinogens. Waiters had the highest risk of bladder cancer in men and tobacco workers in women, and a pattern that can be accounted for by smoking. The second-highest SIRs were among chimney sweepers and hairdressers. Table 26.4 shows the RR for occupations with the highest risks in men and Table 26.5 in women in the Nordic study.

Table 26.2 Industries showing a statistically significant excess bladder cancer risk among European men

Industry (ISIC code)	Odds ratio	95 % confidence interval
Salt mining (2,903)	4.41	(1.43–13.6)
Manufacture of carpets and rugs (3,214)	4.07	(1.44–11.5)
Manufacture of paints, varnishes, and lacquers (3,521)	2.94	(1.48–5.84)
Manufacture of plastic products NEC (356)	1.79	(1.06–3.00)
Manufacture of industrial chemicals (351)	1.58	(1.07–2.33)
Education services (931)	1.47	(1.06–2.05)

Pooled analysis of 11 case-control studies [27]
[a]ORs are adjusted for age, smoking, and study center. The non-exposed group does not include subjects who had worked in any of the a priori defined high-risk occupations

Table 26.3 Blue-collar occupations at highest risk for bladder cancer in Europe among men (top) and women (bottom)

	Odds ratio	95 % confidence intervals
Occupation, men		
Other electrical fitters	3.99	1.10–14.51
Other nursery workers and gardeners	3.57	1.24–10.29
Textile machinery mechanics	2.86	1.50–5.47
Knitters	2.56	1.24–5.30
Excavating-machine operators	2.43	1.18–5.00
Electric arc welders – hand	2.27	1.04–4.98
Supervisors – metal processing	2.11	1.04–4.32
Metal casters	1.96	1.06–3.64
Automobile painters	1.95	1.01–3.75
Metal processers NEC	1.85	1.15–2.97
Supervisors – machinery and metal	1.59	1.05–2.42
Machine-tool setter operators	1.50	1.07–2.12
Printers and related workers	1.45	1.07–1.97
Miners and quarrymen	1.30	1.02–1.64
Transport equipment operators	1.17	1.02–1.34
Machinery fitters and assemblers	1.16	1.01–1.34
Occupation, women		
Mail sorting clerks	4.43	1.01–19.5
Tobacco product makers	3.12	1.05–9.28
Other saleswomen	2.63	1.01–6.85
Blacksmiths, machine-tool operators	1.94	1.06–3.57
Lathe operators	4.61	1.11–19.2
Field crop, vegetable farmers	1.78	1.03–3.08
Tailors and dressmakers	1.44	1.01–2.06

Pooled analysis of European case-control studies [27, 29]

Table 26.4 Occupations at high risk of cancer (standardized incidence ratio (SIR) >1.20) in the Nordic countries 1961–2005, in men and women [25]

Occupation, men	SIR (95 % confidence interval)
Waiters	1.50 (1.32–1.69)
Chimney sweepers	1.49 (1.23–1.81)
Hairdressers	1.31(1.18–1.45)
Assistant nurses	1.28 (1.09–1.49)
Seamen	1.23 (1.17–1.30)
Plumbers	1.21(1.14–1.29)
Cooks and stewards	1.21(1.08–1.35)
Beverage workers	1.20 (1.02–1.40)
Occupation, women	
Tobacco workers	2.01 (1.49–2.65)
Printers	1.46 (1.22–1.74)
Waiters	1.44 (1.32–1.56)
Chemical process workers	1.29 (1.07–1.57)
Sales agents	1.26 (1.15–1.39)
Hairdressers	1.24 (1.08–1.43)
Mechanics	1.21 (1.04–1.40)
Administrators	1.20 (1.06–1.36)

Evidence on Other Occupations and White-Collar Occupations

Less consistent associations have been found for numerous other occupations including tailors and dressmakers, plumbers and welders, mechanics, electrical fitters, firefighters, managers, sales workers, petroleum refining, garage workers, medical occupations, cooks, waiters, nursery workers, miners, paper workers, food processors and preservers, slaughterers and meat processors, teachers, insulation workers exposed to asbestos, construction workers, engine drivers, and railway workers.

Various case-control studies, particularly those conducted in recent years, have found excess risks for white-collar occupations such as managers and service and sales workers, even after adjusting for potential confounding variables [27, 43, 67, 80]. This coincides with the changes observed in the socioeconomic pattern of this disease. These excess risks are difficult to attribute directly to exposures in the workplace and are more likely to be attributed to general lifestyle factors. A meta-analysis of studies evaluated risks reported in 18 studies for bladder cancer in sales workers [81]. Meta-estimates were elevated for both men (OR = 1.11, 95 % CI 1.01–1.21) and women (OR = 1.36, 95 % CI 1.11–1.67) although results indicated publication bias for women. In an analysis including only smoking-adjusted estimates, no increase was observed for men sales workers (OR = 0.99, 95 % CI 0.90–1.08), while a small increase was still observed among women (OR = 1.18, 95 % CI 0.99–1.39) without an indication of publication bias.

Occupational Bladder Cancer in Women

In most studies on occupational bladder cancer, the study population has been too small to evaluate occupations separately in women although some large studies exist [30]. Overall the importance of occupational exposures for the occurrence of bladder cancer in women has received little attention, although some studies did report these results [36, 67, 82–85]. Most well-established occupational risks such as employment in the rubber and dye industries have been recognized on the basis of findings in exposed men. Two large case-control studies on occupational bladder cancer risks in women have been published. The first included 652 cases and 1,266 controls from ten areas of the USA [72]. The pattern of bladder cancer risk among women was, to some extent, similar to those in men with excess risk found for metal workers (OR = 1.4), those in the chemical industry (OR = 2.1), rubber processing workers (OR = 4.5), and saleswomen (OR = 2.5). A pooled analysis of European case-control studies including 700 cases and 2,425 controls ([29], Table 26.3) identified statistically significant excess risks in metal workers, farm workers, tailors and dressmakers, saleswomen, and mail clerks. In an analysis of cancer registration data from England and Wales (1971–1990) including 6,792 female cases with bladder cancer [86], statistically significant high PRR (proportional registration ratios) were found for rubber workers (PRR = 3.0), textile fabric process workers (PRR = 2.0), clothing (PRR = 1.6), electricians (PRR = 2.1), caretakers (PRR = 1.5), waitresses (PRR = 1.2), and nurses (PRR = 1.1). In a joint analysis of cancer incidence data in the Nordic countries, the highest risks among women were found for tobacco workers (RR = 2.01, 95 % CI 1.49–2.65), printers, waiters, chemical process workers, sales agents, and hairdressers [25]. A large study in Shanghai, China (mentioned in the section on the textile industry) [30], found a decreased risk among textile workers compared to urban Shanghai women.

Attributable Risk for Occupational Bladder Cancer

Estimates of the attributable risk derived from the early case-control studies had suggested that around 15–20 % of all bladder cancers in men could be attributed to occupation [74, 87, 26, 88]. In the pooled analysis of European case-control studies which included recent studies on occupational bladder cancer [27], the attributable risks for having been employed in eight high-risk occupations/industries (chemical, leather, machinists and metal product workers, painting, rubber workers, textile, transport, and hairdressers) were estimated to be 4 % in men. The attributable risk for a wider list of occupations including 18 additional occupations such as launderers/dry cleaners, nursery workers, miners, metal processors, printers, and others was estimated to be 9.5 %. In women in the US study [72], it was estimated that 11 % of the bladder cancer cases could be attributed to occupational exposure. In the European study [29] about 8 % of all bladder cancers could be attributed to occupation. When, however, the attributable risk was calculated on the basis of established high-risk occupations such as dyestuff workers, rubber workers, etc., no excess risk whatsoever was found among women. In a recent evaluation of occupational cancer in Britain [89], the overall attributable fraction for bladder cancer was 5.3 % (95 % CI 3.4–7.7 %). The attributable fraction was calculated for selected exposures including mineral oil, aromatic amines, PAHs (in coal tar and coal-tar pitches, aluminum production, coal gasification, coke production, and petroleum refining), and diesel engine exhaust and for selected occupation (painters, hairdressers, and barbers). It was assumed that risk for bladder cancer in the rubber industry was confined to before 1950 in the UK. The attributable fraction was 7 % for men (95 % CI 5–10 %) and 2 % for women (1–4 %).

There are no extensive and fairly representative data on exposure and time trends in most developing or newly developed countries [90], and a reliable estimation of attributable risks in these countries is, therefore, not possible.

Time Trends in Occupational Bladder Cancer in Industrialized Countries

Extensive measures have been taken in the last decades in major industries in industrialized countries to prevent exposure to occupational carcinogens. An open question is whether current occupational exposures in those industries identified in the past as high risk are still related to some excess bladder cancer risk. There are more than 30 studies published after 1990s or later reporting risks for bladder cancer for specific occupations or industries. Among blue-collar workers, the most consistent results are found for aromatic amine exposure, for painters, and occupations in the metal industry such as sheet metal workers and blacksmiths, machinists, and mechanics. These risks reflect, in part, past exposure to chemicals which are not currently used such as benzidine or b-naphthylamine, but others may reflect more recent exposures possibly to aromatic amines, PAHs, diesel engine exhaust, paints, cutting oils, and solvents. The proportion of cancers attributed to occupation was higher in the European case-control study [27] in subjects first employed in a high-risk occupation before the 1950s as compared to those employed later. The attributable risk seemed also to be related to age with a higher proportion of cancers attributed to occupation observed for subjects less than 50 years of age first employed in a high-risk occupation before 1950 (63 %) compared to those first employed after 1950 (15 %). The corresponding attributable fractions for

subjects above 50 years were 9 and 0 %, respectively. The main reason for the decrease of the attributable risk by calendar period was that risks were considerably lower among subjects first employed after the 1950s, while the prevalence of employment in these occupations remained fairly stable both before and after 1950.

Epidemiology of Bladder Cancer and Non-occupational Risk Factors

It has been estimated that there are approximately 380,000 new cases per year worldwide [1], most occurring among men and about two thirds occurring in more developed regions. Among the countries with the highest incidence are the USA, Spain, the UK, Poland, and Egypt. The dominant histological type in industrialized countries is urothelial cell carcinoma. In some developing countries with a high prevalence of *Schistosoma haematobium* such as Egypt, squamous cell carcinoma is the most frequent histological form. There are several recent reviews of the causes of bladder cancer [41, 91].

About 50 % of all bladder cancers are caused by tobacco consumption, although this percentage may vary in different parts of the world. Black tobacco smoke consumed historically in southern European countries has been associated with a higher risk. Findings on the role of dietary factors in bladder cancer etiology are less consistent. Consumption of fresh fruits and vegetables and increased total fluid intake may be protective factors in this cancer. Heavy coffee consumption of around ten cups per day is possibly associated with a modest excess risk, but the evidence is still equivocal particularly regarding the potential for residual confounding from smoking. Early studies mostly in animal experiments indicating that artificial sweeteners were associated with bladder cancer have not been confirmed in humans. Consumption of several medications has been associated with decreased (e.g., barbiturates, certain analgesics, and anti-inflammatory drugs) and increased risks (e.g., analgesics used in the past such as phenacetin). An infectious etiology of bladder cancer is clear regarding infection with *Schistosoma haematobium*, while the evidence on other common urinary infections is less consistent. Studies conducted in areas with high arsenic levels in water have clearly shown an increased risk of bladder cancer related to arsenic in drinking water. There is also increasing evidence that disinfection by-products in drinking water could increase the risk of bladder cancer.

Exposure Assessment in Occupational Bladder Cancer

Methods to evaluate occupational exposures have been considerably developed in recent years and incorporate modeling techniques and application of biomarkers. New approaches have also been applied in the construction of questionnaires and methods to evaluate them. These methods are not specific to bladder cancer.

Strategies applied to evaluate occupational exposures depend on the study design applied, the population studied, and the resources and prior information available. Exposure could be directly measured at the workplace in a prospective study and could be assessed using questionnaires in a case-control study or based on job records in a retrospective cohort study. Several techniques can be further applied to estimate past exposures, for example, the use of expert opinions, job-exposure matrices (JEM), or application of exposure models. Furthermore biomarkers of exposure can be applied in prospective studies.

Questionnaires have been extensively used in case-control studies and usually request detailed information on jobs, tasks, industries worked, specific exposures, use of protective equipments, etc. It has generally been observed that questions on specific chemical exposures have a low sensitivity, i.e., many exposed subjects do not report that they have been exposed. Supplementary questionnaires have been used in several occupational cancer case-control studies to retrieve more detailed information for specific carcinogens, e.g., asbestos. These supplementary questionnaires are administered in subjects who report having worked in jobs or industries in which a specific carcinogenic exposure may occur. Specific questions related to the materials used, tools, machineries, and tasks were asked, so as to evaluate with more certainty the probability and level of exposure. These detailed questionnaires are further analyzed using a predetermined algorithm or through a case-by-case evaluation by experts. For example, a study on occupational causes of bladder cancer in Spain used 63 supplementary questionnaires for specific occupations, e.g., welders and machinists, or for specific industries based on methodology developed by Jack Siemiatycki and using questionnaires as described in Stewart and Stewart, 1994. An analysis of a specific module in the textile industry can be found in [73]. These modules covered several exposures of interest, e.g., PAHs, diesel engine exhaust, and solvents, that could occur in multiple work places. The use of such questionnaires, undoubtedly, provides important exposure information but requires a considerable expense in time and money and also requires a very good knowledge of the workplace in order to prepare the questionnaires. Cohort studies may also use industry questionnaires that collect information on industrial processes, exposures, accidents, etc. of specific industries that have been used in studies on occupational cancer, for example, the IARC study in the pulp and paper industry [92].

Job-exposure matrices have been extensively used in occupational cancer epidemiology. JEMs are simply a matrix (table) showing which occupations are exposed to specific chemicals, and this information is based on prior knowledge on exposures of specific occupations. This method allows a

nearly automatic assignment of exposures in the matrix to the subjects of the study, provided a complete occupational history is available for each subject. Several general and specific JEMs, using different methodologies, have been described. FINJEM that has been developed in Finland is among the most widely used general JEMs (FINJEM) [93] and has been applied in an international study on bladder cancer [27]. The main advantages of JEMs is the low cost for using them once they have been created and the high repeatability of the estimates since for a specific job one would attribute the same specific exposure estimate. The main problem of the JEMs is the potentially important exposure misclassification even though this should be in principle non-differential.

Evaluation by experts has been extensively used when examining occupational exposure assessment [94, 95]. In this approach, a group of experts (industrial hygienists, chemists) use their professional experience to evaluate if a worker has been exposed to a chemical or physical agent, on the basis of information they have on the occupational history of the worker and their own knowledge on exposures in the specific occupation/industry. Frequently the evaluation by experts is used in combination with other methods. For example, exposure levels were modeled among subjects considered to be exposed through the application of a JEM [96].

The most precise methods evaluating occupational exposures are those using direct measurements in the workplace sometimes combined with the use of biomarkers. However in most cases, this type of information is not available or is available only for a subgroup of workers. In these cases the use of exposure models can be considered attributing exposure levels to the whole study population.

Clinical and Pathological Features of Occupational Bladder Cancer

In industrialized countries, urothelial cell carcinomas (previously defined as transitional cell) constitute 93–95 % of malignant tumors in the urinary bladder. The 5–7 % remaining carcinomas include squamous cell carcinomas, adenocarcinomas, undifferentiated carcinomas, and other minor histological types such as small cell carcinomas and lymphomas. In east African and Middle Eastern countries, squamous cell carcinoma is much more common than in Europe and North America, a pattern associated with a high prevalence of infection with *Schistosoma haematobium*. About 70 % of all tumors occur in the lateral and posterior wall and near the trigone, about 20 % in the trigone, and 10 % in the dome. A consensus (IARC/WHO) classification of neoplasms of the urinary bladder was published in 2004 [97]. Around 75 % of bladder tumors present as superficial disease and the remaining as muscle invasive. Among superficial tumors, around three quarters appear as low-grade superficial lesions (Ta) and less than 10 % as high-grade carcinoma in situ.

A visible but painless bleeding (hematuria) is the cardinal symptom of bladder cancer, sometimes accompanied by urgency, other voiding problems, or urinary obstruction. Various imaging modalities are used not only for detection but also for staging of infiltrating urothelial carcinoma. They include ultrasound, intravenous urography (IVU), computed tomography (CT), and magnetic resonance imaging (MRI). Diagnosis is confirmed through visual inspection by a cystoscope, combined with histopathologic examination of a biopsy specimen or resected tumor tissue.

The recognition of work-related factors is vital in the prevention of ill health and eventually for compensation. With very few exceptions, cancers that are of occupational origin are not distinguishable from non-occupational cancers in clinical features, natural history, or pathological findings. A patient with bladder cancer due to occupational exposures will be diagnosed in the same way and through the same procedures as one produced by nonwork-related exposures. The identification of work-related medical problems depends most importantly on the occupational history, and it is essential that this enquiry of "work relatedness" goes back far enough in the patient's life to be sure of including relevant exposures. That means at least 20 years and sometimes as many as 40. Several databases and publications may help in the identification of occupational causes of cancer. These include lists and frequency of occurrence of carcinogenic exposures by industry such as CAREX [98] or lists of carcinogens by cancer site as identified by the IARC [99] that are regularly updated (http://monographs.iarc.fr/ENG/Classification/index.php).

Some studies on occupational bladder cancer and other tumors have noted the possibility that the occupational cancer may present earlier than the cancers related to non-occupational exposures. The pooled analysis on bladder cancer mentioned earlier [27] and other studies [33, 71, 74, 76] has found higher risks among younger as compared to older people (the cutoff being around 60 years of age) indicating that occupational exposures seem to be more important determinants of the risk among younger ages. Thus a patient aged 45 years with bladder cancer – particularly if there is no history of tobacco consumption – should heighten the suspicion of the clinician that this might be an occupationally related tumor.

Genetic Susceptibility and Bladder Cancer

The role of genetic susceptibility in bladder cancer has been evaluated principally in relation to metabolic polymorphisms rather than to monogenic, high-penetrance conditions. Familial clustering of bladder cancer has been reported, and studies examining familial aggregation have found excess

risks [100, 101] indicating that familial aggregation in bladder cancer can be estimated to be around 1 %. Two metabolic polymorphisms have been extensively examined in relation to bladder cancer, namely, the N-acetyltransferase 2 (NAT2) slow acetylators and the glutathione S-transferase M1 (GSTM1) null. Both polymorphisms, which are prevalent in diverse populations, increase the risk of bladder cancer by around 30–50 %. Meta-analyses have also evaluated the role of DNA repair gene XRCC1 [102] and oxidative metabolism genes NQO1 and SOD2 [103] identifying an association with bladder cancer. These may be relevant for occupational exposures, although no data are available for occupational bladder cancer.

NAT2 acetylation status is the most extensively examined metabolic polymorphism in relation to bladder cancer and exposure to aromatic amines from tobacco smoke or occupational exposures. The lack of two functional alleles of NAT2 results in slower detoxification of aromatic amines and subsequently in higher susceptibility to metabolic activation by P450 enzymes. The slow acetylation genotype is common in Caucasians (55 %) and less common in populations of African (30 %) and Asian descent (15 %).

Aminobiphenyls (ABPs) in tobacco, which have been implicated in bladder cancer etiology in smokers, are detoxified by the NAT2 enzyme. Smokers with the NAT2 slow polymorphism have higher concentrations of urinary mutagens and ABP adducts than smokers with the rapid acetylator phenotype [104, 105, 106], A meta-analysis revealed a modest 30–50 % increase in the risk of bladder cancer among slow compared to rapid acetylators [107]. Studies conducted in the occupational environment had identified an increased bladder cancer risk among subjects exposed to b-naphthylamine or other aromatic amines among slow acetylators [108]. A study in China among workers exposed to benzidine, however, found a protective effect with an odds ratio of 0.3 (95 % CI 0.1–1.0) for workers with the slow *NAT2* genotype after adjustment for cumulative benzidine exposure and lifetime smoking [7]. These findings may indicate that the association between slow acetylation and bladder cancer risk may depend on the specific aromatic amine exposed. The same study showed increased bladder cancer risk with specific polymorphisms in the *NAT1* gene, while no association was found for *GSTM1* polymorphisms.

Several genome-wide association studies (GWAS) have been published. The largest included a primary scan of around 600,000 SNPs in about 8,500 cases and controls followed by a replication analysis in a much larger population [109]. GWAS identified new regions associated with bladder cancer on chromosomes 22q13.1, 19q12, and 2q37.1 and replicated findings from previous GWAS on chromosomes 3q28, 4p16.3, 8q24.21, and 8q24.3. This analysis also validated previous associations identified in the past through a candidate gene approach for the GSTM1 deletion and a tag SNP for NAT2 acetylation status. A recent analysis based on populations studied through GWAS [110] examined a combination of several genes associated with bladder cancer and identified that the potential impact of eliminating smoking on the number of bladder cancer cases prevented is larger for individuals at higher than lower genetic risk. There are no large studies based on GWAS analyses evaluating gene–environment interactions for occupational exposures.

Conclusion

Occupation has been identified, after smoking, as the second important risk factor for bladder cancer. Early estimates of the attributable risk for occupational exposures suggested that around 15–20 % of all bladder cancers in men could be attributed to occupation. Recent studies in industrialized countries reported lower percentages, and a recent extensive evaluation in the UK estimated an attributable fraction of 7 % for men and 2 % for women. There are no extensive and fairly representative data on exposure and time trends in most developing or newly developed countries, and a reliable estimation of attributable risks in these countries is not possible.

Several exposures, occupations, and industries have been associated with increased bladder cancer risk. Aromatic amines (benzidine, 4-aminobiphenyl, b-naphthylamine, 4-chloro-o-toluidine) in dyestuff manufacture and in the rubber and other industries are the only specific agents in the workplace which have been unequivocally associated with bladder cancer in humans. Excess risks have been observed among aluminum process painters, machinists and other metal workers, workers in the textile industry, leather workers and shoemakers, printers, hairdressers, dry cleaners, and transport workers. Exposures associated with the increased risk in these occupations/industries include polycyclic aromatic hydrocarbons (PAHs), diesel engine exhaust, paints, dyes, chlorinated hydrocarbons, and other solvents, metals, and industrial oils/cutting fluids. A recent analysis of census data in the Nordic European countries identified waiters in men and tobacco workers in women as the occupations with highest risks, a pattern that can be accounted for by smoking, while the second-highest risks were observed for chimney sweeps and hairdressers. Less consistent associations have been found for numerous other occupations, while various case-control studies, particularly those conducted in recent years, have found excess risks for white-collar occupations such as managers and service and sales workers.

Genetic susceptibility had been evaluated mainly in relation to metabolic polymorphisms, in particular the N-acetyltransferase 2 (NAT2) slow acetylators and the glutathione S-transferase M1 (GSTM1) null genotype. Both metabolic polymorphisms are prevalent in diverse

populations and increase the risk of bladder cancer by around 30–50 %. Meta-analyses have also evaluated the role of DNA repair genes such as XRCC1 and oxidative metabolism genes. Recent GWAS have identified new genes associated with bladder cancer. Very few studies have evaluated genetic variation in conjunction with occupational exposures. Some studies have identified an increased bladder cancer risk among subjects exposed to b-naphthylamine or other aromatic amines among slow acetylators, but this pattern differed in workers exposed to benzidine, possibly indicating that the association between slow acetylation and bladder cancer risk may depend on the specific aromatic amine exposed.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v2.0, cancer incidence and mortality worldwide: IARC Cancer Base No. 10 [Internet]. Lyon: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr Accessed on 15 May 2013.
2. Theriault G, Tremblay C, Cordier S, Gingras S. Bladder cancer in the aluminium industry. Lancet. 1984;323:947–50.
3. Bosetti C, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. Ann Oncol. 2007;18(3):431–46.
4. Armstrong BG, Hutchinson E, Fletcher T. Cancer risk following exposure to Polycyclic Aromatic Hydrocarbons (PAHs): a meta-analysis (Rep. No. 068), Sudbury: Health and Safety Executive. Available at: http://hse.gov.uk/research.rrhtm/rr068.htm (2002). Accessed 15 May 2013.
5. Collins JJ, Strauss ME, Levinskas GJ, Conner PR. The mortality experience of workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin in a trichlorophenol process accident. Epidemiology. 1993;4:7–13.
6. IARC. Monographs on the evaluation of carcinogenic risks to humans; v. 99 some aromatic amines, organic dyes, and related exposures/IARC working group on the evaluation of carcinogenic risks to humans (2008). Lyon: IARC: 2010.
7. Carreón T, Ruder AM, Schulte PA, et al. NAT2 slow acetylation and bladder cancer in workers exposed to benzidine. Int J Cancer. 2006;118:161–8.
8. Case RA, Hosker ME, McDonald DB, Pearson JT. Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. I. The role of aniline, benzidine, alpha-naphthylamine, and beta-naphthylamine. Br J Ind Med. 1954;11:75–104.
9. Rubino GF, Scansetti G, Piolatto G, Pira E. The carcinogenic effect of aromatic amines: an epidemiological study on the role of o-toluidine and 4,4´-methylene bis (2-methylaniline) in inducing bladder cancer in man. Environ Res. 1982;27:241–54.
10. Veys CA. Bladder tumours in rubber workers: a factory study 1946–1995. Occup Med (Lond). 2004;54(5):322–9.
11. Guha N, Steenland NK, Merletti F, Altieri A, Cogliano V, Straif K. Bladder cancer risk in painters: a meta-analysis. Occup Environ Med. 2010;67(8):568–73.
12. Bachand A, Mundt KA, Mundt DJ, Carlton LE. Meta-analyses of occupational exposure as a painter and lung and bladder cancer morbidity and mortality 1950-2008. Crit Rev Toxicol. 2010;40:101–25.
13. Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S. Cancer risk in the rubber industry. A review of the recent epidemiological evidence. Occup Environ Med. 1998;55:1–12.
14. Ward MH, et al. Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline. J Natl Cancer Inst. 1991;83:501–6.
15. Carreón T, Hein MJ, Viet SM, et al. Increased bladder cancer risk among workers exposed to o-toluidine and aniline: a reanalysis. Occup Environ Med. 2010;67:348–50.
16. Sorahan T. Bladder cancer risks in workers manufacturing chemicals for the rubber industry. Occup Med (Lond). 2008;58:496–501.
17. Sorahan T, Hamilton L, Jackson JR. A further cohort study of workers employed at a factory manufacturing chemicals for the rubber industry, with special reference to the chemicals 2-mercaptobenzothiazole (MBT), aniline, phenyl-beta-naphthylamine and o-toluidine. Occup Environ Med. 2000;57:106–15.
18. Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res. 2007;168:1–64.
19. Stasik MJ. Carcinomas of the urinary bladder in a 4-chloro-o-toluidine cohort. Int Arch Occup Environ Health. 1988;60:21–4.
20. Popp W, Schmieding W, Speck M, et al. Incidence of bladder cancer in a cohort of workers exposed to 4-chloro-o-toluidine while synthesising chlordimeform. Br J Ind Med. 1992;49:529–31.
21. Boffetta P, Burstyn I, Partanen T, et al. Cancer mortality among European asphalt workers: an international epidemiological study. I. Results of the analysis based on job titles. Am J Ind Med. 2003;43:18–27.
22. Burstyn I, Kromhout H, Johansen C, et al. Bladder cancer incidence and exposure to polycyclic aromatic hydrocarbons among asphalt pavers. Occup Environ Med. 2007;64:520–6.
23. Blair A, Petralia SA, Stewart PA. Extended mortality follow-up of a cohort of dry cleaners. Ann Epidemiol. 2003;13:50–6.
24. Calvert GM, Ruder AM, Petersen MR. Mortality and end-stage renal disease incidence among dry cleaning workers. Occup Environ Med. 2011;68:709–16.
25. Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, Weiderpass E, Kjaerheim K. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48(5):646–790.
26. Silverman DT, Levin LI, Hoover RN. Occupational risks of bladder cancer in the United States: II Nonwhite men. J Natl Cancer Inst. 1989;81:1480–3.
27. Kogevinas M, 't Mannetje A, Cordier S, Ranft U, González CA, Vineis P, Chang-Claude J, Lynge E, Wahrendorf J, Tzonou A, Jöckel KH, Serra C, Porru S, Hours M, Greiser E, Boffetta P. Occupation and bladder cancer among men in Western Europe. Cancer Causes Control. 2003;14:907–14.
28. Attfield MD, Schleiff PL, Lubin JH, Blair A, Stewart PA, Vermeulen R, Coble JB, Silverman DT. The diesel exhaust in miners study: a cohort mortality study with emphasis on lung cancer. J Natl Cancer Inst. 2012;104:869–83.
29. Mannetje A, Kogevinas M, Chang-Claude J, Cordier S, Gónzalez CA, Hours M, et al. Occupation and bladder cancer in European women. Cancer Causes Control. 1999;10:209–17.
30. Wernli KJ, Ray RM, Gao DL, Thomas DB, Checkoway H. Cancer among women textile workers in Shanghai, China: overall incidence patterns, 1989–1998. Am J Ind Med. 2003;44(6):595–9.
31. Vineis P, Pirastu R. Aromatic amines and cancer. Cancer Causes Control. 1997;8:346–55.
32. Case RA, Hosker ME, McDonald DB, Pearson JT. Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. Part I. The role of aniline, benzidine, alpha-naphthylamine, and beta-naphthylamine. 1954. Br J Ind Med. 1993;50:389–411.

33. Decarli A, Peto J, Piolatto G, La Vecchia C. Bladder cancer mortality of workers exposed to aromatic amines: analysis of models of carcinogenesis. Br J Cancer. 1985;51:707–12.
34. Meigs JW, Marrett LD, Ulrich FU, Flannery JT. Bladder tumor incidence among workers exposed to benzidine: a thirty-year follow-up. J Natl Cancer Inst. 1986;76:1–8.
35. Schulte PA, Knut R, Hemstreet GP, Altekruse EB, Gullen WH, Tillett S, Allsbrook WC, Crosby JH, Witherington R, Stringer W, Brubaker MM. Risk factors for bladder cancer in a cohort exposed to aromatic amines. Cancer. 1986;58:2156–62.
36. Risch HA, Burch JD, Miller AB, Hill GB, Steele R, Howe GR. Dietary factors and the incidence of cancer of the urinary bladder. Am J Epidemiol. 1988;127(6):1179–91.
37. Sorahan T, Sole G. Coarse fishing and urothelial cancer: a regional case-control study. Br J Cancer. 1990;62:138–41.
38. IARC. Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Volume 28. The rubber industry. Lyon: International Agency for Research on Cancer; 1982.
39. Checkoway H, Smith AH, McMichael AJ, Jones FS, Monson RR, Tyroler HA. A case-control study of bladder cancer in the United States rubber and tyre industry. Br J Ind Med. 1981;38(3):240–6.
40. Delzell E, Monson R. Mortality among rubber workers. III. Cause-specific mortality, 1940–1978. J Occup Med. 1981;23:677–84.
41. Kogevinas M, Garcia-Closas M, Trichopoulos D. Urinary bladder cancer: chapter 22. In: Adami HO, Hunter D, Trichopoulos D, editors. Textbook of cancer epidemiology. 2nd ed. New York: Oxford University Press; 2007. p. 573–96.
42. Taeger D, Weiland SK, Sun Y, Keil U, Straif K. Cancer and non-cancer mortality in a cohort of recent entrants (1981–2000) to the German rubber industry. Occup Environ Med. 2007;64(8):560–1.
43. Siemiatycki J, Dewar R, Nadon L, Gerin M. Occupational risk factors for bladder cancer: results from a case-control study in Montreal, Quebec, Canada. Am J Epidemiol. 1994;140:1061–80.
44. IARC. Monographs on the evaluation of carcinogenic risks to humans, vol. 100 F. A review of human carcinogens. Part F: Chemical agents and related occupations/IARC working group on the evaluation of carcinogenic risks to humans (2009). Lyon:IARC;2012.
45. Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control. 1997;8:444–72.
46. IARC. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures, Monographs on the evaluation of carcinogenic risks to humans, vol. 92. Lyon: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; 2010.
47. Partanen T, Boffetta P. Cancer risk in asphalt workers and roofers: review and meta-analysis of epidemiologic studies. Am J Ind Med. 1994;26(6):721–40.
48. Claude J, Kunze E, Frentzel-Beyme R, Paczkowski K, Schneider J, Schubert H. Life-style and occupational risk factors in cancer of the lower urinary tract. Am J Epidemiol. 1986;124:578–89.
49. Jensen OM, Wahrendorf J, Knudsen JB, Sorensen BL. The Copenhagen case-referent study on bladder cancer. Risks among drivers, painters and certain other occupations. Int J Cancer. 1987;13:129–34.
50. Schifflers E, Jamart J, Renard V. Tobacco and occupation as risk factors in bladder cancer: a case-control study in southern Belgium. Int J Cancer. 1987;39:287–92.
51. Silverman D, Morrison A, Devesa S. Bladder cancer. In: Schottenfeld D, Fraumeni J, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 1996. p. 1156–79.
52. Steineck G, Plato N, Gerhardsson M, Norell SE, Hogstedt C. Increased risk of urothelial cancer in Stockholm during 1985–87 after exposure to benzene and exhausts. Int J Cancer. 1990;45(6):1012–7.
53. Bonassi S, Merlo F, Pearce N, Puntoni R. Bladder cancer and occupational exposure to polycyclic aromatic hydrocarbons. Int J Cancer. 1989;44(4):648–51.
54. Clavel J, Mandereau L, Limasset JC, Hemon D, Cordier S. Occupational exposure to polycyclic aromatic hydrocarbons and the risk of bladder cancer: a French case-control study. Int J Epidemiol. 1994;23:1145–53.
55. Band PR, Le ND, MacArthur AC, Fang R, Gallagher RP. Identification of occupational cancer risks in British Columbia: a population-based case-control study of 1129 cases of bladder cancer. J Occup Environ Med. 2005;47(8):854–8.
56. Kellen E, Zeegers M, Paulussen A, Vlietinck R, Vlem EV, Veulemans H, Buntinx F. Does occupational exposure to PAHs, diesel and aromatic amines interact with smoking and metabolic genetic polymorphisms to increase the risk on bladder cancer? The Belgian case control study on bladder cancer risk. Cancer Lett. 2007;245(1–2):51–60.
57. Siemiatycki J, Gerin M, Stewart P, Nadon L, Dewar R, Richardson L. Associations between several sites of cancer and ten types of exhaust and combustion products. Results from a case-referent study in Montreal. Scand J Work Environ Health. 1988;14(2):79–90.
58. IARC. Painting, firefighting, and shiftwork, Monographs on the evaluation of carcinogenic risks to humans, vol. 98. Lyon: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; 2010.
59. La Vecchia C, Tavani A. Epidemiological evidence on hair dyes and the risk of cancer in humans. Eur J Cancer Prev. 1995;4:31–43.
60. IARC. Dry cleaning, some chlorinated solvents and other industrial chemicals, Monographs on the evaluation of carcinogenic risks to humans, vol. 63. Lyon: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; 1995.
61. Lynge E, Andersen A, Rylander L, et al. Cancer in persons working in dry cleaning in the Nordic countries. Environ Health Perspect. 2006;114:213–9.
62. Guha N, Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Baan R, Mattock H, Straif K, International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of trichloroethylene, tetrachloroethylene, some other chlorinated solvents, and their metabolites. Lancet Oncol. 2012;13(12):1192–3.
63. IARC. Printing processes and printing inks, carbon black and some nitro compounds, Monographs on the evaluation of carcinogenic risks to humans, vol. 65. Lyon: International Agency for Research on Cancer; 1996.
64. Samanic CM, Kogevinas M, Silverman DT, Tardón A, Serra C, Malats N, Real FX, Carrato A, García-Closas R, Sala M, Lloreta J, Rothman N, Dosemeci M. Occupation and bladder cancer in a hospital-based case-control study in Spain. Occup Environ Med. 2008;65:347–53.
65. IARC. IARC working group on the evaluation of carcinogenic risks to humans. Some flame retardants and textile chemicals, and exposures in the textile manufacturing industry, vol. 48. Lyon: IARC; 1990.
66. Cartwright R. Occupational bladder cancer and cigarette smoking in West Yorkshire. Scand J Work Environ Health. 1982;8 Suppl 1:79–82.
67. Cordier S, Clavel J, Limasset JC, Boccon-Gibod L, Moua NLE, Mandereau L, et al. Occupational risks of bladder cancer in France: a multicentric case-control study. Int J Epidemiol. 1993;22:403–11.
68. González CA, López-Abente G, Errezola M, Escolar A, Riboli E, Izarzugaza I, Nebot M. Occupation and bladder cancer in Spain: a multi-centre case-control study. Int J Epidemiol. 1989;18(3):569–77.
69. Vineis P, Magnani C. Occupation and bladder cancer in males: a case-control study. Int J Cancer. 1985;35:599–606.

70. Kabat GC, Dieck GS, Wynder EL. Bladder cancer in nonsmokers. Cancer. 1986;57(2):362–7.
71. Morrison AS, Ahlbom A, Verhoek WG, Aoki K, Leck I, Ohno Y, Obata K. Occupation and bladder cancer in Boston, USA, Manchester, UK, and Nagoya, Japan. J Epidemiol Community Health. 1985;39:294–300.
72. Silverman DT, Levin L, Hoover RN. Occupational risks of bladder cancer among white women in the United States. Am J Epidemiol. 1990;132:453–61.
73. Serra C, Kogevinas M, Silverman DT, Turuguet D, Tardon A, Garcia-Closas R, Carrato A, Castaño-Vinyals G, Fernandez F, Stewart P, Benavides FG, Gonzalez S, Serra A, Rothman N, Malats N, Dosemeci M. Work in the textile industry in Spain and bladder cancer. Occup Environ Med. 2008;65:552–9.
74. Cole P, Hoover R, Friedell GH. Occupational and cancer of the lower urinary tract. Cancer. 1972;29:1250–60.
75. Iscovich J, Castelletto R, Esteve J, Munoz N, Colanzi R, Coronel A, et al. Tobacco smoking, occupational exposure and bladder cancer in Argentina. Int J Cancer. 1987;40:734–40.
76. Schoenberg JB, Stemhagen A, Mogielnicki AP, Altman R, Abe T, Mason TJ. Case-control study of bladder cancer in New Jersey. I. Occupational exposures in white males. J Natl Cancer Inst. 1984;72(5):973–81.
77. Malker HS, McLaughlin JK, Silverman DT, Ericsson JL, Stone BJ, Weiner JA, Malker BK, Blot WJ. Occupational risks for bladder cancer among men in Sweden. Cancer Res. 1987;47:6763–6.
78. Porru S, Aulenti V, Donato F, Boffetta P, Fazioli R, CoscianiCunico S, et al. Bladder cancer and occupation: a case-control study in northern Italy. Occup Environ Med. 1996;53:6–10.
79. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Occupation and the risk of bladder cancer. Int J Epidemiol. 1990;19:264–8.
80. Barbone F, Franceschi S, Talamini R, Bidoli E, La Vecchia C. Occupation and bladder cancer in Pordenone (North-East Italy): a case-control study. Int J Epidemiol. 1994;23:58–65.
81. 't Mannetje A, Pearce N. Bladder cancer risk in sales workers: artefact or cause for concern? Am J Ind Med. 2006;49(3):175–86.
82. Anton-Culver H, Lee-Feldstein A, Taylor TH. Occupation and bladder cancer risk. Am J Epidemiol. 1992;136(1):89–94.
83. Maffi L, Vineis P. Occupation and bladder cancer in females. Med Lav. 1986;77(5):511–4.
84. Piper JM, Matanoski GM, Tonascia J. Bladder cancer in young women. Am J Epidemiol. 1986;123:1033–42.
85. Swanson GM, Burns PB. Cancer incidence among women in the workplace: a study of the association between occupation and industry and 11 cancer sites. J Occup Environ Med. 1995;37:282–7.
86. Simpson J, Roman E, Law G, Pannett B. Women's occupation and cancer: preliminary analysis of cancer registrations in England and Wales, 1971-1990. Am J Ind Med. 1999;36:172–85.
87. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981;66:1191–308.
88. Vineis P, Simonato L. Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach. Arch Environ Health. 1991;46:6–15.
89. Brown T, Slack R, Rushton L. British occupational cancer burden study group. Occupational cancer in Britain. Urinary tract cancers: bladder and kidney. Br J Cancer. 2012;107 Suppl 1:S76–84.
90. Pearce N, Matos E, Vainio H, Boffetta P, Kogevinas M, editors. Occupational cancer in developing countries. IARC Scientific Publications No 129. Lyon: IARC; 1994. p. 63–95.
91. Silverman DT, Devesa SS, Moore LE, Rothman N. Bladder cancer. In: Schottenfeld D, Fraumeni J, editors. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006. p. 1101–27.
92. Teschke K, Ahrens W, Andersen A, Boffetta P, Fincham S, Finkelstein M, Henneberger P, Kauppinen T, Kogevinas M, Korhonen K, Liss G, Liukkonnen T, Osvoll P, Savela A, Szadkowska-Stanczyk I, Westberg H, Widerkiewicz K. Occupational exposure to chemical and biological agents in the nonproduction departments of pulp, paper, and paper product mills: an international study. Am Ind Hyg Assoc J. 1999;60(1):73–83.
93. Kauppinen T, Toikkanen J, Pukkala E. From cross-tabulations to multipurpose exposure information systems: a new job-exposure matrix. Am J Ind Med. 1998;33(4):409–17.
94. Bouyer J, Hémon D. Retrospective evaluation of occupational exposures in population based case-control studies. General overview with special attention to job exposure matrices. Int J Epidemiol. 1993;22:S57–67.
95. Siemiatycki J, editor. Risk factors for cancer in the workplace. Boca Raton: CRC Press; 1991.
96. Peters S, Kromhout H, Portengen L, Olsson A, Kendzia B, Vincent R, Savary B, Lavoué J, Cavallo D, Cattaneo A, Mirabelli D, Plato N, Fevotte J, Pesch B, Brüning T, Straif K, Vermeulen R. Sensitivity analyses of exposure estimates from a quantitative job-exposure matrix (SYN-JEM) for use in community-based studies. Ann Occup Hyg. 2013;57(1):98–106.
97. IARC. Pathology and genetics of tumors of the urinary system and male genital organs. In: Epstein JI, Eble JN, Sesterhenn I, Sauter G, editors. World health organization classification of tumors, Volume 7. Lyon: IARC Press; 2004. p. 93.
98. Kauppinen T, Toikkanen J, Pedersen D, Young R, Ahrens W, Boffetta P, Hansen J, Kromhout H, Maqueda J, Mirabelli D, de la Orden V, Pannett B, Plato N, Savela A, Vincent R, Kogevinas M. Occupational exposure to carcinogens in the European Union. Occup Environ Med. 2000;57:10–8.
99. Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Wild CP. Preventable exposures associated with human cancers. J Natl Cancer Inst. 2011;103(24):1827–39.
100. Kiemeney LA, Schoenberg M. Familial transitional cell carcinoma. J Urol. 1996;156(3):867–72.
101. Pina K, Hemminki K. Familial bladder cancer in the national Swedish family cancer database. J Urol. 2001;166:2129–33.
102. Li S, Peng Q, Chen Y, You J, Chen Z, Deng Y, et al. DNA repair gene XRCC1 polymorphisms, smoking, and bladder cancer risk: a meta-analysis. PLoS One. 2013;8:e73448.
103. Chao C, Zhang ZF, Berthiller J, Boffetta P, Hashibe M. NAD(P)H:quinone oxidoreductase 1 (NQO1) Pro187Ser polymorphism and the risk of lung, bladder, and colorectal cancers: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15:979–87.
104. Gabbani G, Hou SM, Nardini B, Marchioro M, Lambert B, Clonfero E. GSTM1 and NAT2 genotypes and urinary mutagens in coke oven workers. Carcinogenesis. 1996;17(8):1677–81.
105. Probst-Hensch NM, Bell DA, Watson MA, Skipper PL, Tannenbaum SR, Chan KK, et al. N-acetyltransferase 2 phenotype but not NAT1*10 genotype affects aminobiphenyl-hemoglobin adduct levels. Cancer Epidemiol Biomarkers Prev. 2000;9:619–23.
106. Vineis P, Bartsch H, Caporaso N, Harrington AM, Kadlubar FF, Landi MT, et al. Genetically based N-acetyltransferase metabolic polymorphism and low-level environmental exposure to carcinogens. Nature. 1994;369:154–6.
107. Marcus PM, Hayes RB, Vineis P, Garcia-Closas M, Caporaso N, Autrup H, et al. N-acetyltransferase 2 acetylation status, and bladder cancer risk: a case-series meta-analysis of a gene–environment interaction. Cancer Epidemiol Biomarkers Prev. 2000;9:461–7.
108. Vineis P, Marinelli D, Autrup H, Brockmoller J, Cascorbi I, Daly AK, et al. Current smoking, occupation, N-acetyltransferase-2 and bladder cancer: a pooled analysis of genotype-based studies. Cancer Epidemiol Biomarkers Prev. 2001;10(12):1249–52.

109. Rothman N, Garcia-Closas M, Chatterjee N, Malats N, Wu X, Figueroa JD, et al. A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. Nat Genet. 2010;42(11):978–84.

110. Garcia-Closas M, Rothman N, Figueroa JD, Prokunina-Olsson L, Han SS, Baris D, et al. Common genetic polymorphisms modify the effect of smoking on absolute risk of bladder cancer. Cancer Res. 2013;73(7):2211–20.

Malignant Tumors of the Central Nervous System

27

Anssi Auvinen and Peter D. Inskip

Keywords
Central nervous system tumors • Brain tumors • Agricultural workers • Physicians • Ionizing radiation

Classification

Malignant tumors of the central nervous system (CNS) occur mainly in the brain, as the anatomic site is in the other parts of the CNS only in <10 %. Less than 10 % of gliomas are spinal, and their most common histological type is ependymoma, but low-grade astrocytomas are not infrequent. Gangliogliomas occur also in the spine and are most common in adolescence. Optic nerve gliomas are typically childhood tumors related to neurofibromatosis type I and account for 1 % of all intracranial tumors.

Brain cancer is an extremely heterogeneous group of tumors with 37 entries under gliomas alone in ICD-O-3 and 54 codes for neuroepithelial tumors in the WHO classification [1]. The grouping of brain cancer is based on histopathology, i.e., morphological appearance in microscopic examination, with a relation to the presumed cell type of origin (Fig. 27.1). Malignant tumors of the brain arise primarily from the neuroepithelial tissue, mainly glial cells and their precursors. Glial cells include astrocytes and oligodendrocytes, which constitute 85 % of the cells of the brain. The diversity of diagnostic entries involves, however, a large number of relatively rare tumor types, and astrocytic tumors make up at least two thirds of all primary brain cancers, more when only adults are concerned. Other main types of gliomas include oligodendroglioma, ependymoma, mixed oligoastrocytoma, and anaplastic ganglioglioma. Rare malignant tumors include astroblastoma (as well as germ cell tumors such as germinoma and choriocarcinoma, which appear mainly in children). In children, embryonal tumors are common, most notably medulloblastoma and primitive neuroepithelial tumor (PNET), but they are not discussed here. CNS malignancies can also arise from the lymphatic system in the CNS (lymphoma, with a frequency 2–5 % of the neuroepithelial tumors) and connective tissue (sarcoma, rare).

Astrocytomas account for three quarters of all gliomas and include diffuse astrocytoma (WHO grade II, approximately 5 % of all astrocytic tumors, subdivided into fibrillary, gemistocytic, and protoplasmic types), anaplastic astrocytoma (WHO grade III, 10 % of all astrocytomas), and GBM (WHO grade IV, also called GBM multiforme, 60 % of astrocytomas). Some of these tumors have a tendency to progress toward a more malignant phenotype. Grade I astrocytomas (pilocytic and subependymal giant cell astrocytoma, 5–10 % of all astrocytic tumors) appear mainly in children. The two key features defining the grade are anaplasia (assessed as nuclear atypia) and proliferative capacity (indicated by mitotic activity), as well as neovascularization and necrosis (the latter two features defining glioblastoma). Morphologically, grade II tumors show atypia, grade III also increased mitotic activity, and grade IV vascular proliferation [2]. Perhaps the sharpest distinction is between grade I and grade II astrocytoma, which appear to be largely separate entities. The other neuroepithelial tumors, i.e., oligodendroglioma and oligoastrocytoma, are also divided into grades II and III (anaplastic tumors), with also some grade I tumor

A. Auvinen, MD, PhD (✉)
Department of Epidemiology, University of Tampere, Medisiinarinkatu 3, Tampere 33014, Finland
e-mail: anssi.auvinen@uta.fi

P.D. Inskip, ScD
Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_27,

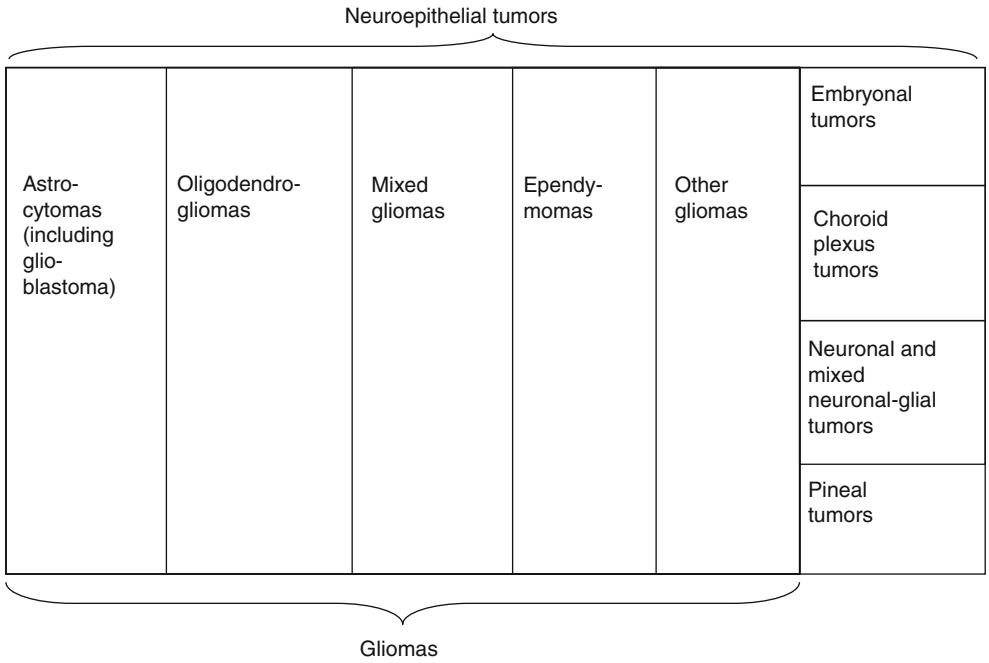


Fig. 27.1 Brain tumor types

Note: The sizes of the boxes do not represent the frequencies of the tumor types

Table 27.1 A summary of common genetic abnormalities in astrocytomas

Low-grade astrocytoma	High-grade astrocytoma
BRAF mutation	PTEN mutation
IDH1 mutation	EGFR, PDGFR amplification
TP53 mutation	P16/CDKN2A loss/ downregulation/mutation
PDGF overexpression	MDM2/MDM4 amplification

types for ependymoma (subependymoma and myxopapillary ependymoma). Grades I–II are sometimes referred to as low-grade tumors, while III–IV are termed high-grade cancers.

Pathogenesis

The presumed cell type of origin for astrocytic tumors is the glial cell, though it remains uncertain if the main route of gliomagenesis is dedifferentiation of mature cells or transformation of stem or progenitor cells [3]. Within a single tumor, heterogeneity in various cellular features can be found, including a mixed pattern of differentiation. Diverse genetic alterations are encountered in gliomas, and genetic characterization of brain cancers is becoming increasingly important in the diagnosis of glioma, complementing classic morphological criteria [4]. For astrocytoma, the diversity of genetic and molecular alterations increases with grade (Table 27.1).

Changes involving the BRAF gene involved in the mitogen-activated protein kinase (maPK) pathway occur mainly in low-grade glioma. Other early events in glioma tumorigenesis include isocitrate dehydrogenase (IDH1) and p53 mutations, as well as platelet-derived growth factor (PDGF) overexpression and chromosome 1p loss or 1p/19q codeletion [5, 6]. Such characteristics are found commonly in grade II tumors. IDH1 mutations are also associated with improved survival.

The spectrum of genetic changes in anaplastic astrocytoma resembles those in GBM, but with lower frequency, e.g., anaplastic tumors commonly harbor phosphatase and tensin homologue (PTEN) mutations, epidermal growth factor (EGFR) abnormalities, and p16/CDKN2A (cyclin-dependent kinase inhibitor) loss or downregulation [5].

Multiple molecular and chromosomal abnormalities are typical for GBM. Features that can distinguish glioblastoma from anaplastic astrocytoma include p16 and PTEN deletions or mutations, as well as EGFR amplification [2]. Primary GBM arises de novo, while the less common secondary GBM is preceded by a lower-grade astrocytoma and evolves through gradual dedifferentiation [5]. The two tumor types are thought to involve partly different genetic mechanisms. Epidermal growth factor receptor (EGFR) mutation, overexpression, or amplification is common in primary GBM [3, 6]. Somewhat in an analogous fashion to EGFR in primary GBM, PDGFR amplification appears important for secondary GBM [5]. IDH1 and IDH2 mutations are also typical for secondary, but uncommon in primary GBM [6]. Both are surface receptors for growth factors involved in controlling cell proliferation with ras- and Akt-mediated signaling pathways linked to the cyclin-dependent

kinase CDKN2 [3]. Another related event is MDM2/MDM4 (murine double minute) amplification [6]. The normal function of EGFR is transducing both EGF and TGF signals from the membrane to the cell, resulting in tyrosine kinase activation and other mechanisms increasing proliferation and decreasing apoptosis. Amplification or overexpression of MDM2, which codes for a transcription factor that interacts with p53, occurs in about one-tenth of GBM [5]. PTEN mutations (or 10q loss) are found in a third of GBM cases, but rarely encountered in low-grade glioma [6]. Methylguanine methyl transferase (MGMT) promoter methylation is found in both glioblastoma and other gliomas, and it can be used to assess sensitivity to alkylating agent-based chemotherapy. In terms of chromosomal alterations, loss of heterozygosity on chromosome 10 is common in GBM [2].

In oligodendroglioma, the combined LOH of 1p and 19q is common (>50 %) and also important in the sense that it predicts a favorable therapeutic response and survival [5]. p53 mutations, on the other hand, are clearly less frequent than in other gliomas. IDH1 mutations are encountered in more than half of oligodendrogliomas. Downregulation of PTEN is also common, occurring in roughly half of the tumors and predicts poorer prognosis [5].

IDH1 mutations also are common in oligodendroglioma and oligoastrocytoma (frequently co-occurring with p53 mutation or 1p19q loss), but not in ependymoma. In ependymoma, the loss of 21q is the most frequent chromosomal aberration, and genetic alterations include increased expression of cell cycle-related NOTCH/JAGGED pathway and EphB/ephrin signaling.

Occurrence

Brain and other CNS cancers make up approximately 2 % of all primary cancers and, with a global total of 238,000 cases, rank as the 16th most common type of cancer [7]. The age-standardized incidence rates (world standard population) reported for different populations are generally of the order of 5–7 per 100,000 person-years for men and around 3–6 per 100,000 in women (Cancer Incidence in Five Continents) [8]. The incidence of benign tumors is higher than that for malignant tumors (the U.S. NCI cancer registration program Surveillance Epidemiology and End Results, SEER). When comparing different sources, the estimates are strongly affected by the reference population used in age standardization. For instance, the weighting factor for the age group 0–19 years ranges from <20 to >30 % in widely used standard populations, and weights for the age group 75+ years range from 2 to 8 %, with the world population representing the youngest age structure. The incidence of brain cancer reported by SEER with US standard population as reference is nearly a quarter higher than that shown using the world standard population. Examination of published age-specific incidence rates suggests comparability between the United States, England, and Nordic countries. Though the data reported are not uniform, the incidence rate in the age group around 50 years for both sexes combined was roughly 6–7 per 100,000 in the Central Brain Tumor Registry of the U.S. (CBTRUS) for all neuroepithelial tumors (mostly gliomas) and for glioma in the Nordic countries [9]. Also for high-grade glioma, incidence rates of high-grade astrocytoma around 4–5 per 100,000 are seen in both England and the United States [10, 11]. The quality of the data also depends on completeness of coverage and ascertainment, availability of histological diagnosis, exclusion of metastases, and extent of double counting. As is apparent from the gender-specific rates, there is a slight male predominance in astrocytic tumors, with a male to female ratio of 1.2–1.5:1, with a slightly lower sex ratio for oligodendroglioma and little gender difference for ependymoma. In the United States, incidence rates for whites are 1.5–2-fold higher than among blacks, while the rates for Hispanics are intermediate.

As for specific subtypes, the incidence of glioblastoma has ranged from 3 to 5 per 100,000 among men and 2–3 per 100,000 in women (Fig. 27.2). Anaplastic astrocytomas constitute less than 10 % of all gliomas and diffuse astrocytoma usually less than half of this. Incidence rates of around 0.3–0.4 per 100,000 have been reported for oligodendroglioma, while rates for ependymoma are slightly lower [10, 11, 9].

The classification of nervous system tumors is very heterogeneous in different data sources, which makes compilation of information in a consistent fashion challenging. First, brain tumors are not always reported separately from other central nervous system or nervous system tumors, though brain tumors make up approximately 90 % of CNS tumors. The brain is the site of gliomas in >95 % of cases, though spinal and optic nerve gliomas also occur. Second, benign tumors sometimes also are included. Meningiomas can be equally common as gliomas among women, while the incidence of schwannomas (neurinomas) occurring particularly in the vestibular part of the eighth cranial or acoustic nerve has ranged from 0.5 to1.5 per 100,000. Yet another factor to be considered is the proportion of microscopically verified diagnoses, as brain metastases from other cancer sites (particularly breast and lung) are more common than primary brain cancer. Finally, the proportion of cases with specific histological type versus unspecified glioma or astrocytoma affects the rates by tumor subtype.

Of the key sources of cancer occurrence data, for instance, GloboCan and NordCan include only the brain and other nervous system without breakdown by anatomic site. This also applies to SEER statistical tables, though data by anatomic

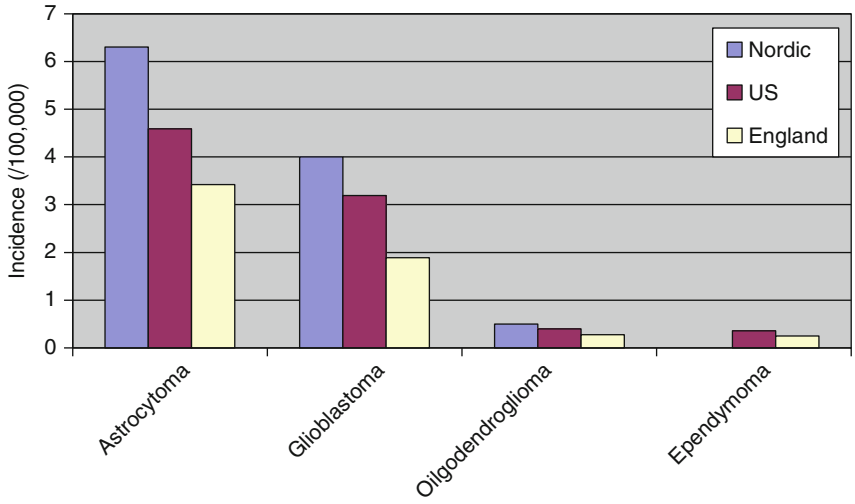


Fig. 27.2 Brain tumor incidence

site can be obtained using SEERStat [12]. Until recently, SEER covered only malignant tumors, and GloboCan still does, while NordCan includes both malignant and benign brain tumors. In the United States, the CBTRUS compiles detailed information on malignant and benign brain tumors from 12 cancer registries.

The age-specific incidence of all brain tumors combined in adults increases monotonically with age up to approximately 75 years, but then flattens or turns downward, possibly reflecting under-ascertainment at older ages rather than a true downturn in incidence. The spectrum of astrocytic tumors changes with age, with the proportion of poorly differentiated tumors increasing. For instance, diffuse astrocytomas tend to occur approximately 10 years earlier than anaplastic astrocytoma and glioblastoma also in on average 10 years older patients [2]. The age gradient for astrocytic tumors is steeper than for ependymoma and oligodendroglioma, and, consequently, the proportion of astrocytic tumors increases with age.

Some increase in brain cancer incidence over time has been reported in several studies, but it is unclear if they reflect mainly improved comprehensiveness of coverage, quality, and availability of diagnostic technologies, primarily computer-assisted tomography (mainly in the late 1970s and early 1980s) and magnetic resonance imaging (in the 1980s and 1990s). Such increase has been most apparent in the oldest age groups. An increase in incidence from the mid-twentieth century to the 1970s has been reported, particularly in the older age groups; however, relatively stable rates since the 1990s have been reported in several studies in Europe and the United States [9, 13–15].

Variations in availability of detection methods also may explain some of the geographic variation in brain cancer incidence, though the differentials between populations among high-resource countries are not as striking as for some other types of cancer, particularly when comparing Caucasian populations in Europe, North America, and Australasia. In Asia, lower brain tumor rates are reported compared with the Caucasian populations [8]. Within the United States, incidence rates among whites are nearly twice as high as among blacks, but geographic differences within the country (by state) are not striking.

Mortality from brain cancer has been estimated as 2.6 per 100,000 (3.0 for men and 2.2 for women), with 174,000 deaths occurring annually [7] in the world. These figures place brain cancer as the 12th most common cause of cancer death. No substantial increase in brain cancer mortality is obvious from the international compilation of cancer statistics [8]. Mortality reaching up to three quarters of the incidence indicates the poor overall prognosis.

Survival varies by tumor subtype and patient's age. Generally, the outcome of astrocytic tumors is poorer than other gliomas of similar grade. The median survival for glioblastoma is only around 1 year, 2–3 years have been reported for anaplastic (grade III) astrocytoma and 4–8 years for diffuse (grade II) astrocytoma [16, 17–19]. In oligodendroglioma, median survival has been 2–5 years for cases without 1p/19q codeletion and as high as 10+ years for those with this favorable prognostic indicator [20, 21]. For ependymoma, median survival of approximately 10 years has been suggested [22, 23].

Nonoccupational Risk Factors for Brain Cancer in Adults

Few etiologic factors have been firmly established for brain cancer.

A twofold risk of glioma has been found in first-degree relatives of glioma patients [24–28]. A number of rare hereditary syndromes including tuberous sclerosis, Turcot syndrome (involving mutations in the APC- and HNPCC-related genes),

and Li-Fraumeni syndrome (inherited mutation of the p53 gene), as well as neurofibromatosis type 1/2 (NF1/NF2), carry an increased risk of astrocytic tumors (as well as other cancers). However, known hereditary syndromes account for only 1–5 % of all adult brain cancers, as they are very rare (the most common being neurofibromatosis which affects 1/3,000). Genome-wide association studies have indicated some polymorphisms associated with an increased glioma risk, showing odds ratios of 1.2–1.4 [29, 30].

Several studies on the relation between allergic conditions and glioma have consistently shown a reduced risk associated with asthma and eczema by approximately 30 % [31–33], though the evidence is not entirely consistent [34]. Meta-analyses have confirmed the protective effect for asthma, allergy, and eczema [35, 36]. Also, other markers of atopic constitution such as serum IgE levels and use of antihistamines have been associated with a reduced risk [33, 37, 38]. This has been postulated to result from immunological factors, possibly involving increased immunosurveillance with improved antitumor defense mechanisms. The plausibility of the hypothesis is weakened by the lack of a clear association between other immunological conditions and factors with brain cancer. A study focusing on oligodendroglioma showed results that were comparable to glioma: a reduced risk related to allergy and elevated risk for family history of brain tumors [39].

N-nitroso compounds have been associated with brain tumors in animal models. For humans, the exposure patterns are complex, with intake from the diet as well as tobacco and alcohol, with formation, metabolism, and elimination regulated by several hereditary and physiological factors. A meta-analysis did not find consistent evidence for consumption of cured meat, an important dietary source of N-nitroso compounds [40]. Several studies have been conducted on smoking and alcohol use but with inconsistent results [41–43]. A meta-analysis showed a pooled RR of 1.1 for smoking [44]. As for nutritional factors, studies on consumption of coffee and tea or cured meat and fish have not shown consistent results, but some studies have suggested a protective effect of vitamin supplement use [45, 46], which could potentially be related to the N-nitroso compound hypothesis, as some antioxidant vitamins (C and E) reduce formation of such compounds.

Occupational Risk Factors

Exposure Assessment

Several large studies have used job titles as exposure indicators, in some cases only a single occupation was obtained, e.g., from the death certificate. A very crude classification such as “electric occupations” may lack both sensitivity and specificity and even detailed standard classifications may fail to adequately classify people in terms of exposure to a specific agent. More detailed and comprehensive occupational histories are obtained from census data, but sufficient information for assessing presence, intensity, frequency, and duration of exposure to a particular agent can be elicited primarily from personal interview, with information on specific tasks, locations, and processes involved at work. Nevertheless, self-reported exposure information should be assessed in separate validation studies to evaluate the extent of misclassification and bias. In malignant brain tumors, the rapid disease progression and potential deterioration of recall and cognitive abilities pose additional challenges for retrospective collection of exposure data in case-control studies.

The use of job-exposure matrices offers some refinement over occupational title, though the level of information provided depends heavily on the input to the matrix, i.e., level of detail linking tasks, equipment, and facilities to measurements. A key characteristic is homogeneity of exposure within strata, as a small but highly exposed subgroup is difficult to accommodate meaningfully within a stratum. For instance, a job-exposure matrix may accurately reflect exposure within a manufacturing plant, but could add little to job title if applied to a nationwide study. It is difficult to account for changes in exposures over time in particular jobs through the use of job-exposure matrices. Direct measurement of exposure at the relevant time period can be regarded as the gold standard but is achievable only in prospective cohort studies.

Few studies have been able to address the etiology for specific subtypes of brain cancers, particularly other than glioma, due to their rarity. In practice, the results of all studies pertain to astrocytic tumors, above all glioblastoma. In studies prior to the 1990s, brain cancer was rarely distinguished from other central nervous system tumors.

Occupations and Branches of Industry

Putative clusters of brain cancers have been reported from several workplaces including agricultural, health-care, and several chemical industries, but generally investigations have failed to identify an agent that could account for the apparent excess.

Exploratory analyses have given some indications for several job titles and branches of industry. The consistency of the findings across studies has, however, been low, raising the possibility of false-positive results owing to multiple comparisons (some studies have covered up to >100 occupations).

Brain cancer risk among farmers and agricultural workers received attention after several studies had shown increased risks, in particular an early cohort study of pesticide applicators [47]. Prior to the mid-1990s, at least a dozen studies were reported, but with equivocal overall results. Meta-analyses

of some 30 studies conducted up to the mid-1990s showed pooled rate ratios of 1.0–1.3, depending on inclusion criteria [48, 49]. The most recent findings from the Agricultural Health Study do not show excess brain and nervous system cancer incidence or mortality [50, 51]. Some studies have indicated an increased risk of brain cancer in offspring of fathers in agricultural occupations [52–54].

A related occupational group consists of workers involved in pesticide manufacture or spraying (applicators). The epidemiological studies on this population have, however, been based on relatively small numbers of exposed cases. Contacts with farm animals have not been associated with an increased risk [55, 56].

Other studies addressing specific hypotheses have suggested increased risks in petroleum and pulp industries [57–59], but the results have not been consistent. Brain cancer risk among workers in the petrochemical industry was evaluated in more than ten studies in the 1980s, but they failed to provide consistent evidence. A meta-analysis of cohort studies with 350,000 workers in various branches of the petroleum industry showed an overall SMR of 1.01 (95 % CI 0.93–1.09) [60]. An international collaborative cohort study with 60,000 workers in pulp and paper industries did not indicate increased mortality from brain cancer [61].

Increased risks have also been reported for health-care workers, mainly physicians, in several studies [58, 62–68]. Improved diagnostic ascertainment is unlikely to explain the finding for malignant tumors, though no specific agent has been identified. See also below for formaldehyde.

Several studies have evaluated brain cancer risk related to employment in the rubber industry with exposure to dusts, fumes, and solvents, as well as some other carcinogens including aromatic amines. In 1982, IARC concluded that the evidence was inadequate for brain tumors, and the same evaluation was retained in an update in 1998 (IARC). A review covering a total of 90 studies also concluded that the results concerning brain tumors were inconsistent [69].

Some studies have reported elevated risks in the metal industry, but these have been obtained mainly in large exploratory studies [58, 62, 70].

Specific Agents

Ionizing Radiation

Unlike chemical and viral agents, ionizing radiation is unaffected by the blood-brain barrier and other cellular and tissue boundaries and independent of the presence or absence of specific cellular receptors. It deposits energy at random within cells, with most of the associated cellular damage being due to the formation of oxygen-free radicals from water. Ionizing radiation at moderate to high doses is a well-established neurocarcinogen, with most of the evidence coming from studies of persons who received cranial radiotherapy [71, 72] and of survivors of the atomic bomb explosions in Japan [73]. Evidence of carcinogenicity of occupational radiation exposures, which typically involve low doses, is much weaker. A relevant observation from studies of medically irradiated populations is that the risk of brain cancer is inversely associated with age at exposure; risk is considerably higher among those exposed before age ten than at older ages [71, 72]. Worker groups with potential for radiation exposures in excess of those for the general population include radiation workers in the nuclear industry, emergency and cleanup crews exposed from nuclear reactor accidents, underground miners, medical workers who operate x-ray equipment, and airline flight crews exposed to cosmic radiation. Their radiation exposures typically are low in intensity and protracted over a working lifetime, in contrast to the much shorter duration exposures experienced by the atomic bomb survivors and persons receiving radiotherapy. Miners are exposed to alpha-emitting radionuclides primarily through inhalation. Because radiation from alpha particles does not penetrate deeply into tissue, the brain would not receive a large dose.

In a 15-country study of 407,391 radiation workers individually monitored for external radiation, mortality due to brain cancer was not associated with cumulative radiation dose up to 500 mSv (mean, 19 mSv) [74] (Table 27.2). Doses resulted primarily from higher energy photon radiation (x-ray and gamma ray between 100 and 3,000 keV). Among 174,541 radiation workers from the United Kingdom who also were monitored with radiation dosimeters, neither brain cancer incidence nor mortality was associated with lifetime radiation dose over the range of 0–400 mSv (mean, 24.9 mSv) [75]. Preconception radiation exposures did not appear to be associated with an increased risk of childhood cancer, including brain cancer, among offspring of female radiation workers; a weak, unstable association was seen for exposure during pregnancy [76].

After the reactor accident at Chernobyl in April 1986, hundreds of thousands of workers from throughout the former Soviet Union were sent to the area to participate in environmental decontamination work. These workers were allowed to receive up to 25 cGy of external radiation before being sent home. Most workers remained in the area of the reactor for 1–6 months. In a cohort of 10,332 cleanup workers from Estonia and Latvia, brain cancer incidence was increased relative to that in the general populations of those countries (O/E = 2.14; 95 % = 1.07–3.83); however, there was no evidence of a radiation dose-response, and the relationship to radiation exposure remains unclear [77]. The average dose was approximately 0.1 Gy. No similar excess has been reported in other cleanup worker cohorts [78].

Although brain cancer has been reported to be increased in some groups of health professionals with potential expo-

Table 27.2 Cohort studies of ionizing radiation and brain cancer

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	Number of cases/deaths	Relative risk (95 % CI)	Adjustment for potential confounders	Comments
Cardis et al. [74]; 15 countries	407,391 nuclear industry workers	Dosimetric history based on personal dosimeters	Cumulative dose (mSv)	Deaths	O/E	Sex, age, calendar period, SES	O/E calculated from data in paper
			<5	153	1.01		Expected numbers based on internal comparison population
			5–<10	19	0.83		ERR/Sv <0
			10–<20	25	1.09		
			20–<50	25	1.17		
			50–<100	5	0.51		
			100–<150	5	1.52		
			150–<200	3	2.00		
			200–299	0	0.00		
Muirhead et al. [75]; United Kingdom; 1965–2001	174,541 radiation workers with follow-up from 1965 to 2001	Radiation dose records	Lifetime dose (mSv)	Cases	O/E	Age, gender, calendar period, industrial classification, first employer	O/E calculated from data in paper
			<10	199	1.01		ERR/Sv = 0.21, 95 % CI – 1.49–0.69
			10–<20	48	1.19		
			20–<50	45	0.96		
			50–<100	21	0.84		
			100–<200	14	0.90		
			200–<400	7	0.80		
			400+	3	0.69		

sure to x-rays, including dentists, dental nurses, physicians, and veterinarians, they may also be exposed to other agents, such as mercury, chemotherapeutic agents, anesthetic gases, or microbial pathogens [79]. Brain cancer incidence was not significantly elevated among 27,011 medical x-ray workers relative to that in a comparison group of 25,782 other medical specialists with lesser opportunity for occupational exposure to radiation [80]. Individual doses were not available.

The use of interventional radiology, such as for cardiac catheterization, may entail larger doses to physicians and staff, as these procedures last minutes rather than seconds, with the x-ray beam on for fluoroscopic imaging [81]. An average annual dose of 20 mSv was estimated for physicians performing 200 procedures per year [82]. Insofar as the head is unshielded, concerns have been raised about a possible increased risk of brain cancer [81, 83, 84], but there are few data.

Flight crews are exposed to cosmic radiation – primarily neutrons and gamma rays – with dose increasing with altitude and proximity to polar regions [85]. Annual dose equivalents are low, with estimates of between 2 and 5 mSv [85]. Based on results from the radiation worker studies, one would not expect increased risk of brain cancer due to radiation among members of flight crews, and, indeed, excesses of brain cancer have not been reported. No excess brain cancer mortality or incidence was reported among pilots in two large cohort studies [86, 87]. A case-control study of brain cancer within a cohort of approximately 880,000 US Air Force personnel reported no association with ionizing radiation [88].

In summary, available data do not support the view that occupational exposure to low-dose ionizing radiation is a major cause of brain cancer. If there is a risk, it may be that it is too small to detect reliably in epidemiological studies.

Nonionizing Radiation

Extremely low-frequency (ELF) magnetic fields (*MF*). Occupational groups believed to have the potential for high exposure to magnetic fields include electronics, electrical, and electric utility workers, and there have been several reports of modestly increased risks for brain cancer in these groups. Thomas et al. [89] reported elevated mortality due to brain cancer among electrical and electronics workers (OR = 1.6; 95 % CI 1.0–2.4), but many such workers are also exposed to soldering fumes, solvents, and radiofrequency radiation. Robinson et al. [90] noted significant excess mortality due to brain tumors among electrical workers in the US construction industry (proportionate mortality ratio = 136).

In a study of 138,905 electric utility workers from five electric power companies in the United States, brain cancer mortality was associated with indices of magnetic field exposure, increasing by a factor of 1.94 per microT-year [91] (Table 27.3). Exposure was estimated by linking work histories to data from 2,842 workshift magnetic field measurements. A nested case-control study of brain cancer among electric utility workers from Canada and France reported a nonsignificant elevation in risk among workers with the

Table 27.3 Cohort studies of extremely low-frequency radiation and brain cancer

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	Number of cases/deaths	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Savitz and Loomis [91]; United States; 1950–1986	138,905 electric utility workers employed between 1950 and 1986; vital status ascertainment through 1988	Linkage of work histories with work shift magnetic field measurements	Total exposure (microT-years)	Deaths		Age, calendar year, race, social class, work status (active/inactive), PCB and solvent exposure	
			0–<0.6	41	1.00		
			0.6–<1.2	34	1.61 (0.99–2.63)		
			1.2–<2.0	26	1.47 (0.84–2.56)		
			2.0–<4.3	27	1.65 (0.92–2.95)		
			≥4.3	16	2.29 (1.15–4.56)		
Theriault et al. [92]; Canada and France; 1970–1989	223,292 electric utility workers; observation period 1970–1989; median length of employment 23.7–27.0 years	Combining work histories with estimates of exposure for each job held	Years of exposure to magnetic fields	Cases		Year of birth, SES, ionizing radiation, potential chemical confounders (as identified by IARC)	Nested case-control design, with matching on year of birth
			(≥median exposure)	42	1.18 (0.63–2.21)		
			0–5	43	1.87 (0.93–3.75)		
			0–20	14	1.05 (0.20–5.38)		
			≥20	44	1.95 (0.98–3.86)		

highest cumulative magnetic field exposures (OR = 1.95 95 % CI 0.76–5.00) [93]. Sahl et al. [94] linked workplace magnetic field measurements with job history workers for a cohort of 36,221 electric utility workers. Results did not suggest an association of magnetic field exposure with brain cancer, with odds ratios close to 1.0 for all categories of exposure.

Transportation workers and welders also have potential for high magnetic field exposure. In a study of Swiss railway workers with median cumulative exposure of 120 microtesla-years, mortality due to brain tumors was not associated with magnetic field exposure [95]. Håkansson et al. [96] linked a large cohort of Swedish workers employed in occupations that involved resistance welding and observed an association between estimated ELF-MF exposure and brain cancer among women, but not men.

Several case-control studies of brain cancer conducted within the general population rather than in specific occupational cohorts also have described associations with occupational exposure to magnetic fields. Villeneuve et al. 97 reported a nonsignificantly elevated risk of brain cancer among men who had ever held a job with an average magnetic field exposure greater than 0.6 microT relative to those with exposures <0.3 microT (OR = 1.33; CI 0.75–2.36); the association reached statistical significance for glioblastoma (OR = 5.36; CI 1.16–24.78) (Table 27.4). A small study in Sweden (84 cases) found that the relative risk for magnetic field exposure increased from 1.0 when analyses were based on "electrical occupations" as the indicator of exposure to 1.9 (95 % CI 0.8–5.0) when based on measurements [100]. A larger study from the United States (489 cases) evaluated glioma risk with respect to four magnetic field exposure metrics: maximum exposed job, total years of exposure above 1.5 mG, cumulative lifetime exposure, and average lifetime exposure; none of these metrics showed an association with risk of glioma [98]. Results from an Australian study (416 glioma cases) also yielded null results for occupational exposure to ELF radiation, both for glioma overall [99] and for high- and low-grade glioma separately [101].

The possibility has been considered that an effect of occupational exposure to ELF-MF might depend on interactions with chemical substances [102]. The authors noted that an effect on glioma risk was not seen in the absence of chemical agents, but was indicated if there was simultaneous exposure to solvents, pesticides/herbicides, or lead.

The possible role of parental occupational exposures on risk of brain cancer in their offspring also has been examined. A study conducted in Sweden did not find evidence of an association (RR = 0.5; 95 % CI 0.3–1.0) [103]. A German study also found no evidence of an association with preconceptional parental ELF-MF exposure [104].

In summary, evidence of a causal association between brain cancer and occupational exposure to ELF-MF is inconsistent and does not suggest a substantial effect. In a meta-analysis focusing on occupational exposures and considering all relevant publications between 1993 and 2007, Kheifets et al. [105] reported a pooled excess risk estimate of 10 % but observed that internal patterns of association beyond this summary risk estimate did not indicate that electromagnetic fields were responsible for the excess.

Radiofrequency (RF) radiation. The International Agency for Research on Cancer (IARC) recently reviewed the evidence concerning RF radiation and rated it as a "possible human carcinogen" (class 2B), with specific reference to glioma [106]; however, the matter remains controversial. Mobile phone use accounts for the largest part of population exposure to RF radiation. Published epidemiological studies

Table 27.4 Case-control studies of extremely low-frequency radiation and brain cancer

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Villeneuve et al. [97]; Canada; 1994–1997	543 histologically confirmed cases of brain cancer identified through provincial cancer registries; males only	543 population-based controls individually matched on age	Mail questionnaire combined with expert review	Average exposure (microT) <0.3 0.3–<0.6 ≥0.6	1.00 0.89 (0.57–1.37) 1.72 (0.80–3.66)	Age, occupational exposure to ionizing radiation and vinyl chloride	
Coble et al. [98]; United States; 1994–1998	489 histologically confirmed glioma cases enrolled through three hospitals; age 18–90 years	799 hospital-based control frequency matched on age, sex, race/ethnicity, hospital, and distance of residence from hospital	In-person interview combined with job-exposure matrix and review of work history by industrial hygienist	Lifetime average (mG) ≤1.5 1.5–<3 ≥3.0	 1.0 1.0 (0.8–1.3) 0.9 (0.6–1.3)	Gender, age, and hospital No confounding by education or race/ethnicity	Questionnaire included detailed job-specific modules
Karipidis et al. [99]; Melbourne, Australia; 1987–1991	414 histologically confirmed glioma cases, identified by screening medical records at 14 hospitals	421 population controls	Personal interview + review of work histories by industrial hygienist	Tertile of total exposure Unexposed 1 2 3	 1.00 0.75 (0.33–1.71) 0.93 (0.42–2.07) 1.07 (0.47–2.41)	Age, sex, education	Paper also considered high- and low-grade gliomas separately and compared different methods of exposure assessment

do not always separate occupational use from personal use; however, both may be considerable.

Evidence in the occupational literature that RF radiation causes brain cancer is weak. In a study of 40,581 navy veterans of the Korean war with potential exposure to high-intensity radar, mortality due to brain cancer was not elevated among men presumed to have higher exposure to radar [107] (Table 27.5). Mortality due to brain cancer also was not increased among employees of a manufacturer of wireless communication products, and there was no gradient in risk across levels of estimated cumulative, peak, or usual exposure [108]. Risk did not increase with duration of exposure or latency. Brain tumor risk was elevated among electrical and electronics workers judged to have been exposed to microwave/radiofrequency (MW/RF) radiation; however, this may have been confounded by exposure to solvents and/or soldering fumes [89]. The association was attenuated when workers exposed to soldering fumes and lead were excluded, and electrical workers considered to have no exposure to MW/RF radiation also were at increased risk. In a case-control study of brain cancer conducted within a cohort of approximately 880,000 members of the US Air Force and relying on a job-exposure matrix to assess exposure to RF radiation, the odds ratio for ever exposure was 1.39 (95 % CI 1.01–1.90); however, there was little indication of a trend with cumulative exposure [88] (Table 27.6). Two other large glioma case-control studies that relied on job-exposure matrices to evaluate exposure to RF radiation, one in Germany [109] and the other in Australia [99], reported nonsignificant associations with odds ratios close to 1.0.

Ultraviolet (UV) radiation. Direct induction of brain cancer by UV radiation seems unlikely, as it would not penetrate the skull. However, an indirect effect, such as through the immune system or circulating levels of vitamin D, is conceivable. Brain cancer has been reported to be increased in some groups with high levels of sun exposure, such as farmers [110, 111], and a case-control study of glioma conducted in Australia found a significant positive association with occupational exposure to UV radiation [99]. Exposure to UV radiation was assessed through use of a job-exposure matrix. It is difficult to separate a possible effect due to UV radiation from that of correlated exposures.

Table 27.5 Cohort studies of radiofrequency radiation and brain cancer

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	Number of cases/deaths	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Groves et al. [107]; US servicemen; follow-up 1955–1994	40,581 navy veterans of the Korean war with potential exposure to high-intensity radar; males only	Consensus decisions of navy personnel	Radar potential exposure	Deaths		Age at cohort entry, attained age, year of graduation, year of birth, duration of follow-up	Study provides information pertinent to long-term risks
			Low	51	1.01 (0.77–1.33)		
			High	37	0.71 (0.51–0.98)		
Morgan et al. [108]; United States; 1976–1996	195,775 employees of Motorola, including persons involved in the design, manufacturing, and testing of wireless communication devices; males and females included	Expert opinion and job-exposure matrix to categorize 9,724 job titles into 1 of 4 RF exposure groups	Usual exposure	Deaths		Age, gender, race, period of hire	44 % women, who more often worked in jobs with low or no RF exposure
			High	3	1.07 (0.32–2.66)		Cohort (2/3 born 1905 or later)
			Moderate	3	1.18 (0.36–2.92)		
			Low	7	0.92 (0.50–1.80)		
			None	38	1.00		
			Cumulative exposure				
			≥median	10	0.91 (0.41–1.86)		
			<median	7	0.97 (0.37–2.16)		
			None	34	1.00		

Table 27.6 Case-control studies of radiofrequency radiation and brain cancer

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95 % CI)*	Adjustment for potential confounders	Comments
Berg et al. [109]; Germany; 2000–2003	366 glioma cases, aged 30–69 years drawn from four neurosurgical clinics	1,494 population-based controls, identified from regional population registries; matched on sex, age, and center	Personal interviews, including detailed questions on occupational activities related to RF	Probable exposure		Sex, age, center	
				No exposure			
				Not probable	1.00		
				Probable	0.86 (0.45–1.52)		
				High	0.75 (0.40–1.40)		
				Duration of high exposure	1.17 (0.66–2.08)		
				Not highly exposed	1.00		
				<10 years	1.07 (0.44–2.57)		
				≥10 years	1.31 (061–2.80)		
Grayson [88]; United States; 1970–1989	230 brain cancer cases (ICD 191) drawn from members of US Air Force who had completed at least one full year of service; identified from hospital discharge records; age from ≤24 to ≥55 years; males only	920 controls randomly selected from US Air Force personnel records; matched on year of birth and race	Job title-time exposure matrix	Cumulative exposure score			Nested case-control study within approximately 880,000 members of US Air force
				None	1.00		
				2–48	1.26 (071–2.24)		
				49–127	1.50 (0.90–2.52)		
				128–235	1.26 (0.71–2.22)		
				236–610	1.51 (0.90–2.51)		

Chemical Agents

Pesticides. These perhaps are the most extensively studied class of occupational chemical exposures thus far. Evaluation of the carcinogenicity of most pesticides by IARC has classified evidence as inadequate, due to lack or insufficient human data. An international study of nearly 70,000 workers exposed to phenoxy herbicides found no excess of brain cancer mortality [112]. Also, some indirect

Table 27.7 Summary of major studies on pesticides and brain cancer

Reference; setting	Study type and subjects	Exposure assessment	Main results	Adjustment
Kogevinas et al. [112] combined analysis of 36 cohorts from 12 countries	Cohort; 21,863 exposed workers involved in production or spraying of phenoxy herbicides or chlorophenols	Individual tasks/job records, company exposure questionnaires, and blood samples/ambient measurements	For any exposure to phenoxy herbicides or chlorophenol, SMR 0.69 (0.43–1.04) based on 22 deaths from brain cancer; for workers with exposure to pesticides contaminated with TCDD, SMR 0.63 (0.33–1.10)	No multivariate analysis of brain cancer mortality (only overall cancer)
Ruder et al. [113], Iowa, Michigan, Minnesota, Wisconsin; 1995–1997	Case-control; 457 adult male cases with glioma and 648 population-based controls	Interview on specific pesticides; proxies as informants for 47 % of the cases	ORs below 1 for ever use of pesticides, herbicides, and fungicides and 1.1–1.5 after excluding proxy respondents. No significantly elevated ORs for any of the 17 pesticide types examined; highest point estimates (1.3–1.4) for carbamates and dinitroanilines	Age, education, other pesticide exposure
Lee et al [114]; Nebraska; 1988–1993	Case-control; 251 adult cases with glioma and 498 population-based controls	Telephone interview with history of farm pesticide exposure; proxy interview for 76 % of cases	Overall, significantly increased OR for any use of insecticides or pesticides, with twofold OR for organochlorine and organophosphorus insecticides as well as phenoxy and triazine herbicides. No increased risks based on self-reported information, but excess restricted to proxy interviews	Age and respondent type
Carreon et al. [115]; Iowa, Michigan, Minnesota, Wisconsin; 1995–1997	Case-control; 341 adult female glioma cases and 528 population-based controls	Telephone interviews on agricultural pesticide exposures; proxy interviews for 43 % of cases	For ever use of herbicides, fungicides, and insecticides ORs 1.0–1.2; for self-reported exposure OR = 1.6 (0.9–2.7) for ever use of insecticides; for carbamate herbicides OR = 3.0 (0.9–9.5) and estrogenic pesticides OR = 1.4 (0.9–2.2); exclusion of proxy respondents did not materially affect the results	Age, education, farm residence
Ruder et al. [116]; Iowa, Michigan, Minnesota, Wisconsin; 1995–1997	Case-control; 798 adult glioma cases, 1,175 population-based controls	Personal interview, proxies for 45 % of cases	Among those involved in farming, ever exposure to farm insecticides OR = 0.75, 95 % CI 0.59–0.95, herbicides OR = 0.89 (0.70–1.13), fungicides OR = 0.89 (0.58–1.36)	Age, gender, state, education
Samanic et al. [117]; hospitals in Phoenix, Boston, and Pittsburgh; 1994–1998	Case-control; 462 adult glioma cases and 765 hospital-based controls	Personal interview on job history; job-exposure matrix with estimated probability, frequency, and intensity of pesticide exposure in four categories	No significantly increased risks related to ever exposure to insecticides or herbicides (ORs 0.9–1.3 for men and women); no exposure-effect gradient by cumulative lifetime exposure to insecticides or herbicides, and no increased risk in the highest exposure categories	Age, hospital, and interview type
Ruder et al. [56]: Iowa, Michigan, Minnesota, Wisconsin; 1995–1997	Case-control; 288 glioma cases and 474 controls	Interview on farm exposure to pesticides; proxy for 45 % of cases	Never washing face and hands OR = 3.0 (1.8–5.3), changing clothes immediately after applying pesticides OR = 2.8 (1.0–7.8); findings weaker and no longer significant after excluding proxy respondents	Sex, age, education and state

exposure indicators (not washing or changing clothes after handling/spraying) have been associated with glioma risk, but this could be due to recall bias [56]. However, with a substantial number of studies, with refined research hypotheses pertaining to specific classes or agents, the balance of evidence seems to weigh against an increased risk (Table 27.7). Unfortunately, the risk of brain cancer has not been analyzed in the Agricultural Health Study, which has been able to unveil risks of some other cancer types linked to specific pesticides. No consistent evidence linking contact with livestock and brain cancer has been found [56, 118, 119].

Some indications of increased risk of brain cancer in the offspring related to occupational pesticide exposure have been found. In a case-control study of 526 childhood brain cancers, nonsignificantly increased risk was found for occupational exposure, but a significant result was obtained for combined residential and/or occupational exposure, in particular astrocytoma [120]. Similar results have also been observed in some other studies [53, 121, 122].

Other chemical exposures. Some studies have suggested an increased risk of brain cancer related to occupational exposure to various organic solvents, mainly organochlorides or chlorinated hydrocarbons (chemically related to several pesticides) [123–125].

Vinyl chloride is used in the plastics industry and classified as a human carcinogen based on increased risk of liver angiosarcoma. A large US cohort showed an increased brain cancer mortality of borderline significance, but this was not seen in a European study [126, 127]. A meta-analysis of five

studies gave a pooled SMR of 1.26 (0.98–1.62) for brain cancer deaths, which excludes a large excess risk but leaves open the possibility of a slight increase [128].

The epidemiological evidence regarding occupational exposure to lead has failed to lend consistent material support for the hypothesis of increased risk of brain cancer [123, 129–132]. The potential excess risk was originally proposed in a study with measured blood lead concentrations but only 16 cases [133]. A recent study suggested a possible gene-environment interaction that might modify the susceptibility to glioblastoma in relation to lead exposure [129]. Several other studies have also evaluated the role of metabolic variants, e.g., GSTT1 and GSTP1 [68, 134–137] and certain polymorphisms of DNA repair genes including ERCC1 [138–141] in relation to brain tumor risk, but the results have not been highly consistent.

Acrylonitrile is widely used (e.g., in the plastics and rubber industries) and has been shown to cause nervous system tumors in experimental animals. Several epidemiological studies have evaluated brain tumor incidence or mortality among workers exposed to acrylonitrile. The largest was a US cohort with more than 25,000 subjects with an average of 21 years of follow-up [142]. It did not find an association between exposure to acrylonitrile and brain cancer mortality. A meta-analysis with 12 studies and a more recent summary of the latter research also confirmed this finding [143, 144].

Formaldehyde is widely used in several industries, but exposure also occurs in farming as well as certain occupations in health care and biomedical research. A nested case-control study of funeral workers showed some indication of increased risk of brain cancer with any exposure to formaldehyde in embalming, but no dose-response in terms of duration or cumulative formaldehyde exposure [145]. A meta-analysis reported no excess among industrial workers exposed to formaldehyde, but an increased mortality from brain cancer was found for professionals, mainly pathologists [146].

A large cohort study Navas-Acien et al. [17, 70] suggested possible risks related to occupational exposure to mercury, but the result was confined to men. Smaller earlier studies have not revealed an association with inorganic mercury.

Conclusion

In conclusion, occupational etiology of brain cancers has not been well established. Increased brain cancer risks have been reported in agricultural occupations and among physicians. However, the specific agents that could explain the excesses have not been identified. High doses of ionizing radiation increase the risk, but the role of the doses within the current workplace regulations is unclear, with the effect size predicted by linear extrapolation from higher doses being very low. Despite considerable efforts, no consistent evidence linking occupational exposure to electromagnetic fields or pesticides with brain cancer risk has been obtained. Large epidemiological studies with detailed assessment of exposure to specific agents and refined diagnostic classification appear to provide the best approach to advance knowledge in the area.

Acknowledgements We thank Hannu Haapasalo, MD (Tampere University Hospital) for comments on pathology of brain tumors.

References

1. Louis DN, Ohgaki H, Wiestler OD, et al. The WHO 2007 classification of tumors of the nervous system. Acta Neuropathol. 2007;114:97–109.
2. Burger PC, Scheithauer BW. Tumors of the central nervous system. Washington: American Registry of Pathology; 2007.
3. Van Meir EG, Hadjipanayis CG, Norden AD, et al. Exciting new advances in neuro-oncology. CA Cancer J Clin. 2010;60:166–93.
4. Bourne TD, Schiff D. Update on molecular findings, management and outcome in low-grade gliomas. Nature Rev Neurol. 2010;6:695–701.
5. Gladson CL, Prayson RA, Liu WM. The pathobiology of glioma tumors. Annu Rev Pathol. 2010;5:33–50.
6. Huse JT, Holland EC. Targeting brain cancer: advances in molecular pathology of malignant glioma and medulloblastoma. Nat Rev Cancer. 2010;10:319–31.
7. Ferlay J, Shin HR, Bray F, et al. Estimates of world-wide burden of cancer in 2008. Int J Cancer. 2010;127:2918–27.
8. Curado P, Edwards B, Shin HR. Cancer incidence in five continents, vol. IX. Lyon: International Agency for Research on Cancer; 2009.
9. Lönn S, Klaeboe L, Hall P, et al. Incidence trends of adult primary intracerebral tumors in four Nordic countries. Int J Cancer. 2004;108:450–5.
10. Arora RS, Alson RD, Eden TO, et al. Are reported increases in incidence of primary CNS tumours real. Eur J Cancer. 2010;46:1607–16.
11. CBTRUS. Central Brain Tumor Registry of the United States. 2011 CBTRUS statistical report. Available at http://www.cbtrus.org/reports/reports.html.
12. SEER (Surveillance, Epidemiology and End Results). National Cancer Institute; http://seer.cancer.gov/seerstat/. Accessed 16 Sept 2011.
13. De Vocht F, Burstyn I, Cherrie JW. Time trends in brain cancer incidence rates in relation to mobile phone use in England. Bioelectromagnetics. 2011;32:334–9.
14. Deltour I, Johansen C, Auvinen A, et al. Time trends in brain tumor incidence rates in Denmark, Finland, Norway, and Sweden, 1974–2003. J Natl Cancer Inst. 2009;101:1721–4.
15. Inskip PD, Hoover RN, Devesa SS. Brain cancer incidence trends in relation to cellular telephone use in the United States. Neuro Oncol. 2001;12:1147–51.
16. Buckner JC. Factors influencing survival in high-grade gliomas. Semin Oncol. 2003;30 Suppl 19:10–4.
17. Ohgaki H, Kleihues P. Population-based studies on incidence survival rates and genetic alterations in astrocytic and oligodendroglial gliomas. J Neuropathol Exp Neurol. 2005;64:479–89.
18. Schomas DA, Laack NN, Rao RD, et al. Intracranial low-grade gliomas in adults. Neuro Oncol. 2009;11:437–45.
19. Scoccianti S, Magrini SM, Ricardi U, et al. Patterns of care and survival in a retrospective analysis of 105 patients with glioblastoma multiforme. Neurosurgery. 2010;67:446–58.
20. Kouwenhoven MC, Gorlia T, Kros JM, et al. Molecular analysis of anaplastic oligodendroglial tumors in a prospective randomized study. Neuro Oncol. 2009;11:737–46.

21. Parkinson JF, Afabhi V, Payne CA, et al. The impact of molecular and clinical factors on patient outcome in oligodendroglioma. J Clin Neurosci. 2011;18:320–33.
22. Armstrong TS, Vera-Bolanos E, Bekele BN, et al. Adult ependymal tumors. Neuro Oncol. 2010;12:862–70.
23. Reni M, Brandes AA, Vavassori V, et al. A multicenter study of prognosis and treatment of adult brain ependymal tumors. Cancer. 2004;10:1221–9.
24. Hemminki K, Tretli S, Sundqvist J, et al. Familial risks in nervous-system tumours: a histology-specific analysis from Sweden and Norway. Lancet Oncol. 2009;10:481–8.
25. Hill DA, Inskip PD, Shapiro WR, et al. Cancer in first-degree relatives and risk of glioma in adults. Cancer Epidemiol Biomarkers Prev. 2003;12:1443–8.
26. Malmer B, Henriksson R, Grönberg H. Familial brain tumours – genetics or environment? A nationwide cohort study of cancer risk in spouses and first-degree relatives of brain tumour patients. Int J Cancer. 2003;106:260–3.
27. Scheurer ME, Etzel CJ, Liu M, et al. Familial aggregation of glioma: a pooled analysis. Am J Epidemiol. 2010;172:1099–107.
28. Wrensch M, Lee M, Miike R, et al. Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. Am J Epidemiol. 1997;145:581–93.
29. Shete S, Hoskins FJ, Robertson LB, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet. 2009;41:899–904.
30. Wrensch M, Jenkins RB, Chang JS, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. Nat Genet. 2009;41:905–8.
31. Brenner AV, Linet MS, Fine HA, et al. History of allergies and autoimmune diseases and risk of brain tumors in adults. Int J Cancer. 2002;99:252–9.
32. Wigertz A, Lönn S, Schwartzbaum J, et al. Allergic conditions and brain tumor risk. Am J Epidemiol. 2008;166:141–50.
33. Scheurer ME, El-Zein R, Thompson PA, et al. Long-term anti-inflammatory and antihistamine medication use and adult glioma risk. Cancer Epidemiol Biomarkers Prev. 2008;17:1277–81.
34. Schwartzbaum J, Jonsson F, Ahlbom A, et al. Cohort studies of association between self-reported allergic conditions, immune-related diagnoses and glioma and meningioma risk. Int J Cancer. 2003;106:423–8.
35. Chen C, Xu T, Chen J, et al. Allergy and risk of glioma. Eur J Neurol. 2011;18:387–95.
36. Linos E, Raine T, Alonso A, et al. Atopy and risk of gliomas. J Natl Cancer Inst. 2007;99:1544–50.
37. Schlehofer B, Blettner M, Preston-Martin S, et al. Role of medical history in brain tumour development. Int J Cancer. 1999;82:155–60.
38. Wiemels JL, Wilson D, Patil C, et al. IgE, allergy, and risk of glioma. Int J Cancer. 2009;125:680–7.
39. McCarthy BJ, Rankin KM, Aldape K, et al. Risk factors for oligodendroglial tumors. Neuro Oncol. 2011;13:242–50.
40. Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: a meta-analysis of nine observational studies. J Environ Pathol Toxicol Oncol. 2003;22:129–37.
41. Benson VS, Pirie K, Green J, et al. Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. Br J Cancer. 2008;99:185–90.
42. Efird J, Friedman GD, Sidney S, et al. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. J Neuro Oncol. 2004;68:57–69.
43. Holick CN, Giovannucci E, Rosner B, et al. Prospective study of cigarette smoking and adult glioma. Neuro Oncol. 2007;9:326–34.
44. Mandelzweig L, Novikov I, Sadetzki S. Smoking and risk of glioma. Cancer Causes Control. 2009;20:1927–38.
45. Holick CN, Smith SG, Giovannucci E, Michaud DS. Coffee, tea, caffeine intake, and risk of adult glioma in three prospective cohort studies. Cancer Epidemiol Biomarkers Prev. 2010;19:39–47.
46. Michaud DS, Gallo V, Schlehofer B, et al. Coffee and tea intake and risk of brain tumors in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Am J Clin Nutr. 2010;92:1145–50.
47. Blair A, Grauman DJ, Lubin JH, Fraumeni Jr JF. Lung cancer and other causes of death among licensed pesticide applicators. J Natl Cancer Inst. 1983;71:31–7.
48. Acquavella J, Olsen G, Cole P, et al. Cancer among farmers. Ann Epidemiol. 1998;8:64–74.
49. Khuder SA, Mutgi AB, Schaub EA. Meta-analyses of brain cancer and farming. Am J Ind Med. 1998;34:252–60.
50. Alavanja MCR, Sandler DP, Lynch CF, et al. Cancer incidence in the Agricultural Health Study. Scand J Work Environ Health. 2005;21 Suppl 1:39–45.
51. Waggoner JK, Kullman GJ, Henneberger PK, et al. Mortality in the Agricultural Health Study, 1993–2007. Am J Epidemiol. 2010;173:71–83.
52. Cordier S, Mandereau L, Prston-Martin S, et al. Parental occupations and childhood brain tumors. Cancer Causes Control. 2002;12:865–74.
53. Feychting M, Plato N, Nise G, et al. Paternal occupational exposures and childhood cancer. Environ Health Perspect. 2001;109:193–6.
54. McKinney PA, Fear NT, Stockton D. Parental occupation at periconception: findings from the UK Childhood Cancer Study. Occup Environ Med. 2003;60:901–9.
55. Ménégoz F, Little L, Colonna M, et al. Contacts with animals and humans as risk factors for adult brain tumors. Eur J Cancer. 2002;38:696–704.
56. Ruder AM, Carreon T, Butler MA, et al. Exposure to farm crops, livestock, and farm tasks and risk of glioma: the Upper Midwest Health Study. Am J Epid. 2009;169:1479–91.
57. Andersson E, Nilsson R, Toren K. Gliomas among men employed in the Swedish pulp and paper industry. Scand J Work Environ Health. 2002;28:333–40.
58. McLaughlin JK, Malmer H, Blot WJ, et al. Occupational risks for intracranial gliomas in Sweden. J Natl Cancer Inst. 1987;78:253–7.
59. Navas-Acién A, Pollán M, Gustavsson P, Plato N. Occupation, exposure to chemicals and risk of gliomas and meningiomas in Sweden. Am J Ind Med. 2002;42:214–27.
60. Wong O, Raabe GK. A critical review of cancer epidemiology in the petroleum industry. Regul Toxicol Pharmacol. 2000;32:78–98.
61. McLean D, Pierce N, Langseth H, et al. Cancer mortality in workers exposed to organochlorine compounds in the pulp and paper industry. Environ Health Perspect. 2006;114:1007–12.
62. Aronson KJ, Howe GR, Carpenter M, et al. Surveillance of potential associations between occupations and causes of death in Canada, 1965–91. Occup Environ Med. 1999;56:265–9.
63. Carozza SE, Wrensch M, Miike R, et al. Occupation and adult gliomas. Am J Epid. 2000;152:838–46.
64. Carpenter LM, Swerdlow AJ, Fear NT. Mortality of doctors in different specialties. Occup Environ Med. 1997;54:388–95.
65. Heineman EF, Gao YT, Dosemeci M, et al. Occupational risk factors for brain tumors among women in Shanghai, China. J Occup Environ Med. 1995;37:288–93.
66. Krishnan G, Felini M, Carozza SE, et al. Occupation and adult gliomas in San Francisco bay area. J Occup Environ Med. 2003;45:639–47.
67. Rix BA, Lynge E. Cancer incidence in Danish health care workers. Scand J Soc Med. 1996;24:114–20.
68. de Roos AJ, Rothman N, Inskip PD, et al. Genetic polymorphisms in GSTM1, -P1, -T1 and CYP2E1 and the risk of adult brain tumors. Cancer Epidemiol Biomarkers Prev. 2003;12:14–22.

69. Kogevinas M, Sala M, Boffetta P, et al. Cancer risk in the rubber industry. Occup Environ Med. 1998;55:1–12.
70. Pan SY, Ugant AM, Mao Y. Occupational risk factors for brain cancer in Canada. J Occup Environ Med. 2005;47:704–17.
71. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2006;98:1528–37.
72. Sadetzki S, Chetrit A, Freedman L, et al. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. Radiat Res. 2005;163:424–32.
73. Preston DL, Ron E, Yonehara S, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. J Natl Cancer Inst. 2002;94:1555–63.
74. Cardis E, Vrijheid M, Blettner M, et al. The 15-Country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiat Res. 2007;167:396–416.
75. Muirhead CR, O'Hagan JA, Haylock RGE, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Br J Cancer. 2009;100:206–12.
76. Bunch KJ, Muirhead CR, Draper GJ, et al. Cancer in the offspring of female radiation workers: a record linkage study. Br J Cancer. 2009;100:213–8.
77. Rahu M, Rahu K, Auvinen A, et al. Cancer risk among Chernobyl cleanup workers in Estonia and Latvia, 1986–1998. Int J Cancer. 2006;119:162–8.
78. Ivanov VK, Gorski AI, Tsyb AF, et al. Solid cancer incidence among the Chernobyl emergency workers residing in Russia: estimation of radiation risks. Radiat Environ Biophys. 2004;43:35–42.
79. Inskip PD, Linet MS, Heineman EF. Etiology of brain tumors in adults. Epidemiol Rev. 1995;17:382–414.
80. Wang JX, Zhang LA, Zhao YC, et al. Cancer incidence and risk estimation among medical x-ray workers in China, 1950–1995. Health Phys. 2002;82:455–66.
81. Wenzl T, McDonald JC. Is there an elevated risk of brain cancer among physicians performing interventional radiology procedures. Radiat Prot Dosimetry. 2002;102:99–100.
82. Renaud L. A 5-year follow-up of the radiation exposure to in-room personnel during cardiac catheterization. Health Phys. 1992;62:10–5.
83. Finkelstein MM. Is brain cancer an occupational disease of cardiologists. Can J Cardiol. 1998;14:1385–8.
84. Kim KP, Miller DL, Balter S. Occupational radiation doses to operators performing cardiac catheterization procedures. Health Phys. 2008;94:211–27.
85. Boice Jr JD, Blettner M, Auvinen A. Epidemiologic studies of pilots and aircrew. Health Phys. 2000;79:576–84.
86. Blettner M, Zeeb H, Auvinen A, et al. Mortality from cancer and other causes among male airline cockpit crew in Europe. Int J Cancer. 2003;106:946–52.
87. Pukkala E, Aspholm R, Auvinen A, et al. Incidence of cancer among Nordic airline pilots over five decades: occupational cohort study. Br Med J. 2003;325:567–72.
88. Grayson JK. Radiation exposure, socioeconomic status, and brain tumor risk in the US Air Force: a nested case-control study. Am J Epidemiol. 1996;143:480–6.
89. Thomas TL, Stolley P, Stemhagen A, et al. Brain tumor mortality risk among men with electrical and electronics jobs: a case-control study. J Natl Cancer Inst. 1987;79:233–8.
90. Robinson CF, Petersen M, Palu S. Mortality patterns among electrical workers employed in the U.S. construction industry, 1982–1987. Am J Ind Med. 1999;36:630–7.
91. Savitz DA, Loomis DP. Magnetic field exposure in relation to leukemia and brain cancer mortality among electric utility workers. Am J Epidemiol. 1995;141:123–34.
92. Theriault G, Goldberg M, Miller AB, et al. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada and France. Am J Epidemiol. 1994;139:550–72.
93. Thériault G, Goldberg M, Miller AB, et al. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France: 1970–1989. Am J Epidemiol. 1994;139:550–72.
94. Sahl JD, Kelsh MA, Greenland S. Cohort and nested case-control studies of hematopoietic cancers and brain cancer among electric utility workers. Epidemiology. 1993;4:104–14.
95. Röösli M, Lörtscher M, Egger M, et al. Leukaemia, brain tumours and exposure to extremely low frequency magnetic fields: a cohort study of Swiss railway employees. Occup Environ Med. 2007;64:553–9.
96. Håkansson N, Floderus B, Gustavsson P, et al. Cancer incidence and magnetic field exposure in industries using resistance welding in Sweden. Occup Environ Med. 2002;59:481–6.
97. Villeneuve PJ, Agnew DA, Johnson KC, et al. Brain cancer and occupational exposure to magnetic fields among men: results from a Canadian population-based case-control study. Int J Epidemiol. 2002;31:210–7.
98. Coble JB, Dosemeci M, Stewart PA, et al. Occupational exposure to magnetic fields and the risk of brain tumors. Neuro Oncol. 2009;11:242–9.
99. Karipidis KK, Benke G, Sim MR, et al. Occupational exposure to ionizing and non-ionizing radiation and risk of glioma. Occup Med (London). 2007;57:518–24.
100. Rodvall Y, Ahlbom A, Stenlund C, et al. Occupational exposure to magnetic fields and brain tumours in central Sweden. Eur J Epidemiol. 1998;14:563–9.
101. Karipidis KK, Benke G, Sim MR, et al. Occupational exposure to low frequency magnetic fields and the risk of low grade and high grade glioma. Cancer Causes Control. 2007;18:305–13.
102. Navas-Acién A, Pollán M, Gustavsson P, et al. Interactive effect of chemical substances and occupational electromagnetic field exposure on the risk of gliomas and meningiomas in Swedish men. Cancer Epidemiol Biomarkers Prev. 2002;11:1678–83.
103. Feychting M, Floderus B, Ahlbom A. Parental occupational exposure to magnetic fields and childhood cancer (Sweden). Cancer Causes Control. 2000;11:151–6.
104. Hug K, Grize L, Seidler A, et al. Parental occupational exposure to extremely low frequency magnetic fields and childhood cancer: a German case-control study. Am J Epidemiol. 2010;171:27–35.
105. Kheifets L, Monroe J, Vergara X, et al. Occupational electromagnetic fields and leukemia and brain cancer: an update to two meta-analyses. J Occup Environ Med. 2008;50:677–88.
106. Baan R, Grosse Y, Lauby-Secretan B, et al. Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol. 2011;12:624–6.
107. Groves FD, Page WF, Gridley G, et al. Cancer in Korean war navy technicians. Am J Epidemiol. 2002;55:810–8.
108. Morgan RW, Kelsh MA, Zhao K, et al. Radiofrequency exposure and mortality from cancer of the brain and lymphatic/hematopoietic systems. Epidemiology. 2000;11:118–27.
109. Berg G, Spallek J, Schüz J, et al. Occupational exposure to radio frequency/microwave radiation and the risk of brain tumors: Interphone study group, Germany. Am J Epidemiol. 2006;164:538–48.
110. Blair A, Zahm S, Pearce NE, et al. Clues to cancer etiology from studies of farmers. Scand J Work Environ Health. 1992;18:209–15.

111. Blair A, Dosemeci M, Heineman EF. Cancer and other causes of death among male and female farmers from twenty-three states. Am J Ind Med. 1993;23:729–42.
112. Kogevinas M, Becher H, Benn T, et al. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols and dioxins. Am J Epidemiol. 1997;145:1061–75.
113. Ruder AM, Waters MA, Butler MA, et al. Gliomas and farm pesticide exposure in men. Arch Environ Health. 2004;59:650–7.
114. Lee WJ, Colt JS, Heineman EF, et al. Agricultural pesticide use and risk of glioma in Nebraska, United States. Occup Environ Med. 2005;62:786–92.
115. Carreon T, Butler MA, Ruder AM, et al. Glomas and farm pesticide exposure in women. Environ Health Perspect. 2005;113:546–51.
116. Ruder AM, Waters MA, Carreon T, et al. The Upper Midwest Health Study: a case-control study of primary intracranial gliomas in farm and rural residents. J Agric Saf Health. 2006;12:255–742006.
117. Samanic CM, de Roos AJ, Stewart PA, et al. Occupational exposure to pesticides and risk of adult brain tumors. Am J Epidemiol. 2010;167:676–85.
118. Morrison HI, Semenciw RM, Morison D, et al. Brain cancer and farming in western Canada. Neuroepidemiology. 1992;11:267–76.
119. Reif J, Pierce N, Fraser J. Cancer risks in New Zealand farmers. Int J Epidemiol. 1989;18:768–74.
120. Shim YK, Mlinarek SP, van Wijngaarden E. Parental exposure to pesticides and childhood brain cancer. Environ Health Perspect. 2009;117:1102–6.
121. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer. J Toxicol Environ Health. 2007;10:81–99.
122. Van Wijngaarden E, Stewart PA, Olshan AF, et al. Parental occupational exposure to pesticides and childhood brain cancer. Am J Epidemiol. 2003;157:989–97.
123. Wesseling C, Pukkala E, Neuvonen K, et al. Cancer of the brain and nervous system and occupational exposures in Finnish women. J Occup Environ Med. 2002;44:663–8.
124. Heineman EF, Cocco P, Gomez MR, et al. Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. Am J Ind Med. 1994;26:155–69.
125. Cocco P, Heineman EF, Dosemeci M. Occupational risk factors for cancer of the central nervous system among US women. Am J Ind Med. 1999;36:70–4.
126. Mundt KA, Dell LD, Austin RP, et al. A historical cohort study of 10,109 men in the American vinyl chloride industry. Occup Environ Med. 2000;57:774–81.
127. Ward E, Boffetta P, Andersen A, et al. Update of the follow-up for mortality and incidence of cancer among European workers employed in the vinyl chloride industry. Epidemiology. 2001;12:710–8.
128. Boffetta P, Matisane L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health. 2003;29:220–29.
129. Bhatti P, Stewart PA, Hutchinson A, et al. Lead exposure, polymorphisms in genes related to oxidative stress, and risk of adult brain tumors. Cancer Epidemiol Biomarkers Prev. 2009;18:1841–8.
130. Cocco P, Dosemeci M, Heineman EF. Brain cancer and occupational exposure to lead. J Occup Environ Med. 1998;40:937–42.
131. Rajaraman P, Stewart PA, Samet JM, et al. Lead, genetic susceptibility and risk of adult brain tumors. Cancer Epidemiol Biomarkers Prev. 2006;15:2514–20.
132. Van Wijngaarden E, Dosemeci M. Brain cancer mortality and potential occupational exposure to lead. Int J Cancer. 2006;119:1136–44.
133. Anttila A, Hiekkilä P, Nykyri E, et al. Risk of nervous system cancer among workers exposed to lead. J Occup Environ Med. 1996;38:131–6.
134. Elexipuru-Camiruaga J, Buxton N, Kandula V, et al. Susceptibility to astrocytoma and meningioma: influence of allelism at glutathione S-transferase and cytochrome P-450 loci. Cancer Res. 1995;55:4237–39.
135. Kelsey KT, Wrensch M, Zuo ZF, et al. A population-based case-control study of CYP2D6 and GSTT1 polymorphisms and malignant brain tumors. Pharmacogenetics. 1997;7:463–8.
136. Wrensch M, Kelsey KT, Liu M, et al. Glutathione-S-transferase variants and adult glioma. Cancer Epidemiol Biomarkers Prev. 2004;13:461–67.
137. Schwartzbaum J, Ahlbom A, Lönn S, et al. An international case-control study of glutathione transferase and functionally related polymorphisms and risk of primary adult brain tumors. Cancer Epidemiol Biomarkers Prev. 2007;16:559–65.
138. Bethke L, Murray A, Webb E, et al. Comprehensive analysis of the role of DNA repair gene polymorphisms on risk of glioma. Hum Mol Genet. 2008;17:800–5.
139. Chen P, Wiencke J, Aldape K, et al. Association of an ERCC1 polymorphism with adult-onset glioma. Cancer Epidemiol Biomarkers Prev. 2000;9:843–47.
140. Liu Y, Scheurer ME, El-Zein R, et al. Association and interactions between DNA repair gene polymorphisms and adult glioma. Cancer Epidemiol Biomarkers Prev. 2009;18:204–14.
141. McKean-Cowdin R, Barnholtz-Sloan J, Inskip PD, et al. Associations between polymorphisms in DNA repair genes and glioblastoma. Cancer Epidemiol Biomarkers Prev. 2009;18:1118–26.
142. Blair A, Stewart PA, Zaebst DD, et al. Mortality in industrial workers exposed to acrylonitrile. Scand J Work Environ Health. 1998;24 Suppl 2:25–41.
143. Cole P, Mandel JS, Collins JJ. Acrylonitrile and cancer. Regul Toxicol Pharmacol. 2008;52:342–51.
144. Collins JJ, Strather DE. CNS tumors and exposure to acrylonitrile. Neuro Oncol. 1999;1:221–30.
145. Hauptmann M, Stewart PA, Lubin JH, et al. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. J Natl Cancer Inst. 2009;101:1696–708.
146. Bosetti C, McLaughlin JK, Tarone RE, et al. Formaldehyde and cancer risk. Ann Oncol. 2008;19:29–43.
147. Michaud DS, Gallo V, Schlehofer B, et al. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. Cancer Epidemiol Biomarkers Prev. 2010;19:2562–9.

Lymphohematopoietic Malignancies

28

Anneclaire J. De Roos and Parveen Bhatti

Keywords
Lymphoma • Leukemia • Benzene • 1,3-Butadiene • Ionizing radiation • Formaldehyde • Ethylene oxide • Pesticides • Animal exposures • Trichloroethylene • Solvents

Lymphohematopoietic malignancies encompass a heterogeneous, but related group of cancers that, collectively, are among the top 5 or 6 most common cancers in women and men worldwide [1]. Environmental factors, broadly, are suspected to contribute to risk of NHL, since the incidence rate increased dramatically during the latter half of the twentieth century in the United States (USA), Europe, and other developed regions, increasing by approximately 4 % per year in the USA [2–4]. The incidence of non-Hodgkin lymphoma (NHL) has recently leveled off in the USA for both men and women [5]; however, causes of this dramatic increase remain unidentified, and the magnitude of the increase cannot be explained by changes in known risk factors such as HIV [4].

Epidemiologic research of lymphohematopoietic cancers has been complicated by the incredible heterogeneity of these malignancies, which continues to be revealed as new molecular techniques suggest even greater heterogeneity than previously thought. Evolving understanding of these cancers has led to changes in classification systems over time, hindering comparison of epidemiologic study results from different time periods and regions.

NHL is traditionally considered a large grouping of solid tumors deriving from lymphocytes that excludes Hodgkin lymphoma (HL); however, NHL groupings used in epidemiologic research have continued to shift over the years. Earlier studies of NHL usually did not include lymphoid cell cancers presenting as leukemias. However, chronic lymphocytic leukemia (CLL) is now typically included in studies of NHL based on consensus of the World Health Organization that CLL and small lymphocytic lymphoma (SLL) are biologically similar, deriving from the same cell line, but with different clinical presentations (liquid vs. solid) [6]. Multiple myeloma (MM) has traditionally been treated separately in epidemiologic research, although it is technically another "non-Hodgkin" lymphoid neoplasm – in this case deriving from lymphocytes that have differentiated into plasma cells. Based on the World Health Organization classification system, more recent studies have often focused on the entire spectrum of lymphoid cell neoplasms, including both lymphomas (with NHL, HL, and MM) and lymphoid leukemias, and have examined risk factors for all lymphoid cancers combined and for major subtypes. The subtypes examined are usually limited to the most common, due to small numbers in individual studies, including diffuse large B-cell lymphoma (DLBCL), CLL/SLL, follicular lymphoma (FL), MM, and HL. Hodgkin lymphoma (HL) has been less studied than the other lymphoid neoplasms in relation to occupational risk factors, primarily because its lower incidence and the fact that a large proportion of cases occurs in young adulthood, not long after the typical age that adults start to work full time.

Many older studies reported results for "leukemia" as a group, combining myeloid cell and lymphoid leukemias – specifically, acute myeloid leukemia (AML, which includes acute monocytic and myelomonocytic leukemias [6]), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), and acute lymphocytic leukemia (ALL). Leukemia as an overall grouping in epidemiologic research

A.J. De Roos, PhD, MPH (✉)
Department of Occupational and Environmental Health, School of Public Health, Drexel University, Philadelphia, PA, USA
e-mail: aderoos@drexel.edu

P. Bhatti, BS, MS, PhD
Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_28, © Springer-Verlag London 2014

would only be useful for identifying risk factors that have a common mechanism for both myeloid and lymphoid cell leukemias but may mask associations that are specific to one cell lineage. Other myeloid cell diseases, the myelodysplastic syndromes (MDS) and myeloproliferative diseases (MPD), are now considered cancers based on their clonal nature and are classified as malignant by the World Health Organization [7]. Because approximately one-third of MDS patients develop AML, MDS has sometimes been considered as "preleukemia" or "aleukemia" in epidemiologic studies or has been grouped with AML.

Very little is known about risk factors for lymphohematopoietic cancers as a group and even less is known about subtype-specific risks. There are strong and consistent associations linking NHL, MM, and lymphoid leukemias to states of altered immunity – for immune suppression as well as chronic immune stimulation – including increased risks in transplant recipients [8–10], autoimmune disease patients [11–25], and persons with viruses such as HIV and hepatitis C virus [4, 9]. However, the majority of these cancers occur in apparently immunocompetent individuals [9, 19]. Several lifestyle factors have been implicated for lymphohematopoietic cancers, albeit with limited data, including smoking for myeloid cell neoplasms [26–29] and obesity for myeloid leukemias and MM [27, 30]. Any risk related to these lifestyle factors may differ between NHL subtypes; for example, obesity has been associated with increased risk of DBLCL but less consistently with other subtypes [31, 32], and smoking has been most frequently associated with FL and T-cell lymphoma [26, 33, 34]. Reduced risk of NHL in association with alcohol consumption has been observed with some consistency [26, 35]. Further characterization of lifestyle risk factors is needed to continue to describe heterogeneity of effects between subtypes and etiologically relevant scenarios of exposure timing and dose. In addition, an understanding of biologic mechanisms underlying lifestyle-related risk factors can provide direction for investigation of occupational exposures with a priori evidence of similar biologic effects.

Occupational exposures that are universally accepted as causes of lymphohematopoietic cancers are limited at this time to benzene and ionizing radiation and possibly 1,3-butadiene for the myeloid cell leukemias [36]. Many other exposures are suspected to contribute to lymphohematopoietic cancer risks but are as yet debated, including chlorinated solvents, formaldehyde, and certain pesticides such as phenoxy herbicides (e.g., 2,4-D) and organophosphate insecticides [37]. Several of these exposures have been declared as carcinogenic to humans by the International Agency for Research on Cancer (IARC) of the World Health Organization, whose mission is to coordinate and conduct research on the causes of human cancer. Nevertheless, the grouping of an exposure as a carcinogen by IARC is more often than not based only on sufficient evidence for non-lymphohematopoietic cancers, and even for exposures declared specifically as lymphohematopoietic carcinogens by IARC, there are often ongoing debates for a causal association within the scientific community. These exposures and others with a fair amount of research are discussed in this chapter. Occupational exposures may exert their effects on lymphohematopoietic cancers through a variety of mechanisms, including genotoxicity, hormonal action, and immunotoxicity, and for most exposures, potential mechanisms are not well understood.

Farming and Pesticides

An occupation in farming has been associated with increased risks of leukemia, NHL, HL, and MM [38]. As seen in Table 28.1, a summary of the various meta-analyses of farming in relation to lymphohematopoietic cancers that have been conducted, associations tend to be small in magnitude (3–25 % increases) but indicate a consistent increase in risk for farmers compared to the general population [39–44]. Meta-analyses of leukemia subtypes and farming have not been conducted, but individual studies have demonstrated excess risks for AML, ALL, CML, and CLL [40].

Pesticides have been the primary focus in terms of specific farm-based exposures that may be associated with increased cancer risk. In a meta-analysis of 44 risk estimates (based on various metrics of exposure) from 13 case-control studies published between 1990 and 2005 (6 of the studies were exclusively conducted among farmers, while the other 7 examined exposures across all occupations), occupational exposure to pesticides was associated with a 1.3-fold increased risk (95 % CI: 1.2–1.5) of any lymphohematopoietic cancer [45]. When stratified by cancer type, pesticide exposure was associated with a significantly increased risk of NHL (relative risk [RR] = 1.4, 95 % CI: 1.2–1.6), particularly for those exposed longer than 10 years (RR = 1.7, 95 % CI: 1.1–2.5). Nonsignificant increased risks of MM (RR = 1.2, 95 % CI: 1.0–1.4) and leukemia (RR = 1.4, 95 % CI: 0.9–2.0) were also observed. An evaluation of sources of heterogeneity between the leukemia studies revealed that MDS was the subtype most strongly related to pesticide exposure (RR = 3.0, 95 % CI: 1.7–5.3). A meta-analysis of leukemia limited to pesticide manufacturing cohorts (14 studies publishing standardized incidence ratios [SIRs] and standardized mortality ratios [SMRs] between 1984 and 2004) found a significant 1.4-fold increased risk of leukemia (95 % CI: 1.1–1.9) [46]. In a focused review of myeloid leukemia in pesticide-exposed cohorts, the relative risk of myeloid leukemia was highest among pesticide manufacturing workers (three risk estimates from two studies of phenoxy herbicide, chlorophenol, and alachlor pesticide manufacturing workers, RR = 6.3, 95 % CI: 1.9–21), followed by pesticide applicators (five studies of

Table 28.1 Meta-analyses examining association of lymphohematopoietic cancers with farming

Reference	Cancer	# of studies	RR	95 % CI
Blair [39]	Leukemia	23	1.07	1.03–1.11
	Non-Hodgkin lymphoma	14	1.05	0.99–1.12
	Hodgkin lymphoma	12	1.16	1.03–1.29
	Multiple myeloma	12	1.12	1.04–1.21
Keller-Byrne [40]	Leukemia	19	1.09	0.99–1.19
Khuder [41]	Multiple myeloma	32	1.23	1.14–1.32
Acquavella [42]	Leukemia	27	1.10	1.02–1.18
	Non-Hodgkin lymphoma	23	1.03	0.96–1.12
	Hodgkin lymphoma	26	1.09	0.96–1.24
	Multiple myeloma	22	1.09	0.99–1.19
Khuder [43]	Non-Hodgkin lymphoma	36	1.10	1.03–1.19
Khuder [44]	Hodgkin lymphoma	30	1.25	1.11–1.42

applicators of a variety of pesticides, RR = 2.1, 95 % CI: 1.4–3.3), and there was no significant increase for farmers and agricultural workers (nine studies with pesticide exposure mostly assumed based on agricultural occupation, RR = 1.03) [47]; these results imply a causal role for pesticides in development of myeloid leukemias, given more frequent and intense exposures in manufacturing and applicator jobs than in typical farming occupations. When examining overall risk by myeloid leukemia subtype for all the pesticide-exposed jobs combined, a nonsignificant increased risk was observed among three studies of CML (RR = 2.0, 95 % CI: 0.6–6.4), and a significant increased risk was observed among five studies of AML (RR = 1.6, 95 % CI: 1.0–2.3); no appreciable differences by sex were observed [47]. Overall, the evidence suggests the existence of an association between occupational pesticide exposure and NHL and leukemia and possibly multiple myeloma, with higher-magnitude relative risk estimates for myeloid cell leukemias than for lymphoid cell neoplasms.

Few studies have evaluated specific pesticide formulations in relation to lymphohematopoietic cancer risk. Most of these are case-control studies that relied on retrospective exposure assessment (Table 28.2). However, the Agricultural Health Study (AHS), a cohort of 57,310 licensed private and commercial pesticide applicators in Iowa and North Carolina (as of 2007, *n* = 133 cases of leukemia, 195 NHL, 71 MM, 18 HL ascertained in the cohort) [57], has become a primary source of information regarding cancer risks associated with specific pesticides because of its large size and prospective design (see Figs. 28.1, 28.2, and 28.3 for summaries of findings from the AHS) [58–83]. The AHS and other prospective cohorts of agricultural workers hold promise for elucidating risks associated with specific pesticides and farming practices as these cohorts mature [84]. In the next few sections, studies of occupational exposures to specific pesticide classes and compounds in association with lymphohematopoietic cancers are described.

Herbicides

Phenoxyacetic acids ("phenoxy herbicides") are a widely used class of herbicides, of which 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) received much attention because of inherent contamination with the carcinogenic "dioxin," 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD). While 2,4,5-T use has been banned in most countries, 2,4-dichlorophenoxyacetic acid (2,4-D) continues to be used worldwide. Based on US agricultural market sector data, in 2007, 2,4-D was the seventh most commonly used pesticide, with 25–29 million pounds of it applied [85]. A meta-analysis of pesticide manufacturing cohort studies observed a significantly increased risk of leukemia when restricting analyses to the three cohorts with exposures to phenoxy herbicides that were unlikely to be contaminated with dioxins and furans (RR = 1.6, 95 % CI: 1.0–2.5) [46]. Two case-control studies found no evidence of an association between phenoxy herbicides and risk of NHL [50, 56]; however, most studies have reported positive or suggestive findings (Table 28.2). In a large case-control study conducted in Italy by Miligi et al. [51] (*n* = 1,145 cases of NHL including CLL) that included both men and women, increased risk of NHL was observed with exposure to phenoxy herbicides among participants who reported never using protective equipment (odds ratio [OR] = 2.4, 95 % CI: 0.9–7.6) [51]; increased risks were also observed specifically for 2,4-D and MCPA. McDuffie et al. observed significantly increased risk of NHL in association with occupational phenoxy herbicide exposure (OR = 1.4, 95 % CI: 1.1–1.8), as well as with the individual phenoxy herbicides 2,4-D (OR = 1.3, 95 % CI: 1.0–1.7) and mecoprop (OR = 2.3, 95 % CI: 1.6–3.4), but not MCPA, in a multisite Canadian case-control study of NHL in men (*n* = 517 cases, 1,506 controls) [86]. In a small case-control study of lymphohematopoietic cancers (*n* = 51 leukemia, 60 NHL) nested within a cohort of members of a farm workers union in California, Mills et al. observed that a history

Table 28.2 Case-control studies of specific pesticides classes and compounds in relation to non-Hodgkin lymphoma (odds ratios and 95 % confidence intervals)

Reference	Study details	Exposure assessment	Organochlorine insecticides		Organophosphate insecticides		Carbamate pesticides		Phenoxyacetic acid herbicides		Other herbicides	
McDuffie [48]	517 cases, 1,506 controls Population based, men Canada, 6 provinces, 1991–1994	Structured questionnaire with detailed questions on farming history and pesticide use	Aldrin	3.8 (1.3–10.8)	Organophosphates	1.7 (1.3–2.3)	Carbamate insecticides	2.0 (1.3–3.1)	Phenoxy herbicides	1.5 (1.1–1.8)	Glyphosate	1.3 (0.9–1.8)
			Chlordane	1.1 (0.7–1.6)	Diazinon	1.7 (0.9–3.2)	Carbaryl	2.1 (1.2–3.6)	2,4-D	1.3 (1.0–1.6)	Dicamba	1.9 (1.4–2.7)
			DDT	1.6 (1.0–2.6)	Dimethoate	1.2 (0.8–2.0)	Carbofuran	1.6 (0.7–3.7)	MCPA	1.1 (0.6–1.9)		
			Lindane	2.1 (1.0–4.2)	Malathion	1.8 (1.3–2.5)	Methomyl	1.9 (0.7–5.2)	Mecoprop	2.2 (1.4–3.1)		
			Toxaphene	1.1 (0.6–2.0)			Thiocarbamate herbicides	1.4 (0.6–2.2)				
Hardell [49]	515 cases (includes HCL), 1,141 controls Population based Sweden, 1987–1992	Questionnaires eliciting use of specific pesticides	DDT	1.3 (0.9–1.7)					Phenoxy herbicides	1.7 (1.2–2.3)	Glyphosate	3.0 (1.1–8.5)
									2,4-D and 2,4,5-T	1.5 (1.0–2.2)		
									MCPA	2.6 (1.4–4.9)		
De Roos [50]	650 cases, 1,933 controls Population based USA, Midwest, 1980–1986	Questionnaires eliciting use of specific pesticides	DDT	1.0 (0.7–1.3)	Coumaphos	1.7 (0.9–1.3)	Carbaryl	1.1 (0.6–1.9)	2,4-D	0.9 (0.6–1.2)	Glyphosate	1.6 (0.9–2.8)
			Lindane	1.2 (0.8–1.9)	Diazinon	1.7 (1.0–2.8)	Carbofuran	1.0 (0.4–2.3)	2,4,5-T	0.9 (0.5–1.6)	Atrazine	1.5 (1.0–2.2)
			Toxaphene	1.1 (0.6–2.0)	Dichlorvos	0.9 (0.5–1.7)	Butylate	1.2 (0.7–2.0)	MCPA	0.9 (0.4–2.0)	Dicamba	1.2 (0.7–2.1)
					Famphur	0.8 (0.4–1.5)	EPTC	1.1 (0.5–2.3)				
					Fonofos	1.5 (0.9–2.7)						
					Malathion	1.1 (0.7–1.7)						

					Phorate	0.9 (0.5–1.5)						
					Terbufos	0.8 (0.5–1.6)						
Miligi [51, 52]	1,145 cases (includes CLL), 1,232 controls Population based Italy, multiple centers, 1990–1993	Structured questionnaire with detailed questions on pesticide use, in addition to expert review	DDT (men)	0.6 (0.3–1.1)	Tyolophosphates (men)	1.1 (0.7–2.9)	Carbamate insecticides (men)	0.9 (0.4–1.6)	Phenoxy herbicides	1.0 (0.5–2.0)	Atrazine (men)	0.8 (0.3–2.0)
			Lindane (men)	2.0 (0.6–7.7)	Tyonophosphates (men)	1.0 (0.6–1.6)	Carbaryl (men)	2.2 (0.9–6.4)	Phenoxy herbicides (with no protective equipment)	2.4 (0.9–7.6)		
					Phosphonates (men)	4.1 (0.7–79)	Carbamate herbicides (men)	1.2 (0.5–3.6)				
					Phosphoroamidon (men)	1.4 (0.6–3.7)	Dithiocarbamate fungicides (men)	0.9 (0.6–1.4)				
Fritschi [53]	694 cases, 694 controls Population based Australia, New South Wales, 2000–2001	Structured questionnaire with job-specific modules to elicit information on tasks and exposures, in addition to expert review	Organochlorines (substantial)	3.3 (0.7–16.4)	Organophosphates (substantial)	2.1 (0.8–5.7)			Phenoxy herbicides (substantial)	1.8 (0.4–7.4)		
Mills [54]	60 cases, 5 controls per case Nested within a California farm worker labor union (139,000 members) USA, California, 1988–2001	Union records linked to CA Department of Pesticide Regulation pesticide usage databases	Toxaphene	0.9 (0.5–1.9)	Diazinon	1.4 (0.8–2.5)	Mancozeb	0.9 (0.5–1.9)	2,4-D	3.8 (1.9–7.8)	Simazine	1.7 (0.9–3.0)
					Malathion	1.8 (1.0–3.2)	Maneb	1.1 (0.6–2.1)				
					Methyl parathion	0.6 (0.3–1.2)						

(continued)

Table 28.2 (continued)

Reference	Study details	Exposure assessment	Organochlorine insecticides	Organophosphate insecticides	Carbamate pesticides	Phenoxyacetic acid herbicides		Other herbicides	
Eriksson [55]	910 cases (with CLL), 1,016 controls Population based Sweden, 4 of 7 health services regions, 1999–2002	Questionnaire with detailed questions on occupational history and pesticide use	DDT (>37 days) 1.8 (1.0–3.2)			Phenoxy herbicides	2.0 (1.2–3.4)	Glyphosate	2.0 (1.1–3.7)
						MCPA	2.8 (1.3–6.2)		
						2,4-D and/or 2,4,5-T	1.6 (0.9–3.0)		
Orsi [56]	244 cases, 436 controls Hospital based France, 6 centers, 2000–2004	Structured questionnaire with detailed questions on pesticide use, in addition to expert review	Organochlorines 1.8 (0.9–3.8)	Organophosphates 1.7 (0.9–3.3)	Carbamates 1.8 (0.9–3.7)	Phenoxy herbicides	0.9 (0.4–1.9)	Glyphosate	1.0 (0.5–2.2)

Includes studies published since 2000

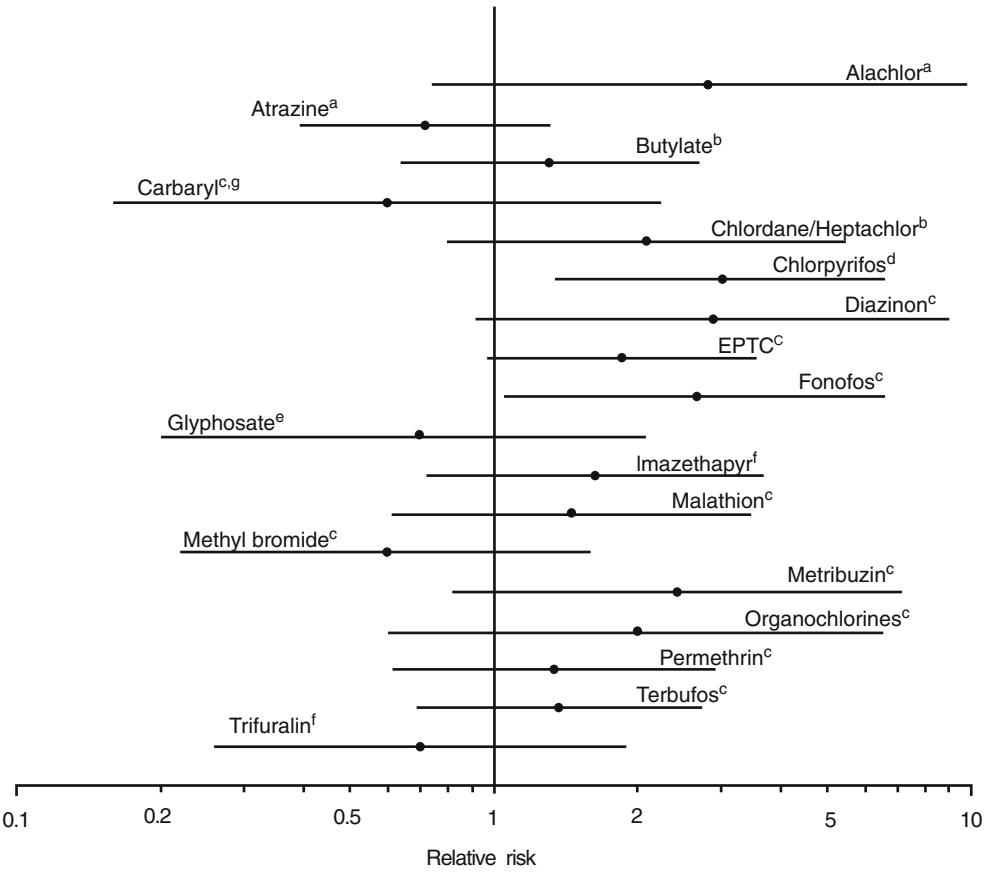


Fig. 28.1 Relative risks of leukemia from exposure to various pesticides in the Agricultural Health Study. Exposure is intensity-weighted lifetime exposure days, unless otherwise specified; the exposure contrast for each risk estimate is denoted by footnote. *a* highest vs. lowest quartile; *b* above median vs. none; *c* highest tertile vs. none; *d* highest quartile vs. none; *e* highest vs. lowest tertile; *f* above median of highest tertile vs. none; *g* exposure is lifetime exposure days

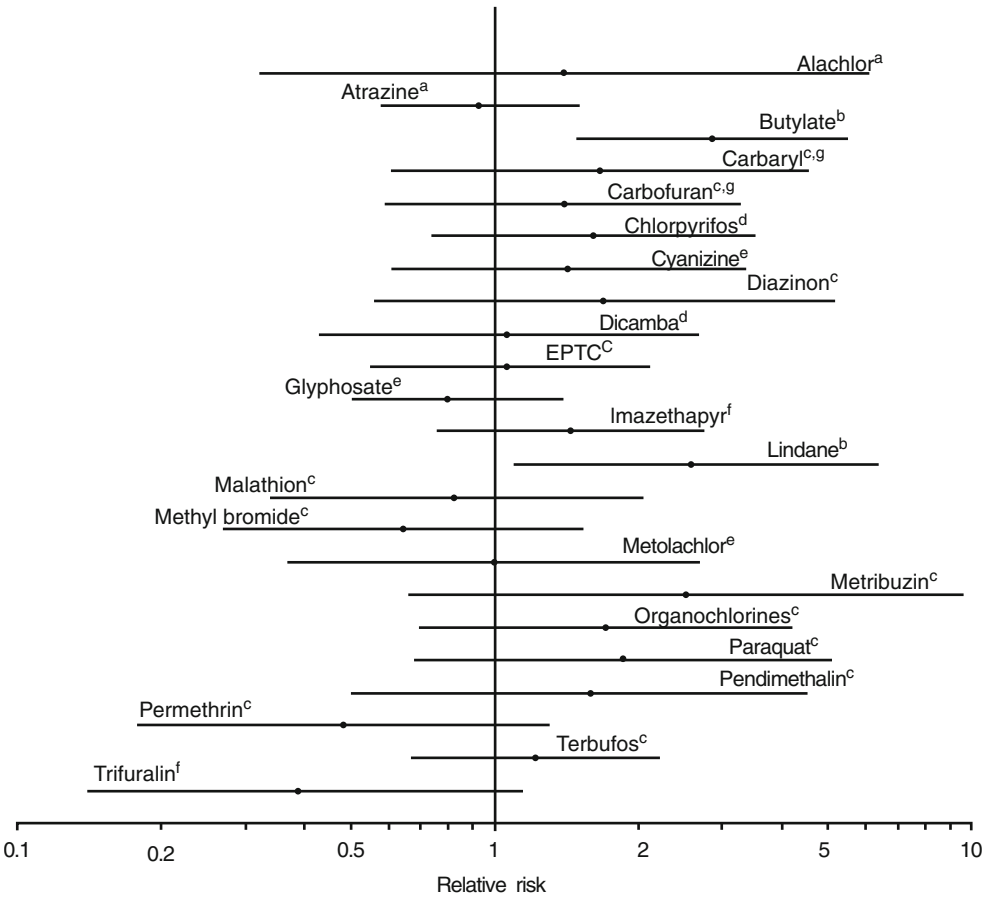


Fig. 28.2 Relative risks of non-Hodgkin lymphoma (NHL) from exposure to various pesticides in the Agricultural Health Study. Exposure is intensity-weighted lifetime exposure days, unless otherwise specified; the exposure contrast for each risk estimate is denoted by footnote. *a* highest vs. lowest quartile; *b* above median vs. none; *c* highest tertile vs. none; *d* highest quartile vs. none; *e* highest vs. lowest tertile; *f* above median of highest tertile vs. none; *g* exposure is lifetime exposure days

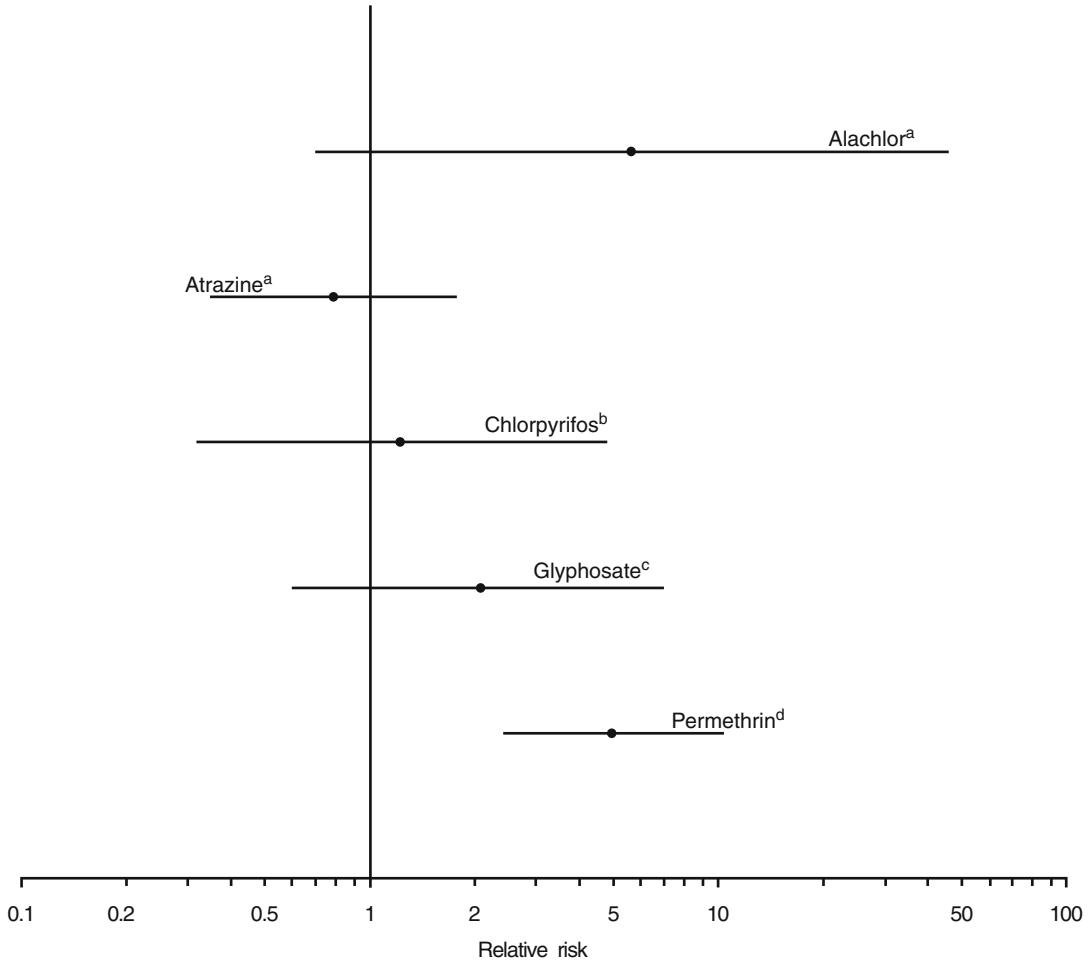


Fig. 28.3 Relative risks of multiple myeloma (MM) from exposure to various pesticides in the Agricultural Health Study. Exposure is intensity-weighted lifetime exposure days; the exposure contrast for each risk estimate is denoted by footnote. *a* highest vs. lowest quartile; *b* highest quartile vs. none; *c* highest vs. lowest tertile; *d* highest tertile vs. none

of high exposure to 2,4-D (based on linkage of employment records to California Department of Pesticide Regulation databases) was associated with a 3.8-fold increased risk of NHL when compared to those with a low exposure history (95 % CI: 1.9–7.8), and this association appeared in both women (OR = 5.2, 95 % CI: 1.3–21) and men (OR = 3.8, 95 % CI: 1.6–9.1) [54]. However, there were only small, non-significant increases of leukemia associated with phenoxy herbicides. In their study of lymphoid cancers among men in France (n = 244 NHL, 87 HL, 56 MM, 77 CLL, n = 27 hairy cell leukemia), Orsi et al. did not observe any association between a history of phenoxy herbicide exposure and NHL but did observe a significant association with hairy cell leukemia (OR = 4.1, 95 % CI: 1.1–15.5), as well as nonsignificant increases for HL (OR = 2.5, 95 % CI: 0.8–7.7) and MM (OR = 2.6, 05 % CI: 0.9–7.0) [56]. Phenoxy herbicides were also associated with NHL (OR = 2.6, 90 % CI: 1.1–6.1) and MM (OR = 2.2, 90 % CI: 1.2–4.7) in case-control studies conducted in Sweden [87, 88]. Results from follow-up of the AHS and other prospective cohorts will add important information to evaluate the possible association between phenoxy herbicides and risk of NHL and other lymphohematopoietic cancers.

In a pooled analysis of three case-control studies of NHL in men (n = 879 cases, 2,569 controls), conducted in the mid-western USA, De Roos et al. (2003) observed that atrazine, a commonly used triazine herbicide (with 73–78 million pounds used in the USA in 2007) [85], was associated with an increased risk of NHL (OR = 1.5, 95 % CI: 1.0–2.2) but found no association with cyanazine [50]. Orsi et al. reported that exposure to triazine herbicides was associated with increased risk of lymphoid cancers overall (OR = 1.8, 95 % CI: 1.0–3.3), with elevated risk estimates for the subgroups NHL, DLBCL, follicular lymphoma, HL, and MM, and a significant association with hairy cell leukemia (OR = 5.1, 95 % CI: 1.4–19.3, n = 4 exposed cases) [56]. Mills et al. found nonsignificantly increased risks of NHL (OR = 1.7, 95 % CI: 0.9–3.0) and lymphocytic leukemia (OR = 1.5, 95 %

CI: 0.5–6.6) in association with the triazine herbicide, simazine [54]. In contrast, no significant associations were observed between lymphohematopoietic cancers and exposure to atrazine or cyanazine in the AHS [71, 89] or with triazine herbicides in the Italian case-control study by Miligi et al. [52].

Several case-control studies have reported that exposure to glyphosate, the most widely applied agricultural pesticide in the USA (180–185 million pounds used in 2007) [85], was associated with an increased risk of NHL, with relative risks ranging from 1.6 to 3.0 for ever exposed [49, 50, 55]. McDuffie et al. found no overall association of NHL risk with glyphosate exposure (OR = 1.3, 95 % CI: 0.9–1.8) but did observe a 2.1-fold increased risk associated with exposure more than 2 days per year (OR = 2.1, 95 % CI: 1.2–3.7) [86]. Eriksson et al. also observed increasing NHL risk with higher frequency of use (OR for ≤10 days use = 1.7, 95 % CI: 0.7–4.1; OR for >10 days use = 2.4, 95 % CI: 1.0–5.4) [55]. One case-control study found no association with NHL [56]. In the AHS, there was no association between glyphosate exposure and NHL but suggestive evidence of an elevated risk of MM when comparing the highest tertile of intensity-weighted cumulative exposure days to the lowest tertile (RR = 2.1, 95 % CI: 0.6–7.0, $n = 8$ cases in the highest tertile) [63]. While these results are intriguing, there is little evidence of biologic effects of glyphosate in humans; therefore, no clear biologic mechanism has been proposed.

The use of carbamate herbicides has declined in recent years, but in 2001, the carbamate herbicide *S*-ethyl-*N*-*N*-dipropylthiocarbamate (EPTC) was among the 25 most commonly used agricultural pesticides in the USA (5–8 million pounds) [85, 90]. The highest tertile of exposure days (but not intensity-weighted exposure days) to EPTC was associated with a 2.4-fold increased risk of leukemia in the AHS (95 % CI: 1.2–4.8), and there was evidence of a trend with increasing exposure (p-trend = 0.02) [82], based on five, three, and ten cases in the lowest, middle, and highest tertiles of exposure, respectively. Significant associations were also observed between the highest tertile of intensity-weighted lifetime exposure days to the carbamate herbicide butylate and lymphohematopoietic cancers overall (RR = 2.0, 95 % CI: 1.3–3.1, p-trend = 0.001) and with NHL (RR = 2.9, 95 % CI: 1.5–5.5, p-trend = 0.002); these associations were consistent when examining unweighted lifetime exposure to butylate [72]. However, several case-control studies have not observed any association between lymphohematopoietic cancers and carbamate herbicide exposures [50, 52, 86].

Among less well-studied herbicides, increasing risk of lymphohematopoietic cancers overall was seen in the AHS with increasing lifetime alachlor exposure days (p-trend = 0.02) and intensity-weighted exposure days (p-trend = 0.03) [69]. For the latter metric, a significantly elevated risk was observed when comparing the highest quartile of exposure to the lowest quartile (RR = 2.4, 95 % CI: 1.0–5.9). When looking by subtype, there were few exposed cases, but nonsignificant elevated risks and suggestions of trends for leukemia and MM were found. De Roos et al. did not observe any association between alachlor and NHL [50].

Insecticides

Organophosphate insecticides are the most widely used class of insecticides in the USA, in particular, chlorpyrifos, of which 7–9 million pounds was used in 2007 [85]. These chemicals act against insects by inhibiting acetylcholinesterase, which is critical to nerve function. Several studies have observed increased risks of lymphohematopoietic cancers associated with organophosphates, as a group [53, 56, 86, 91]. Fritschi et al. observed that exposure to organophosphates was associated with an elevated risk of NHL (OR = 2.1, 95 % CI: 0.8–5.7), and the relative risk was higher for follicular lymphoma (OR = 4.3, 95 % CI: 1.4–13) than for DLBCL (OR = 2.1, 95 % CI: 0.6–7.7) [53]. Orsi et al. also observed a higher relative risk for FL than DLBCL in association with organophosphates, and they additionally observed a threefold increased risk of HL (95 % CI: 1.0–9.4, $n = 6$ exposed cases) and over twofold increased risk of MM (95 % CI: 0.8–6.2, $n = 6$ exposed cases) [56]. Miligi et al. did not observe any significant associations between organophosphate insecticide exposures and NHL but did observe an increased risk of leukemia among women (OR = 5.4, 95 % CI: 1.4–30, $n = 6$ exposed cases) [52].

Several studies have looked at specific organophosphate compounds. In the AHS, increased risks of leukemia were observed with number of lifetime exposure days to the organophosphate insecticides diazinon (RR for highest tertile compared to unexposed = 3.4, 95 % CI: 1.1–10, p-trend = 0.03, $n = 3$, 4 and 4 cases from lowest to highest tertile of exposure) and number of intensity-weighted exposure days to fonofos (RR for highest tertile compared to unexposed = 2.7, 95 % CI: 1.1–6.7, p-trend = 0.04, $n = 6$, 4 and 6 cases from lowest to highest tertile of exposure) [73, 92]. The highest quartile of intensity-weighted exposure days to chlorpyrifos was also associated with an increased risk of leukemia (RR compared to unexposed = 3.0, 95 % CI: 1.4–6.7), but there was no evidence of a trend with increasing exposure [68]. Associations of terbufos with leukemia and NHL were also observed, but significant increased risks were restricted to middle tertile categories of cumulative exposure and there was no evidence of a trend [61]. No significant associations with lymphohematopoietic cancers have been observed for exposure to malathion, coumaphos, dichlorvos, or phorate in the AHS [60, 62, 67, 74]. In the De Roos et al. pooled analysis, there was evidence of increased risks of NHL with report of exposure to diazinon (OR = 1.7, 95 %

CI: 1.0–2.8), fonofos (OR = 1.5, 95 % CI: 0.9–2.7), and coumaphos (OR = 1.7, 95 % CI: 0.9–3.3), but not malathion, dichlorvos, or phorate [50]. Mills et al. observed nonsignificantly elevated risk estimates for malathion and diazinon in relation to NHL and leukemia, and the increases were significant for malathion in relation to extranodal NHL (OR = 3.5, 95 % CI: 1.2–10) and among women (OR = 4.9, 95 % CI: 1.2–20) [54]. McDuffie et al. also found increased risk of NHL associated with malathion exposure (OR = 1.8, 95 % CI: 1.3–2.6) and a nonsignificant increase with diazinon exposure (OR = 1.7, 95 % CI: 0.9–3.2), but no association with dimethoate [86]. The overall evidence suggests increased risks of lymphohematopoietic cancers associated with at least some organophosphate insecticides that should be investigated further, given the widespread current use of many of these chemicals.

Most organochlorine insecticides have been banned in the USA because of concerns of effects on wildlife, but the use of these compounds does continue in many parts of the world. Orsi et al. found that organochlorine insecticide exposure was associated with increased risk of lymphoid cancers overall (OR = 1.6, 95 % CI: 1.0–2.5) and with increased risk of HL (OR = 4.7, 95 % CI: 1.1–20.8), though the latter observation was based on only four exposed cases [56]. De Roos et al. observed suggestive evidence of small increased risks of NHL with exposure to organochlorine insecticides, specifically chlordane (OR = 1.3, 95 % CI: 0.8–2.1) and dieldrin (OR = 1.4, 95 % CI: 0.8–2.6) [50], and a detailed analysis of lindane in the same midwestern US pooled studies found significant associations between lindane and NHL risk with longer latency since exposure (OR for ≥20 years latency = 1.7, 95 % CI: 1.1–2.5), with no use of protective equipment (OR = 1.5, 95 % CI: 1.0–2.2), and with greater frequency of use (OR for ≥5 days per year use = 2.0, 95 % CI: 0.6–6.4), consistent with a causal relationship [93]. Though McDuffie et al. observed significantly increased risks with organochlorine insecticides aldrin, lindane, and DDT in individual analyses, aldrin was the only insecticide to remain a significant predictor of NHL in a multivariate analysis considering multiple pesticides in the same model (OR = 3.4, 95 % CI: 1.2–10) [86]. In the AHS, there were nonsignificantly elevated risk estimates for organochlorine pesticide exposure, as a group (including aldrin, chlordane, DDT, dieldrin, and toxaphene), in relation to NHL and leukemia, particularly for higher lifetime days exposed or intensity-weighted exposure compared to unexposed (RRs ranged from 1.5 to 2.4 for the highest exposure categories) [78]. The authors also reported significant associations between lindane and NHL and a trend with increasing exposure (RR for highest category of intensity-weighted exposure compared to unexposed = 2.6, 95 % CI: 1.1–6.4, *p*-trend = 0.04), between lindane and leukemia for ever exposed (RR = 2.0, 95 % CI: 1.1–3.5), and between chlordane/heptachlor and leukemia with increasing risk by exposure (RR for highest category of lifetime days exposed compared to unexposed = 2.6, 95 % CI: 1.2–6.0, *p*-trend = 0.02) [78]. In studies of the general population in which risk of NHL was correlated with organochlorine concentrations in blood, most studies found no association between NHL and p,p'-DDE (the major metabolite of the pesticide DDT) [94–99]. However, several studies found significant increases in NHL risk with measured concentrations of chlordane-related compounds [97, 100–102]. In summary, there is fairly consistent evidence of modestly increased lymphoid cancer risks associated with certain organochlorine insecticides, although the specific organochlorines relating to increased risk have not been clearly identified. These risks are relevant to continued use of these pesticides outside of the USA, as well as for ongoing environmental exposures.

Though not as commonly used as other pesticides discussed here, pyrethrin insecticide use has been on the rise. In 2006, it was estimated that 2 million pounds of the pyrethrin insecticide permethrin was applied, though over 70 % of use was in nonagricultural settings [103]. While Hardell et al. and De Roos et al. did not observe significant associations with pyrethrin insecticides and NHL risk (n = 13 and 6 exposed cases, respectively) [49, 50], Orsi et al. observed increased risks of HL (OR = 3.6, 95 % CI: 1.2–11.2, n = 7 exposed cases) and MM (OR = 3.1, 95 % CI: 1.0–10, n = 5 exposed cases) with pyrethrin exposure [56]. In the AHS, increased risk of MM was observed for exposure to the pyrethrin insecticide, permethrin, with the highest tertile of intensity-weighted exposure days associated with a fivefold increased risk of disease (95 % CI: 2.4–10, *p*-trend < 0.01) compared to those never exposed (n = 2, 3 and 10 cases from lowest to highest tertile of exposure) [80]. Results were very similar when analyzing lifetime exposure days.

Fungicides

Fungicides have not been addressed in a consistent manner across multiple studies as have some herbicides and insecticides. Mills et al. observed an association between occupational exposure to mancozeb, a widely used carbamate fungicide which, in 2007, was among the 25 most used agricultural pesticides in the USA (4–6 million pounds) [85], and leukemia risk (OR = 2.4, 95 % CI: 1.1–5.0), and the relative risk was higher when restricting to granulocytic (myeloid cell) leukemias (OR = 3.4, 95 % CI: 1.1–10) [54]. Mills et al. also observed nonsignificant increased risk of leukemia, but not NHL, associated with the carbamate fungicide, maneb (OR = 1.8, 0.9–3.8) [54]. In contrast, Miligi et al. observed no significant associations of carbamate fungicides, in general, or mancozeb specifically, with leukemia or NHL [52]. Miligi et al. did find that exposure to dinocap, a dinitrophenol

fungicide, was associated with a significantly increased risk of NHL (OR = 5.9, 95 % CI: 1.4–41, *n* = 8 exposed cases) and leukemia (OR = 8.5, 95 % CI: 1.7–63, 5 exposed cases) among women, but not in men [52]. Benomyl, a benzimidazole fungicide, was also found to be significantly associated with risk of leukemia among women (OR = 4.1, 95 % CI: 1.0–21, *n* = 5 exposed cases) and with a nonsignificant increase in NHL/CLL among men (OR = 1.7, 95 % CI: 0.6–5.8). Orsi et al. found that exposure to triazole fungicides was associated with an 8.4-fold increased risk of HL (95 % CI: 2.2–32) and nonsignificant increases in NHL, MM, DLBCL, and follicular lymphoma [56]. McDuffie et al. found increased risk of NHL associated with the amide fungicide captan (OR = 2.5, 95 % CI: 1.3–4.6) and for sulfur-compound fungicides (OR = 2.3, 95 % CI: 1.2–4.4) [86].

Several chemicals have been used as fungicides (and insecticides) in lumber, such as in utility poles and railroad ties. Pentachlorophenol, used heavily for wood preservation before severe restrictions starting in the 1980s, has been fairly consistently associated with increased risk of NHL, with elevated risk estimates observed in both case-control studies [49, 104] and cohorts [105–108]. Pentachlorophenol, like phenoxy herbicides, is produced from chlorophenol and is frequently contaminated with dioxins, in addition to other chlorophenols. While the contaminants are also of concern as risk factors for lymphohematopoietic cancers, a recent review concluded that the risks observed in relation to pentachlorophenol are unlikely to be accounted for by the contaminants [109], supported by differing patterns of cancer risk in dioxin-exposed and pentachlorophenol-exposed cohorts. In addition, a study of sawmill workers in British Columbia, Canada, with expert exposure assessment, observed exposure-response patterns of risk for NHL and MM in association with pentachlorophenol (with RRs of 2.0 and 3.8 for NHL and MM, respectively, for ≥5 exposure years vs. <1 year), but not with tetrachlorophenol, the primary contaminant in pentachlorophenol products [106]. Other chemicals used as wood preservatives have also been associated with lymphohematopoietic cancers, including arsenate-based pesticides [49, 50, 55, 91, 110] and creosote [49, 55, 110, 111].

Conclusion

While the overall evidence suggests a causal role for occupational pesticide exposures in the etiology of lymphohematopoietic cancers, more research is needed to identify specific pesticides posing increased risk. Inconsistencies in research results are likely attributable to the small numbers of exposed cases in studies conducted thus far; and consortium-based efforts may be helpful in this regard. Research in this area is challenging due to the vast variety of pesticide active ingredients and formulations, in addition to the fact that farmers and other pesticide-exposed workers are usually exposed to multiple types of pesticides in addition to other occupational exposures. Continued follow-up of agricultural cohorts is needed, with a continued focus on generating quantitative exposure estimates to allow for the detailed evaluation of dose-response relationships. Further research is also needed to clarify whether risks are specific to certain lymphohematopoietic cancer subtypes. There are few studies until now of myeloid leukemias in relation to specific pesticides, despite some indication from studies of farming or any pesticide exposure of higher relative risks for myeloid cell neoplasms than for lymphomas. Mechanisms of carcinogenesis should be further investigated in human, animal, and in vitro studies to add weight to epidemiologic data. Molecular subtyping may be useful in refining etiologically related cancer subgroups as well as in elucidating potential mechanisms, as two studies have found increased risks of NHL associated with pesticide exposures to be specific to NHL with a t(14;18) chromosomal translocations [112, 113].

Animal Exposures

Exposure to animals has also received attention as a possible cause for increased lymphohematopoietic cancer risks among farmers, with zoonotic viruses suspected as causal agents. In a case-control analysis of adult death certificate data from 24 states in the USA (*n* = 38,598 leukemia, 72,589 NHL, 5,479 HL, 35,857 MM), occupational exposure to animals (assessed based on usual occupation as reported on the death certificate) was found to be associated with increased mortality of each lymphohematopoietic cancer case group, with risk estimates between 1.2 and 1.3 [114]. Significantly increased risks were also seen for various histological subtypes, including ALL (OR = 1.5, 95 % CI: 1.3–1.9), CLL (OR = 1.2, 95 % CI: 1.1–1.4), AML (OR = 1.4, 95 % CI: 1.3–1.6), CML (OR = 1.3, 95 % CI: 1.2–1.5), and diffuse NHL (OR = 1.5, 95 % CI: 1.3–1.7), but not follicular NHL (OR = 1.1, 95 % CI: 0.8–1.6). Results were consistent when stratifying by sex. The majority of exposed occupations were agricultural, and the risks associated with employment in the livestock industry exceeded the corresponding risks associated with the crop industry for all outcomes except HL (OR for livestock industry in relation to NHL = 1.45, 95 % CI: 1.34–1.58; OR for crop industry in relation to NHL = 1.17, 95 % CI: 1.11–1.23) [114]. Men who worked as livestock breeders were at nonsignificantly increased risk of NHL in a study based on Swedish censuses in 1960 and 1970 (SIR = 1.6, 95 % CI: 0.6–4.3, *n* = 4 exposed cases), and the elevation was stronger when limiting to men reporting the same occupation in both censuses (RR = 2.8, 95 % CI: 0.7–11.2, *n* = 2 exposed cases) [115]. A smaller, but more precise increased

risk was observed in the same study for dairy workers (RR = 1.6, 95 % CI: 0.9–2.7, *n* = 14 exposed cases).

Several studies have examined lymphohematopoietic cancer risks associated with specific types of farm animals and have observed increased risks associated with cattle exposure for NHL [56, 91, 116, 117], leukemia [116, 118], MM [87, 116, 119], hairy cell leukemia [120, 121], and HL [122]. However, several studies observed no associations for lymphohematopoietic cancers with cattle [48, 123, 124] or found risks with beef cattle, but not dairy cattle [116, 118, 119], suggesting that any observed risks may be due to animal husbandry practices specific to beef cattle rather than infectious agents from cattle in general. Hog farming was associated, with or without statistical significance, with lymphoid cancers in most [48, 56, 87, 91, 116, 117, 119–121, 123], but not all [122, 124] studies that examined the association, and higher relative risks were estimated based on longer duration [120] or greater number of hogs [48]. Increased lymphoid cancer risks have also been observed in relation to raising sheep [87, 91, 119, 121, 124, 125] and poultry [56, 116, 120, 123, 125], but several studies also found no association for each of these types of animals. Lymphohematopoietic cancer mortality was increased in a cohort of poultry processing workers (*n* = 2,639), relative to workers at nonmeat companies (RR = 2.9, 95 % CI: 1.0–8.1, *n* = 8 exposed deaths), and the increase was particularly pronounced, but not statistically significant, for MM [126]. Most studies that assessed exposure to horses found no association with lymphohematopoietic cancers [48, 91, 116, 122, 125], although associations have been observed with MM [87] and hairy cell leukemia [120].

Nonfarming occupations with exposure to animals or animal products have also been inconsistently associated with lymphohematopoietic cancers, such as work in an abattoir with AML (OR = 2.3, 95 % CI: 1.0–5.2), particularly among those reporting direct contact with animals or animal products (OR = 5.2, 95 % CI: 1.2–22.2) [127], and with all lymphomas [128]. Several other studies have observed increased risk of NHL with butchering and meat packaging/processing [129, 130]. A proportionate mortality study among US veterinarians (*n* = 5,016) showed an elevated proportion of deaths from lymphohematopoietic cancers, with a significant excess for HL [131]; however, no increase was found in British veterinary surgeons (*n* = 3,440) [132]. Veterinarians were more likely to have MM as a cause of death compared to all other occupations without animal exposure in a US case-control study (OR = 2.0, 95 % CI: 1.2–3.3), and a similar, nonsignificant increase was seen for HL (OR = 2.0, 95 % CI: 0.6–6.4), but not NHL (OR = 0.8) [114].

There does appear to be a general association between animal exposures and risk of various lymphohematopoietic cancers; however, analyses examining exposure to specific animals have produced mixed results. Furthermore, given that animal exposures occur primarily among farmers, it is difficult to disentangle any impact of pesticide exposure on disease risks. In establishing causality, future studies would benefit from incorporating biomarkers of exposure, such as serological tests to assess the presence or absence of antibodies to specific viruses.

Dioxins, Furans, and Polychlorinated Biphenyls

Dioxins, furans, and polychlorinated biphenyls (PCBs) are pollutants that persist in the environment and in biologic media. These chemicals are lipid soluble, accumulating in the fatty tissue of animals. Thus, the highest concentrations are found in species at the top of the food chain, especially those that eat fish: human beings, marine mammals, and fish-eating birds. Human exposure to persistent organochlorines occurs primarily through the diet, although occupational exposures can also be an important source for certain jobs. Organochlorines continue to be found in humans since bans and tighter regulation starting in the 1970s [133–135], because of their environmental persistence and lipophilic properties. In vivo concentrations have decreased in US populations; nevertheless, data from the 2003–2004 NHANES survey show detectable levels of many organochlorine compounds in a substantial proportion of the population [134]. Older persons have significantly higher concentrations than do younger persons, due to higher use in decades past as well as bioaccumulation in adipose tissue [134, 136]. Men tend to have higher persistent organic pollutant concentrations than women [134, 137, 138], which may partially reflect differing body composition between the sexes or occupational exposures.

Dioxins

"Dioxin" is a general term for the chlorinated dibenzo-p-dioxins, which are formed as by-products of incomplete combustion during manufacturing of certain pesticides such as phenoxy herbicides and chlorophenols, during bleaching of pulp and paper, and during thermal reactions such as waste incineration and wood combustion [139]. Another group of organochlorine compounds, furans, are formed in similar processes as dioxins. Dioxin and furan releases are now aggressively controlled through strict standards on industrial sources.

Dioxins and furans elicit toxicologic effects through their potential to bind to the aryl hydrocarbon (Ah) receptor, subsequently disrupting the transcription of numerous genes including cytochrome P450 1A1 and 1B1 [139]. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is recognized as the most toxic dioxin congener, as it binds most strongly to the Ah-receptor. TCDD and the furan congener 2,3,4,7,

8-pentachlorodibenzofuran have been declared Group 1 human carcinogens for all cancer sites by the International Agency for Research on Cancer (IARC), based on sufficient evidence in animals, a convincing mechanistic model, and limited evidence in humans [139, 140]. For lymphohematopoietic cancers, specifically, there is compelling evidence of TCDD carcinogenicity from highly exposed cohorts. In Seveso, Italy, lymphohematopoietic cancer mortality was increased in the 25 years following an accidental industrial release of TCDD (follow-up from 1976 to 2001), with a trend of increasing risk with higher exposure (RR for zone R with low exposure = 1.0, 95 % CI: 0.8–1.2, *n* = 124 deaths; RR for zone B with medium exposure = 1.6, 95 % CI = 1.1–2.3, *n* = 28 deaths; RR for zone A with high exposure = 2.2, 95 % CI: 1.0–5.0, *n* = 6 deaths) [141]. Lymphohematopoietic cancer mortality was also higher with longer latency since the accident in high-exposure zone A (RR for 15–19 years since first exposure = 3.3, 95 % CI: 0.8–13.3, 2 deaths; RR for ≥20 years since first exposure = 5.4, 95 % CI: 2.0–14.5, *n* = 4 deaths). There was evidence for a role of TCDD in several different types of lymphohematopoietic cancer, based on significant increases in mortality in high-exposure zone A for NHL (RR = 3.4, 95 % CI: 1.1–10.5, *n* = 3 deaths) and MM (RR = 4.3, 95 % CI: 1.1–17.5, *n* = 2 deaths) and a nonsignificant increase for myeloid leukemia (RR = 2.1, 95 % CI: 0.3–15.2, *n* = 1 death).

Occupational groups with exposure to dioxin-like compounds are workers exposed to phenoxy herbicides or chlorophenols, pesticides which in the past have been contaminated by dioxins (most notably, TCDD) and furans [139]. In an analysis combining 36 occupationally exposed cohorts (producers or sprayers) from 12 countries recorded in an IARC register, there was an elevated risk of NHL mortality among workers exposed to TCDD or higher-chlorinated dioxins (SMR = 1.4, 95 % CI: 0.9–2.1, *n* = 24 cases), but not among workers without exposure (SMR = 1.0, 95 % CI: 0.5–1.9, *n* = 9 cases) [142], and the increase was greater with longer latency (SMR for 0–9 years since first exposure = 0.63, 95 % CI: 0.1–2.3; SMR for 10–19 years since first exposure = 1.5, 95 % CI: 0.6–2.9; SMR for ≥20 years since first exposure = 1.6, 95 % CI: 0.9–2.7). In a nested case-control study of several exposed cohorts that included both incident cases and NHL deaths, there was indication of increasing risk by the level of exposure to any dioxin or furan (OR for low exposure = 1.4, 95 % CI: 0.5–4.1; OR for medium exposure = 2.2, 95 % CI: 0.7–7.0; OR for high exposure = 2.5, 95 % CI: 0.8–7.8) or to TCDD (OR for low exposure = 1.4, 95 % CI: 0.4–4.6; OR for medium exposure = 3.6, 95 % CI: 0.7–18.7; OR for high exposure = 3.6, 95 % CI: 0.7–19.2) [108]. These studies support a causal role of dioxins and furans in lymphohematopoietic cancers, although interpretation of cohort studies of phenoxy herbicide and chlorophenol is somewhat complicated by possible independent effects of the pesticides on lymphohematopoietic cancer risks.

There has been very limited investigation of possible effects of dioxins and dioxin-like chemicals at lower levels in the general population, in which exposures are ubiquitous but orders of magnitude lower than in occupationally and accidentally exposed persons. Spatial clusters of NHL and soft tissue sarcoma (but not Hodgkin disease) were identified as the most likely clusters found in a region of France surrounding a municipal solid waste incinerator with high dioxins emissions [143]. Notable associations between furans and risk of NHL were observed in a population-based case-control study (*n* = 100 cases, 100 controls) conducted at four Surveillance, Epidemiology, and End Results (SEER) registry sites in the USA [94], in which a 3.5-fold increased risk of NHL (95 % CI: 1.3–9.5) was associated with plasma concentration of summed furan congeners in the highest vs. lowest quartile, and over sevenfold increased risk was observed for those with concentrations above the 95th percentile (OR = 7.4, 95 % CI: 1.7–32.9). TCDD was not evaluated as it was detected in only seven subjects in this study; however, the toxic equivalency quotient (TEQ), a summed measure of dioxins, furans, and PCBs in which each congener is weighted by its potential to bind to the Ah-receptor relative to TCDD [144], was associated with NHL, with a 35 % increased risk per 10 pg/g lipid TEQ increase (95 % CI: 1.0–1.8) and a nonsignificant 2.3-fold increased risk for the highest compared to the lowest TEQ quartile (95 % CI: 0.8–6.2, *p*-trend = 0.06). These results suggest the importance of a dioxin-like mechanism in lymphomagenesis, even at lower exposure levels than in highly exposed occupations.

Polychlorinated Biphenyls

PCBs are mixtures of up to 209 individual organochlorine compounds that were used as coolants and lubricants in transformers, capacitors, and other electrical equipment prior to a ban on manufacturing in the USA in 1977. Production and use continued until later dates in other parts of the world. Each individual PCB congener is numbered according to its structure, with higher numbers indicating a greater number of chlorine atoms [145]. PCBs include both coplanar and noncoplanar configurations, which differ in their biologic properties. Coplanar (or non-ortho-substituted) PCBs exhibit similar toxicologic properties as dioxins by binding to the Ah-receptor, and largely based on these properties, the coplanar PCB 126 is listed as a Group 1 carcinogen by IARC [140]. Noncoplanar PCBs are thought to elicit biologic responses primarily through other, unknown pathways [146].

There are somewhat conflicting data from occupational and environmental studies regarding the potential for PCB exposure to cause lymphohematopoietic cancers. There are multiple studies showing increased risk of NHL with

increasing concentration of PCBs measured in blood or adipose tissue, from epidemiologic studies of the general population, including both prospective and retrospective designs [94–97, 99, 100]. Despite a few studies showing no association with PCBs [98, 101, 147, 148], the collective results from general population studies suggest that at least some PCB congeners are associated with NHL. In contrast, studies of occupationally exposed cohorts (primarily in electrical capacitor and transformer manufacturing) generally show no association between PCBs and risk of lymphohematopoietic cancers (SMR = 96, 95 % CI: 72–126, *n* = 51 deaths) [149]. The occupational studies do have a number of weaknesses, such as crude exposure assignment based on job title, risk estimation based on deaths (rather than incident disease), and very small numbers of lymphohematopoietic cancer cases in each study. Nevertheless, the discrepancy between the provocative evidence from general population-based studies and null results from the more highly exposed occupational cohorts necessitates further investigation before concluding that PCBs contribute to NHL risk.

Solvents

Solvents have been a suspected and scrutinized group of exposures for risks of lymphohematopoietic cancers, since increased risks have been repeatedly observed in jobs with frequent and/or high-intensity solvent exposures, such as work in the chemical industry [150, 151], machine operation [110, 152, 153], repair work [129], construction [110, 154–156], painting [157–159], metal work [160–162], and farm work [114, 155]. Plausible mechanisms by which various solvents may induce lymphohematopoietic cancer include DNA mutations [163–165], DNA hypomethylation [166], and immune dysregulation [167–169]. "Solvents" is a very broad category that includes many distinct chemicals in various formulations, primarily used for cleaning and degreasing and for blending other products (e.g., paints). Formulations often contain several different chemical solvents, and furthermore, several solvents are often used in the same workplace, for the same or different tasks. Data characterizing cancer risks associated with solvent exposures are needed to inform regulation – which is particularly important given that these chemicals are present as environmental contaminants as well as in occupational settings.

Benzene and Other Aromatic Hydrocarbon Solvents

Benzene is an aromatic hydrocarbon solvent used in petroleum fuel formulations, and thus, workers are exposed in petroleum refineries and petrochemical plants. Other exposed jobs include painting, printing, and shoe and leather production. Benzene is a known cause of AML [170], based on sufficient data from human studies, clear evidence of the bone marrow as a site of benzene toxicity [171], and genotoxicity in bone marrow precursor cells as a mechanism of leukemogenesis [170]. Cohort studies of benzene-exposed workers are individually small and underpowered, but meta-analyses have shown significantly increased risks of AML associated with benzene exposure; for example, Khalade found in a meta-analysis of nine studies that risk of AML was 3.2-fold greater (95 % CI: 1.1–9.5) with high benzene exposure (>100 ppm-yrs) than for unexposed [172]. In a pooled analysis of three cohorts from Australia, Canada, and the UK, with reclassification and grouping of case subtypes by a hematopathologist, benzene was most strongly associated with MDS, with over fourfold increased risk associated with the highest vs. lowest tertile of cumulative exposure (RR = 4.3, 95 % CI: 1.3–14.3) [173]. AML was only weakly associated with benzene exposure in this reanalysis (highest vs. lowest tertile, RR = 1.4, 95 % CI: 0.7–2.9) [173].

In contrast to AML (and possibly other myeloid neoplasms such as MDS), the role of benzene in development of lymphoid neoplasms is unclear and has been debated [174]. In the most recently updated review of benzene in 2009, IARC determined that in addition to the confirmed association with AML, there was also limited evidence that benzene causes ALL, CLL, NHL, and MM in humans [140]. This was supported by dose-response relations of lymphomas in rodents in long-term exposure studies [175–178], as well as in shorter-term animal studies [179, 180], and markers of genotoxicity in circulating lymphocytes of benzene-exposed workers [181–183]. A number of meta-analyses have been conducted on benzene in relation to lymphoid neoplasms, often with conflicting results [184]. In a meta-analysis of cohort studies that stratified results according to study quality criteria, analyses limited to studies deemed as having the highest-quality exposure assessment produced the most convincing evidence of an association between ever exposure to benzene and NHL (RR = 1.3, 95 % CI: 0.9–1.8), MM (RR = 1.5, 95 % CI: 1.0–2.3), ALL (RR = 2.8, 95 % CI: 0.3–29), and CLL (RR = 2.4, 95 % CI: 0.9–6.8), as well as the best confirmatory evidence for an association with AML (RR = 2.3, 95 % CI: 1.6–3.5) [185]. An increased risk of CLL was also found in a meta-analysis of ten studies (RR = 1.3, 95 % CI: 1.1–1.6), with higher risks observed for high cumulative exposure (RR = 3.5, 95 % CI: 0.9–13, based on only one study) [172]. An association between occupational benzene exposure and risk of MM was reported in a meta-analysis of benzene cohort studies (RR = 2.1, 95 % CI: 1.3–3.5) [186], but a meta-analysis limited to petroleum refinery worker cohorts saw no increase in MM mortality [187]; however,

Table 28.3 General population-based case-control studies of occupational solvent exposure in relation to lymphoid neoplasms (for each group of neoplasms: number of exposed cases, odds ratio, 95 % confidence interval)

Reference	Exposure	NHL		DLBCL		FL		CLL/SLL		MM		HL	
Aromatic hydrocarbons													
Miligi [188]	Medium/high intensity	143	1.2 (0.9–1.7)[a]	42	1.7 (1.1–2.7)	9	1.1 (0.5–2.5)	43	1.2 (0.8–1.9)[c]			23	1.2 (0.7–2.1)
	Medium/high intensity, >15 years	56	1.2 (0.7–1.9)[a]									8	2.1 (0.9–5.0
Costantini [189]	Medium/high intensity							27	1.3 (0.8–2.2)[d]	23	1.2 (0.7–2.0)		
	Medium/high intensity, >15 years							12	1.9 (0.9–4.2)[d]	13	1.4 (0.6–3.0)		
Cocco [190]	Ever	343	1.2 (1.0–1.4)[b]	91	1.0 (0.8–1.4)	53	1.7 (1.2–2.5)	86	1.4 (1.0–1.0)[d]	50	1.1 (0.8–1.6)	42	0.9 (0.6–1.4)
	High cumulative exposure, high confidence	89	1.3	21	1.1	10	1.5	23	1.5	16	1.4		
Orsi [191]	Ever	112	1.2 (0.8–1.7)					49	0.6 (0.4–1.0)	25	0.8 (0.4–1.5)	31	1.2 (0.7–2.2)
	High average intensity	6	1.8 (0.6–5.4)									2	2.3 (0.4–13.3)
	High intensity, > median duration	7	1.9 (0.7–5.6)									2	2.3 (0.4–13.1)
Benzene													
Fabbro-Peray [192]	Ever	22	2.0 (1.0–3.9)										
	Duration > 15 years	13	2.4 (0.9–5.9)										
	Exposure > 810 days	8	5.7 (1.4–23.2)										
Fritschi [193]	Ever	68	1.1 (0.8–1.6)										
	Substantial	7	0.3 (0.1–1.5)										
Miligi [188]	Medium/high intensity	58	1.6 (1.0–2.4)[a]	20	2.4 (1.3–4.5)			19	1.6 (0.9–3.1)[c]				
	Medium/high intensity, >15 years	14	2.9 (0.9–9.0)[a]										
Seidler [194]	Cumulative exposure > 130 ppm-yrs	11	1.0 (0.4–2.3)			2	1.3 (0.6–6.4)	2	0.7 (0.1–3.1)	3	1.8 (0.5–6.8)		
Costantini [189]	Medium/high intensity							12	1.8 (0.9–3.9)[d]	14	1.9 (0.9–3.9)		
	Medium/high intensity, >15 years							3	4.7 (0.8–26.5)[d]	5	4.1 (0.8–20.0)		
Tranah [195]	Ever	783	0.9 (0.8–1.1)	306	0.9 (0.7–1.2)	202	0.9 (0.7–1.2)	91	0.9 (0.6–1.3)				
	Medium/high intensity	232	1.0 (0.8–1.2)	98	1.0 (0.8–1.4)	60	0.9 (0.6–1.3)	24	0.8 (0.5–1.4)				
Wang [196]	Ever	120	1.1 (0.9–1.5)[a]										
	Medium-high probability	80	1.3 (0.9–1.8)[a]	29	1.5 (1.0–2.5)	20	1.5 (0.9–2.5)	9	1.3 (0.6–2.7)				
	Medium-high intensity	40	1.5 (0.9–2.4)[a]	15	1.8 (0.9–3.4)	11	1.8 (0.9–3.7)	5	1.6 (0.6–4.3)				
Cocco [190]	Ever, high confidence	118	1.1 (0.8–1.4)	28	0.9 (0.6–1.4)	17	1.6 (0.9–2.9)	34	1.4 (0.9–2.2)[d]	16	0.9 (0.5–1.6)		
	High cumulative exposure, high confidence	55	1.3[b]	11	0.9	4	1.0	17	1.8	10	1.4		
Orsi [191]	Ever	94	1.0 (0.7–1.5)	30	1.2 (0.7–2.0)	13	1.0 (0.5–2.1)	21	0.6 (0.3–1.0)[d]	28	1.3 (0.7–2.5)	21	0.7 (0.4–1.4)
	Cumulative exposure > 5 ppm-yrs	11	1.0 (0.4–2.1)	7	1.7 (0.6–4.4)	3	1.3 (0.3–5.1)	2	0.2 (0.0–0.8)[d]	3	0.4 (0.1–1.5)	2	2.8 (0.5–16.2)
	Ever pure benzene	6	3.0 (0.8–11.2)	2	3.3 (0.5–21.9)	2	5.8 (0.8–40.3)						
Wong [197]	Ever	50	1.1 (0.7–1.5)[a]	9	0.7 (0.3–1.4)	7	7.0 (1.5–34)	10	2.1 (0.8–5.3)				
Toluene													
Miligi [188]	Medium/high intensity	54	1.8 (1.1–2.8)[a]	16	2.4 (1.3–4.6)	5	2.2 (0.8–6.2)	16	2.0 (1.0–4.0)[c]				
	Medium/high intensity, >15 years	19	2.3 (1.0–5.6)[a]										
Seidler [194]	Cumulative exposure > 207 ppm-yrs	13	0.9 (0.4–2.0)	2	0.6 (0.1–2.5)	2	1.1 (0.2–5.3)	2	0.5 (0.1–2.4)	3	1.4 (0.4–5.2)		
Costantini [189]	Medium/high intensity							10	2.1 (0.9–4.7)[d]	5	0.9 (0.3–2.7)		

(continued)

Table 28.3 (continued)

Reference	Exposure	NHL		DLBCL		FL		CLL/SLL		MM		HL	
	Medium/high intensity, >15 years							4	4.4 (1.1–18.0)[d]	3	3.1 (0.6–17.2)		
Cocco [190]	Ever, high confidence	151	1.1 (0.9–1.4)	42	1.0 (0.7–1.4)	20	1.5 (0.9–2.4)	37	1.3 (0.9–1.9)[d]	20	0.9 (0.6–1.6)		
	High cumulative exposure, high confidence	68	1.5	16	1.1	8	1.8	19	1.8	11	0.4		
Wong [197]	Ever	4	1.0 (0.3–3.3)[a]										
Xylene													
Miligi [188]	Medium/high intensity	49	1.7 (1.0–2.6)[a]	15	2.3 (1.2–4.4)	5	2.2 (0.8–6.2)	15	1.9 (0.9–3.8)[c]				
	Medium/high intensity, >15 years	17	2.1 (0.9–5.0)[a]										
Seidler [194]	Cumulative exposure > 230 ppm-yrs	11	0.9 (0.4–1.9)	2	0.6 (0.1–2.6)	2	1.3 (0.3–6.2)			3	1.5 (0.4–5.8)		
Costantini [189]	Medium/high intensity							9	1.9 (0.8–4.5)[d]	6	1.2 (0.4–3.2)		
	Medium/high intensity, >15 years							3	3.3 (0.7–15.2)[d]	3	3.1 (0.6–17.0)		
Cocco [190]	Ever, high confidence	121	1.1 (0.8–1.4)	32	0.9 (0.6–1.4)	18	1.6 (0.9–2.7)	32	1.4 (0.9–2.1)[d]	14	0.8 (0.4–1.4)		
	High cumulative exposure, high confidence	57	1.5	14	1.2	7	1.9	17	2.1	7	1.1		
Wong [197]	Ever	7	1.1 (0.4–3.3)[a]					2	1.3 (0.2–8.0)				
Styrene													
Miligi [188]	Medium/high intensity	14	1.3 (0.6–2.9)[a]	3	1.1 (0.3–4.1)			5	1.6 (0.5–5.1)[c]				
Seidler [194]	Cumulative exposure > 67.1 ppm-yrs	12	0.8 (0.4–1.8)	5	1.5 (0.5–4.4)	3	1.6 (0.5–6.0)	2	0.5 (0.2–2.3)				
Cocco [190]	Ever exposed	66	1.6 (1.1–2.3)[b]	20	1.5 (0.9–2.5)	11	2.6 (1.3–5.2)	10	1.2 (0.6–2.5)[d]	6	0.9 (0.4–2.2)	10	1.1 (0.5–2.3)
Chlorinated hydrocarbons													
Fritschi [193]	Ever	40	1.1 (0.7–1.7)										
	Substantial	4	1.8 (0.5–6.2)										
Miligi [188]	Medium/high intensity	110	1.3 (0.9–1.8)[a]	34	1.9 (1.2–3.1)	10	1.6 (0.7–3.4)	29	1.2 (0.7–1.9)[c]			16	1.1 (0.6–2.0)
	Medium/high intensity, >15 years	44	1.0 (0.6–1.7)[a]									6	1.4 (0.5–3.6)
Seidler [194]	Cumulative exposure > 47.3 ppm-yrs	27	2.4 (1.2–4.7)[b]	5	1.8 (0.6–5.3)	5	3.9 (1.1–12.1)	6	1.8 (0.6–4.9)[d]	2	0.9 (0.2–4.4)		
Costantini [189]	Medium/high intensity							17	1.1 (0.6–2.0)[d]	16	1.1 (0.6–2.1)		
	Medium/high intensity, >15 years							9	1.2 (0.5–3.1)[d]	10	1.5 (0.6–3.9)		
Wang [196]	Ever	196	1.4 (1.1–1.8)[a]										
	Medium-high probability	44	1.5 (0.9–2.3)[a]	20	2.1 (1.2–3.8)	7	1.0 (0.4–2.3)	2	0.6 (0.1–2.5)				
	Medium-high intensity	89	1.5 (1.1–2.1)	39	2.2 (1.4–3.4)	16	1.2 (0.7–2.1)	5	0.6 (0.2–1.7)				
Cocco [190]	Ever	284	1.1 (0.9–1.3)[b]	68	0.8 (0.6–1.1)	44	1.5 (1.0–2.2)	74	1.4 (1.0–1.9)[d]	38	0.9 (0.6–1.3)	42	0.9 (0.6–1.4)
	High cumulative exposure, high confidence	54	1.2	16	1.2	6	1.3	15	1.5	7	0.9		
Orsi [191]	Ever	42	0.7 (0.4–1.0)					26	0.7 (0.4–1.2)	16	1.1 (0.5–2.2)	16	1.1 (0.6–2.2)
	High-intensity exposure, > median duration									2	3.3 (0.5–22.3)		
Trichloroethylene													
Miligi [188]	Medium/high intensity	35	1.2 (0.7–2.0)[a]	13	1.9 (0.9–3.7)			7	0.9 (0.4–2.1)[c]				
	Medium/high intensity, >15 years	12	1.0 (0.5–2.6)[a]										
Seidler [194]	Cumulative exposure > 35 ppm-yrs	17	2.3 (1.0–5.3)	4	2.6 (0.7–3.0)	3	3.2 (0.8–12.9)	2	0.9 (0.2–4.5)			2	2.0 (0.4–10.5)

Costantini [189]	Medium/high intensity							4	0.9 (0.3–2.6)[d]	5	0.9 (0.3–2.4)
	Medium/high intensity, >15 years							2	1.2 (0.2–6.2)[d]	3	1.3 (0.3–5.9)
Wang [196]	Ever	77	1.2 (0.9–1.8)[a]								
	Medium-high probability	34	1.4 (0.9–2.4)[a]	15	1.8 (0.9–3.4)	11	1.8 (0.9–3.7)	5	1.6 (0.6–4.3)		
	Medium-high intensity	13	2.2 (0.9–5.4)[a]								
Cocco [190]	Ever, high confidence	71	0.8 (0.6–1.1)	17	0.7 (0.4–1.1)	11	1.2 (0.6–2.3)	18	0.9 (0.5–1.5)[d]	9	0.6 (0.3–1.2)
	High cumulative exposure, high confidence	29	1.0	7	0.9	3	1.0	9	1.2	4	0.8
Gold [152]	Ever exposed, medium-high confidence									43	1.7 (1.0–2.7)
	High cumulative exposure, medium-high confidence									17	2.3 (1.1–5.0)
Purdue [198]	Ever, probable	45	1.4 (0.8–2.4)	11	0.9 (0.5–2.0)	13	2.1 (1.0–4.2)	11	2.7 (1.2–5.8)		
	Cumulative exposure > 234,000 ppm-hr	16	3.3 (1.1–10.1)								
	Cumulative exposure > 112,320 ppm-hr, probable exposure			9	1.9 (0.7–5.2)	6	3.3 (1.1–10.0)	4	2.7 (0.8–9.5)		
Dichloromethane											
Miligi [188]	Medium/high intensity	13	1.7 (0.7–4.3)[a]					6	3.2 (1.0–10.1)[c]		
Seidler [194]	Cumulative exposure > 175 ppm-yrs	5	2.7 (0.5–14.5)								
Costantini [189]	Medium/high intensity							2	1.6 (0.3–8.6)[d]		
Wang [196]	Ever exposed	52	1.5 (1.0–2.3)[a]								
	Medium-high probability	4	1.2 (0.3–4.4)[a]	15	1.8 (0.9–3.4)	11	1.8 (0.9–3.7)	5	1.6 (0.6–4.3)		
	Medium-high intensity	15	1.6 (0.7–3.3)[a]								
Gold [152]	Ever exposed, medium-high confidence									37	2.0 (1.2–3.2)
	High cumulative exposure, medium-high confidence									10	2.4 (1.0–5.9)
Perchloroethylene											
Miligi [188]	Medium/high intensity	14	1.2 (0.6–2.5)[a]	5	1.9 (0.7–5.7)						
Seidler [194]	Cumulative exposure > 78.8 ppm-yrs	5	3.2 (0.6–16.7)								
Gold [152]	Ever exposed, medium-high confidence									16	1.5 (0.8–2.9)
	High cumulative exposure, medium-high confidence									10	3.3 (1.2–9.5)

Includes studies published since 2000; estimates based on one exposed case are not shown
NHL non-Hodgkin lymphoma, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, *MM* multiple myeloma, *HL* Hodgkin lymphoma
[a]Includes CLL
[b]B-cell NHL only
[c]SLL only
[d]CLL only

concerns have been expressed regarding benzene exposure misclassification and the healthy worker bias in the petroleum refinery cohort [186]. A number of recent case-control studies have also examined lymphoid cancer risks in association with solvents (published since 2000, Table 28.3) and have generally found nonsignificantly increased risks associated with occupational benzene exposure [188–192, 196]. Consortia-based analyses of pooled case-control study data may be beneficial by offering sufficient power to differentiate benzene-associated risks for the various lymphohematopoietic cancer subtypes.

Research of benzene effects in the cohorts may be complicated by differing latencies of effect between the various lymphohematopoietic malignancies. Hayes et al. found in his study of workers in China exposed to an average benzene intensity of less than 10 ppm that increased risk of AML/MDS was significantly associated with exposure within the past 10 years (RR = 5.3, 95 % CI: 1.8–15.6; *p*-trend = 0.003), but was not clearly associated with more distant exposure (*p*-trend = 0.51) [199]. In contrast, NHL risk was increased in association with benzene exposure 10 years or more before diagnosis (RR = 4.9, 95 % CI: 1.3–18.9; *p*-trend = 0.005), but there was no clear pattern of association with more recent exposure [199]. There was no evidence of differential risk according to recency of exposure for AML, MDS, or CLL in the pooled reanalysis of studies from Australia, Canada, and the UK [173].

Several other aromatic hydrocarbon solvents are in widespread use, but have not been studied for cancer risks as extensively as benzene. Toluene and xylene have replaced benzene use in some settings and are typically correlated with benzene exposure. Among subjects ever exposed to benzene in the Miligi et al. study (2006), 69 % were also exposed to xylene, and 70 % were exposed to toluene. These chemicals were associated (nonsignificantly) with increased NHL and MM risks, particularly with longer duration exposures [188, 190]. The risk estimate for benzene was attenuated with exclusion of xylene- or toluene-exposed subjects (OR = 1.2, 95 % CI: 0.7–2.2, attenuated from 1.6). The risk estimate for xylene and/or toluene exposure with adjustment for benzene remained modestly, but not significantly, elevated (OR = 1.4, 95 % CI: 0.7–2.6). Another aromatic hydrocarbon, styrene, occurs less frequently with other solvents. Nonsignificant increases of each of the lymphohematopoietic cancer subtypes were observed in a styrene-based products cohort of chemical workers [200]; however, the excesses did not increase by duration or intensity of styrene exposure. Styrene exposure was associated with a 1.6-fold increased NHL risk (95 % CI: 1.1–2.3) in the European case-control study by Cocco et al. (2010) and, in particular, with follicular lymphoma (OR = 2.6, 1.3–5.2) [190]; however, two other case-control studies did not find any association with styrene [188, 194].

Chlorinated Solvents

Several chlorinated solvents are highly suspected to cause increased risk of lymphohematopoietic cancers. Trichloroethylene has been a widely used chlorinated solvent since the early 1900s, primarily in industrial vapor metal degreasing operations in various industries such as aircraft manufacturing. Trichloroethylene has also been used in the iron/steel industries (as a general solvent and degreaser), as well as in painting occupations (for cleaning or as a solvent in paint), printing (for cleaning and as a solvent in dyes), electronics (for cleaning), in the chemical industry (in production of chemical products), and in glues. Its use declined since environmental and health concerns in the 1970s, with its function replaced by other chlorinated solvents [201]. There has been long-standing concern over the potential carcinogenicity of trichloroethylene, and the chemical was classified by IARC as a probable human carcinogen (Group 2A) in 1995, primarily on the basis of evidence from animal studies and limited human evidence [202]. In 2010, a panel of expert epidemiologists and toxicologists, convened by the National Institute of Occupational Safety and Health's (NIOSH) National Occupational Research Agenda (NORA) to enhance cancer research, identified trichloroethylene as 1 of 20 occupational agents that are high priorities for continued research to clarify their status as human carcinogens [203]. Biologic plausibility for a causal relation between trichloroethylene exposure and development of NHL is supported by evidence that trichloroethylene affects lymphocyte maturation, from a cross-sectional study of workers in China, in which trichloroethylene exposure was associated with decreases in lymphocyte counts, including B- and T-cell subsets, CD4+ T cells, CD8+ T cells, and natural killer cells [204]. In contrast, there were no significant associations with granulocyte, monocyte, or platelet levels. The same researchers also reported significant exposure-response declines in plasma levels of sCD27 and sCD30, possibly indicative of immune suppression [204].

Trichloroethylene exposure has been linked to risk of NHL in various epidemiologic studies. A systematic review and meta-analysis conducted by the EPA reported a modest increase in risk of NHL (RR = 1.2, 95 % CI: 1.1–1.4) associated with any trichloroethylene exposure, with a stronger association estimated for the combined highest exposure groups (RR = 1.4, 95 % CI: 1.1–1.8) [205]. There was some evidence of publication bias, but the authors concluded such bias did not appear to completely account for the association. Three of the studies included in the meta-analysis were from Nordic cohorts of workers monitored for a urinary metabolite of trichloroethylene [206–208], with a combined risk estimate of 2.1 (95 % CI: 1.3–3.1) [209]. Finnish workers with measured exposure were at increased risk of NHL over 25 years of follow-up (RR = 1.8, 95 % CI: 0.8–3.6), and the

highest risk estimate was observed among workers with 20 or more years of exposure [208]. There were also nonsignificant increases in MM (RR = 1.6, 95 % CI: 0.4–4.2) and HL (RR = 1.7, 95 % CI: 0.4–5.0), but not leukemia (RR = 1.1, 95 % CI 0.4–2.5). In Swedish workers, an increased risk of NHL was observed among men with 2 or more years of exposure, and the relative risk was highest among workers with the highest urinary trichloroacetic acid concentrations (≥100 mg/L, RR = 8.3, 95 % CI: 0.2–46) [207]. Male Danish workers exposed to trichloroethylene (mostly in the iron and metal industry) showed increased risk of NHL (RR = 3.5, 95 % CI: 1.5–6.9), although the NHL risks did not vary according to exposure duration or individual exposure [206]. Risk of leukemia was also nonsignificantly elevated in the cohort (RR = 1.9, 95 % CI: 0.6–4.4) [206], but the authors did not present data for leukemia subtypes.

Several case-control studies have evaluated trichloroethylene and other chlorinated solvents in relation to lymphoid neoplasms (Table 28.3), but notably few studies have examined associations with myeloid cell cancers. A recent case-control study with exposure measurement utilizing questionnaires with job-specific modules designed to elicit data on certain exposures including solvents found increased risk of NHL associated with the highest exposure category of cumulative exposure to trichloroethylene (OR = 3.3, 95 % CI: 1.1–10.1) [198]. Relative risk estimates were somewhat more pronounced for follicular lymphoma than for diffuse large B-cell lymphoma or CLL/SLL, although risks were elevated for all three subtypes. A study of MM, also using job-specific exposure questionnaires, found that risk of MM was increased with occupational exposure to trichloroethylene, with exposure-response trends by duration and cumulative exposure [152]; significant associations were also observed with other chlorinated solvents including dichloromethane and perchloroethylene. Several other studies have reported nonsignificantly increased risks of lymphoid neoplasms with dichloromethane and perchloroethylene (Table 28.3) [188, 189, 194, 196]. Other chlorinated solvents such as carbon tetrachloride, chloroform, and 1,1,1-trichloroethane are less studied.

Gene-Environment Interaction with Solvents

Genetic variation is known to play a role in metabolism and excretion of solvents. For example, CYP2E1 metabolizes and activates solvents, including benzene, styrene, dichloromethane, and carbon tetrachloride. In a study of women in Connecticut, USA, increased risks of NHL associated with dichloromethane, carbon tetrachloride, and methyl chloride were only observed among participants with TT genotype of CYP2E1 (rs2070673) [210]. For example, the association of dichloromethane with NHL (OR = 1.7, 95 % CI: 1.1–2.7) was observed among those with the TT genotype (OR = 4.4, 95 % CI: 2.0–9.6), but not those with the TA/AA genotypes (OR = 0.8, 95 % CI: 0.4–1.8). Genes that affect the immune system or DNA repair were also investigated in the same Connecticut study for modification of solvent-related risks. A polymorphism in IL12A (rs582054) was found to interact with benzene and trichloroethylene exposures in risk of NHL, with significant solvent associations observed only among women with the AT or AA genotypes [211]. There were no significant interactions for all NHL with variants in other immune genes studied, including IL10 and TNF – genes strongly suspected to be involved in lymphomagenesis [212]. However, interactions with these genes were observed for NHL subtypes [211], suggesting that subtype-specific biologic mechanisms may differ. Interactions have also been detected with DNA repair genes for risk of NHL, such as chlorinated solvent exposure (as a group) with MGMT (rs12917) and NBS1 (rs1805794) and benzene exposure with BRCA2 (rs144848) [213]. Further identification of susceptible populations can help clarify the potential carcinogenicity of solvents and may also shed light on biologic mechanisms.

Engine Exhaust

Engine exhausts consist of complex mixtures of gases (e.g., nitrogen oxides and carbon monoxide) and particulates (to which other substances adhere, such as polycyclic aromatic hydrocarbons). Both gasoline and diesel exhausts contain mutagenic agents. Many studies have observed increased risks of lymphohematopoietic cancer associated with employment in jobs with probable engine exhaust exposure, such as truck drivers and other transportation occupations in relation to MM [125, 214–216], leukemia and aleukemia [217, 218], and NHL [115, 219], gasoline station attendants in relation to lymphatic leukemia and HL [129, 161], and heavy equipment operators in relation to leukemia [161]. In a cohort study of truck drivers in Denmark (n = 14,225), who were followed for cancer deaths from 1970 to 1980, mortality from lymphohematopoietic cancers was nonsignificantly increased (SMR = 1.3, 95 % CI: 0.8–1.9), and MM, specifically, was increased (SMR = 4.4, 95 % CI: 1.4–10.2, n = 5 exposed deaths) compared to a control cohort of other, unskilled workers [214].

Several studies estimated risk associated with engine exhausts, across multiple types of jobs. Boffetta et al., in a prospective cohort study in the USA, found a small, nonsignificant risk of MM associated with self-reported occupational exposure to diesel exhaust (OR = 1.4, 95 % CI: 0.7–2.7), but not gasoline exhaust (OR = 0.9, 95 % CI: 0.5–1.6) [216]. Very similar modest increases of MM risk were observed in relation to diesel exhaust or general engine

exhaust in several other studies [87, 111, 154, 220], and a meta-analysis focused on gasoline exhaust found a summary 1.3-fold increased risk of MM related to occupational engine exhaust exposure (OR = 1.3, 95 % CI: 1.1–1.6), based on eight risk estimates from seven studies [221]. Engine exhaust exposure has also been associated with NHL [88, 153], CLL [222], and hairy cell leukemia [121], although a prospective cohort study within a prepaid health plan (n = 160,230) did not find any increase for lymphohematopoietic cancers other than MM [220].

Based on the published information, engine exhausts are a likely contributor to risk of some lymphohematopoietic cancers, with the most evidence for MM. Most studies have examined "engine exhausts" in general, without separating out diesel from gasoline engine exhaust; however, the size of risk estimates associated with truck driver occupation is generally larger than those from studies of engine exhaust exposure, suggesting that diesel exhaust may pose a greater risk than gasoline exhaust.

Formaldehyde

Formaldehyde is widely used in industrial processes and as a preservative and disinfectant. Many occupations have exposure, and environmental exposure is ubiquitous. Formaldehyde has been classified as a Group 1 human carcinogen by IARC based on sufficient evidence in humans that it causes both nasopharyngeal cancer and leukemia [140]. Nevertheless, the epidemiologic data are somewhat limited, and the potential for formaldehyde to cause leukemia has been debated. The strongest evidence comes from a cohort study conducted by the National Cancer Institute of over 25,000 workers in industries with formaldehyde exposure, with expert quantitative exposure assessment and information on other workplace exposures as potential confounders [223, 224]. Mortality from myeloid leukemia was significantly associated with formaldehyde in analyses with median 35 years of follow-up, for peak exposure (RR for ≥4.0 ppm vs. >0 to <2.0 ppm = 3.5, 95 % CI: 1.3–9.4; p-trend = 0.009) and average intensity (RR for ≥1.0 ppm vs. >0 to <0.5 ppm = 2.5, 95 % CI: 1.0–6.0; p = 0.09); there were also increased risks of all lymphohematopoietic malignancies combined. In updated analyses of the cohort with follow-up extended an additional 10 years, the associations with myeloid leukemia were no longer significant for peak exposure (RR = 1.8, 95 % CI: 0.9–3.6; p-trend = 0.13 among exposed) or average intensity (RR = 1.6, 95 % CI: 0.8–3.4), but there were strong associations with the peak exposure for HL (RR for highest vs. lowest category = 4.0, 95 % CI: 1.3–12.0; p-trend = 0.01 among exposed) and MM (RR for highest vs. lowest category = 2.0, 95 % CI: 1.0–4.1; p-trend = 0.08 among exposed) [224]. Increased leukemia or myeloid leukemia mortality has also been observed in several studies of embalmers, pathologists, and anatomists [225–227]. A meta-analysis focusing on the highest exposure categories from published studies reported increased risks of leukemia (RR = 1.5, 95 % CI: 1.1–2.2, based on 14 studies) and, specifically, myeloid leukemia (2.5, 95 % CI: 1.4–4.2, based on 4 studies) associated with formaldehyde exposure but found little evidence for an association with lymphatic leukemia [228]. The biologic plausibility of the association has been questioned, primarily because of little evidence that formaldehyde reaches bone marrow and also because of a lack of data demonstrating hematotoxicity of formaldehyde, a typical effect of other myeloid cell leukemogens (e.g., benzene, ionizing radiation). However, several biologic mechanisms have been proposed, including a direct effect of formaldehyde on lymphohematopoietic stem cells or early progenitor cells in the circulating blood [229]. New data from a small study of formaldehyde-exposed workers in China (n = 94) found decreased blood cell counts consistent with toxic effects on the bone marrow, in addition to leukemia-specific chromosome changes in myeloid progenitor cells in the blood [230]. Further research is needed to explain a biologic mechanism(s) for a causal effect of formaldehyde on lymphohematopoietic cancers, as well as to more clearly describe etiologically relevant patterns of exposure (e.g., peaks vs. cumulative exposure).

Ionizing Radiation

Leukemias are well-known radiogenic malignancies for which the largest relative risks of any cancer site in association with ionizing radiation have been observed. In the Life Span Study (LSS) cohort of survivors of the atomic bombings in Hiroshima and Nagasaki, the major source of quantitative risk estimates for cancer and the basis for setting radiation protection standards, the dose-response for all leukemia types combined is linear-quadratic; there is evidence of upward curvature at higher doses for both incidence and mortality [231–233]. In the LSS, ionizing radiation doses to the bone marrow have been calculated as the sum of the absorbed dose to bone marrow from gamma radiation and ten times the absorbed dose to bone marrow from neutron radiation (to account for a greater biological effectiveness of neutrons compared to gamma-rays) and is expressed in units of Gray (Gy). When evaluating leukemia subtypes, significant excess risks of disease or disease mortality have been observed for ALL, AML, and CML (RRs at 1 Gy are 10.1, 4.3 and 7.2, respectively), but not adult T-cell leukemia. Among other lymphohematopoietic malignancies evaluated in the LSS, significant excess risks for MDS (RR at 1 Gy = 5.3) and for NHL (RR at 1 Gy = 1.62), restricted to males for the latter, have been observed [232, 234]. No significant

associations with MM, HL, or CLL, which is very infrequent in Japan, have been reported.

The applicability of cancer risk estimates from the LSS cohort, with acute exposures ranging from 0 to greater than 4 Gy, to occupational settings with comparatively low-dose and highly protracted exposures is unclear. With individual-level exposure monitoring data, some occupational settings, however, have provided unique opportunities to directly estimate cancer risks attributable to low-dose protracted exposures [231].

In the 15-Country Study, an international pooled analysis of cancer mortality among over 400,000 radiation workers in the nuclear industry (encompasses facilities engaged in production of nuclear power, manufacture of nuclear weapons, enrichment and processing of nuclear fuel, production of radioisotopes, and reactor or weapons research), the average bone marrow dose was 15 mGy with a relative risk for leukemia, excluding CLL, at 1 Gy of 2.9 (95 % CI: <1–9.5) [235]. Though not statistically significant, the estimate is consistent with the leukemia risk estimate from a comparable segment of the LSS cohort, men exposed to the A bomb at age 20–60 years (RR at 1 Gy bone marrow dose = 2.5; 95 % CI: <1–6.3) [235, 236]. While an elevated risk of MM was observed in the 15-Country Study (RR = 7.2 at 1 Gy of bone marrow dose), it was not statistically significant (one-sided $p > 0.05$) [237]. No significant associations with leukemia subtypes CLL, NHL, or HL were observed [237, 238].

In a recent meta-analysis, 23 stand-alone and pooled studies (including the 15-Country Study, but not the LSS) of occupational or environmental ionizing radiation exposure and leukemia (excluding CLL) incidence or mortality were considered [236]. Twenty of the studies were of occupationally exposed populations from the nuclear industry. Because the various studies included overlapping study populations, different combinations of studies were analyzed to generate overall risk estimates. The authors preferred an analysis of ten pooled studies that did not include overlapping study populations, excluded one influential study and adjusted for publication bias; the relative risk at 100 mGy (whole body or bone marrow dose) from this analysis was 1.2 (95 % CI: 1.1–1.3). This estimate is consistent with that among adult males in the LSS (RR for 100 mGy = 1.2).

Medical radiation workers constitute another large occupational group exposed to radiation; however, there are no large epidemiologic studies among medical radiation workers with dose estimates allowing for quantitative dose-response analyses. In a study of 2,698 male British radiologists, the risk of developing leukemia was elevated in those radiologists who first registered with a radiological society between 1897 and 1920 (SMR = 2.5; $p > 0.05$) and remained elevated among radiologists who registered between 1920 and 1979 (SMR = 2.4; $p \leq 0.05$) [239]. Risks of NHL (SMR = 3.1; $p < 0.01$) and MM (SMR = 2.2; $p > 0.05$) were also elevated among radiologists who registered after 1920; no case of either cancer was observed before 1920. In a study of 71,894 US radiologic technologists (77.9 % female) first certified during 1926–1980 and followed from completion of a baseline questionnaire (1983–1989) to completion of a second questionnaire (1994–1998), the risk of leukemia excluding CLL was found to be elevated among those reporting working 5 or more years before 1950 (RR = 6.6; 95 % CI: 1.0–42) [240], when radiation exposures to radiologic technologists are presumed to have been higher than later periods. No dose-response relationships with number of years worked were observed, and there were no significant associations with risk of MM, NHL, HL, or CLL.

The Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation of the National Academy of Sciences, in their most recent Biological Effects of Ionizing Radiation report (BEIR VII), concluded that results from occupational studies do not indicate that current radiation risk estimates for low levels of exposure extrapolated from the LSS are appreciably in error [231]. However, the committee also concluded that given the large uncertainties in risk estimates from occupational studies, they are currently unsuitable for the projection of population-based risks.

In summary, studies of occupational ionizing radiation exposure support the continued use of LSS data to extrapolate to lower-dose, protracted exposure settings to estimate lymphohematopoietic cancer risks. Studies of the LSS and various occupationally exposed populations provide sufficient evidence of increased risks of the leukemias, not including CLL, from exposure to ionizing radiation. There is also suggestive evidence of associations with NHL and multiple myeloma. However, associations with other lymphohematopoietic malignancies such as HL and CLL have not been consistently observed. It appears that oncogene activation through the formation of chromosome translocations may be a particularly important radiation-associated event in the induction of leukemias and lymphomas, as opposed to solid tumors which appear to arise from loss of function of gatekeeper genes [231]. The translocation events observed in leukemias and lymphomas tend to involve immunological genes (e.g., T-cell receptor).

Electromagnetic Fields

Various mechanisms, including the induction of magnetic and electric fields in the body, have been proposed for the potential carcinogenicity of electromagnetic fields (EMF), but, thus far, none have been established as plausible [241, 242]. EMF consists of both electric and magnetic fields, with the bulk of research focusing on the latter. Magnetic fields, measured in teslas, are produced by moving currents, while

electric fields, measured in volts per meter, are produced by all charges, moving or not. Thus, it is possible that an energized power line that is carrying no current and, thus, producing no magnetic field is producing an electric field of the same magnitude as when it carries a full load [241].

Kheifets et al. (2008) updated a previous meta-analysis of 38 studies of occupational EMF and risk of leukemia with an additional 21 studies published up to 2007 (most studies focused on magnetic rather than electric field exposures) [243]. In the original meta-analysis, EMF exposure was associated with a significant 18 % increased risk of leukemia (95 % CI: 1.1–1.2) [244]. Among leukemia subtypes, increased risks were observed for AML (OR = 1.4, 95 % CI: 1.2–1.7) and CLL (OR = 1.6, 95 % CI: 1.1–2.2). In the updated analysis, risk estimates decreased, but EMF exposure was still associated with increased risks of leukemia overall (OR = 1.16, 95 % CI: 1.1–1.2) and with AML (OR = 1.2, 95 % CI: 1.1–1.4) and CLL (OR = 1.4, 95 % CI: 1.1–1.7). The authors also combined data from seven studies that reported multiple levels of exposure; no significant dose-response relationship was observed.

In a review of five occupational studies that evaluated electric fields, results were mixed [241]. For example, in a case-control study of French utility workers, there was no evidence of increased risks of leukemia ($n = 72$) with increasing volts per meter per year (V/m-year) [245]. However, in a case-control study of Canadian utility workers with electric field exposures, the risks of leukemia ($n = 50$) for those subjects with exposures from 172 to 344 V/m-year and ≥345 V/m-year were 1.6 (95 % CI: 0.6–7.2) and 4.5 (95 % CI: 1.0–20)-fold greater than those with exposures below 172 V/m-year (the median exposure level) [246]. In subtype analyses, effect estimates were elevated for AML and CLL, but neither association was statistically significant.

Studies of EMF in relation to NHL have also yielded inconsistent results [245–251]. Karipidis et al. conducted a case-control study in which risk of NHL ($n = 694$ cases) was nonsignificantly elevated among people occupationally exposed to the highest quartile of magnetic field exposure [≥9.85 micro-Tesla-years (μT-years)] compared to the lowest quartile (<3.92 μT-years) (OR = 1.1, 95 % CI: 1.0–1.4) [247], and there was evidence of a trend for increasing risk of NHL with increasing quartiles of exposure ($p = 0.03$). In a small case-control study of NHL ($n = 51$ cases) among electric utility workers, Villeneuve et al. did not find an increased risk of NHL with occupational magnetic field exposure [251]. However, there were significantly increased risks when comparing the highest to lowest tertiles of percent time spent in electric fields of 10 V/m (OR = 3.1, 95 % CI: 1.1–8.8) and 40 V/m (OR = 3.6, 95 % CI: 1.3–9.8).

Studies of other lymphohematopoietic malignancies with detailed exposure data are lacking. For HL and MM, studies have examined mortality and incidence in occupational groups with known exposure to EMF, but no evidence of increased risks was observed [249, 252–255]. Overall, there is modest evidence of an association between occupational EMF exposure and lymphohematopoietic cancer risk. A meta-analysis of leukemia studies shows a slightly elevated risk of disease, but a plausible biological mechanism for an association between leukemia and EMF exposure is lacking.

Other Occupations and Exposures

Paint-Related Occupations and Exposures

Paint-related occupations include painters, employed in a variety of settings including construction and auto-body shops, in addition to jobs in industries that manufacture paint products. Painting as an occupation is classified as carcinogenic by IARC (Group 1), based on its association with lung cancer and all cancers combined [256]. Painters are exposed to a wide variety of solvents, pigments, and dyes, as well as various dusts from preparation of surfaces. In addition to several of the solvents discussed above, painters are frequently exposed to paint thinner solvents, such as turpentine, lacquer thinner, and white spirit, which have been associated with NHL [88, 257]. Many epidemiologic studies that have assessed it provide evidence for a relation between a history of paint-related occupations and lymphohematopoietic cancer risk for at least some subtypes, but the results are very inconsistent across studies. A cohort study of Swedish production workers in nine paint manufacturing companies who were employed for 5 years or longer from 1955 to 1975 ($n = 411$) observed a nonsignificant increase in mortality from lymphohematopoietic cancers (SMR = 2.1, 95 % CI: 0.7–5.0, $n = 5$ exposed deaths) that was mostly attributable to a 5.5-fold increased risk of MM (95 % CI: 1.1–16, $n = 3$ exposed deaths); all of the workers who developed myeloma had received "high" exposures (RR = 10, $n = 3$) [159]. Swedish cohort studies using census information on occupation observed a 1.7-fold increased risk of MM ($p > 0.05$, $n = 7$ exposed cases,) associated with employment in paint and varnish making [258], but found no increase in NHL [115], and a study of patients reported by the New Zealand Cancer Registry found MM deaths to be increased among painters (SMR = 352, 95 % CI: 140–729). However, several very large cohort studies of painters observed no increased risks for any of the major types of lymphohematopoietic cancers [259–261]. Although Brown et al. observed no increased risks for painters in a Swedish registry-based cohort, they reported nonsignificant increases associated with laquerer occupations and increases associated with work in the paint and varnish industry for myeloid leukemia (SIR = 2.1, 95 % CI: 1.1–3.6), AML (SIR = 2.2, 95 % CI: 1.0–4.2), and MM

(SIR = 1.4, 95 % CI: 0.8–2.5, *n* = 9 cases), but not NHL (SIR = 1.0, 0.6–1.7) [261]. A meta-analysis of cancer mortality among workers exposed to paints reported significantly increased mortality from leukemia (SMR = 1.9, 95 % CI: 1.2–3.1) [262].

Many case-control studies have reported on associations with painting occupations of significant or nonsignificant increased risks for NHL [88, 156, 263, 264], MM [157, 158, 215, 265–268], leukemia [269, 270], and AML [218, 270], but for each type of cancer, multiple studies also showed no association. One study reported that MM risk increased with duration of employment as a painter (OR for less than 10 years, = 1.4, 95 % CI: 0.6–2.8; OR for 10 years or longer = 4.1, 95 % CI: 1.8–10) and was stronger for individuals who reported relatively high exposure to paints or solvents (compared with low leisure-time exposure: OR for high leisure-time exposure = 1.6, 95 % CI: 1.0–3.2; OR for low occupational exposure = 1.9, 95 % CI: 0.6–5.5; OR for high occupational exposure = 3.1, 95 % CI: 1.5–7.5) [157].

Although the results are inconsistent, risk of lymphohematopoietic cancers among workers in paint-related occupations should be investigated further. In particular, risks associated with paint manufacturing vs. general painting occupations should be distinguished, as well as the specific exposures within those jobs that are related to cancer risk. The existing data suggest that certain types of lymphohematopoietic cancers, such as myeloid leukemias and MM, may be more strongly associated with paint-related exposures; therefore, further research should focus on subtype-specific risks.

Rubber Industry

Occupation in the rubber-manufacturing industry has been declared a Group 1 carcinogen by IARC [140] for both leukemia and lymphoma. Workers in the industry have been exposed to complex mixtures of chemicals, including benzene and 1,3-butadiene (both of which are known carcinogens) and styrene, and the exact causative agents in the rubber industry are unknown. In an updated mortality study among 17,924 North American synthetic rubber industry workers, leukemia mortality was increased, whereas NHL and MM mortality was not [271]. Leukemia mortality increases were most pronounced in workers who had started work 20–29 years earlier and who had worked for 10 or more years in the industry and had been employed in polymerization, coagulation, maintenance labor, and laboratory operations. The increase was not limited to a particular form of leukemia. There were also significant associations observed between exposure to 1,3-butadiene and leukemia [271]. Other cohort studies of rubber workers have also observed increases in all lymphohematopoietic cancers [272], leukemia [273], as well as MM [273, 274], and population-based case-control study with HL [155]; however, not all studies have found increased risks [215, 221, 275–277].

Healthcare Professions

Healthcare workers may be exposed to a number of potential risk factors for lymphohematopoietic cancers including infectious agents from contact with patients and ionizing radiation from use of imaging equipment and radiation treatments. Ethylene oxide, used as a sterilizing agent for heat-sensitive medical equipment, has been declared a human carcinogen by IARC (Group 1) based on limited epidemiologic evidence that it causes lymphoid cancers (NHL, MM, CLL) [278, 279] and strong animal evidence and data supporting a mechanism by cytogenetic effects in lymphocytes in exposed workers [140]. Healthcare professionals may also be exposed to antineoplastic drugs used in cancer treatments. These drugs are known to cause myeloid cell neoplasms in patients with cancer and are therefore a suspected risk factor in certain groups of healthcare workers administering the drugs or caring for patients on these treatments [36].

Many studies have evaluated cancer risks associated with healthcare professions, but there have been no meta-analyses summarizing these findings. In cohort studies, an increased risk of leukemia was observed for registered and practical nurses in the Portland-Vancouver area of Oregon, USA [161], and for registered nurses in British Columbia, Canada [280]. Increased risk of leukemia was also observed in Danish healthcare workers, but the increase was mostly due to an excess risk in hospital cleaners, rather than nurses or physicians [281]. A study in Sweden with occupation based on the 1960 and 1970 censuses found the risk of NHL to be elevated for both men and women working as physicians and surgeons (RR in men = 1.5, 95 % CI: 1.0–2.2; RR in women = 2.3, 95 % CI: 0.9–6.2). There were also nonsignificant excesses in NHL risk among male practical nurses and physiotherapists and female dental nurses, medical technicians, and psychiatric care attendants (RRs ranged from 1.3 to 2.0) [115]. In a relatively small study comparing cancer risk of oncology nurses exposed to antineoplastic drugs (*n* = 1,282) to that of nurses in other departments (*n* = 2,572), leukemia risk was elevated in oncology nurses, based on two cases of myeloid cell leukemia (RR = 10.7, 1.3–38.5) [282].

Case-control studies have shown mixed results. Very small excesses of lymphohematopoietic cancer risk in female nurses were found in a case-control study based on death certificates from 24 US states (1984–1993), with the only notable increases observed for myeloid leukemia among whites (OR = 1.3, 95 % CI: 1.1–1.4) and MM among blacks (OR = 1.3, 95 % CI: 1.0–1.7) [283]. The same study reported increased risks among dental hygienists and assistants for

NHL (OR = 1.6, 95 % CI: 1.1–2.4); among clinical laboratory technicians for NHL (OR = 1.4, 95 % CI: 1.0–2.0), MM (OR = 1.7, 95 % CI: 1.0–2.6), leukemia and aleukemia (OR = 1.9, 95 % CI: 1.4–2.6), and myeloid leukemia (OR = 2.3, 95 % CI: 1.5–3.4); and among pharmacists for leukemia/aleukemia (OR = 95 % CI: 1.9, 1.0–3.4) and myeloid leukemia (OR = 2.0, 95 % CI: 2.8–4.6, n = 5 exposed cases). A study conducted in Iowa and Minnesota, USA, found a significant increase of leukemia with employment in the health services (OR = 1.8, 95 % CI: 1.1–3.1) and hospitals industries (OR = 2.1, 95 % CI: 1.1–3.8), and these increases were significant for both AML and CLL [218]. In terms of lymphomas, several studies have found no excess in association with healthcare occupations [160, 215, 216]. However, other studies found excesses of all lymphoma [284], HL [284], and follicular lymphoma [155, 162]. Meta-analyses summarizing risk across multiple studies for specific job titles would be helpful to narrow the focus of future research.

Teachers

Teaching professions have been associated with lymphohematopoietic cancer risks in multiple studies, but not consistently, and are suspected risk profession due to exposure to infectious agents through contact with students. Both lymphomas and leukemias have been associated with teaching occupations in multiple case-control studies [114, 162, 270, 285]; however, many other studies have found no association [153, 155, 160, 215, 216]. In a meta-analysis of lymphohematopoietic cancer risks in teachers, based primarily on registry and census-based studies, summary risk estimates were elevated for NHL (RR = 1.4, 95 % CI: 1.1–1.6) and lymphatic leukemia (RR = 1.8, 95 % CI: 1.2–2.5), but no significant increase was observed for non-lymphocytic leukemia, HL, or MM [286]. A later study based on death certificate data from 24 US states found increased risks associated with teaching occupation for NHL (OR = 1.15, 95 % CI: 1.10–1.20), MM (OR = 1.21, 95 % CI: 1.13–1.29), HL (OR = 1.41, 95 % CI: 1.20–1.66), and leukemia (OR = 1.11, 95 % CI: 1.06–1.16) [114]. Confounding by socioeconomic status is a possible explanation for observed increases that cannot be fully dismissed, as most of the lymphohematopoietic cancers (with the exception of MM) occur more frequently in white people of middle to upper class.

Firefighters

Firefighters are exposed under uncontrolled conditions to a wide variety of potentially toxic chemicals during the burning of building materials, including wood and plastics. There is fairly consistent evidence for an association between firefighting occupations and lymphohematopoietic cancers, including both lymphomas and leukemias [287]. Cohort studies of firefighters observed increased NHL and MM mortality in Philadelphia, USA, increased lymphohematopoietic cancer mortality (and leukemia, specifically) in the Northwest USA, and increased MM in Canada (SMR = 10.0, 95 % CI: 1.2–36.1) [288]. These increases were particularly strong with longer duration of employment in Philadelphia (SMR for NHL for ≥20 years employment = 1.7, 95 % CI: 0.9–3.3; SMR for MM for ≥20 years employment OR = 2.3, 95 % CI: 1.0–5.2) [289] and in the Northwest, USA (SMR for all lymphohematopoietic cancer = 1.3, 95 % CI: 1.0–5.4, n = 7 exposed cases; SMR with ≥30 years employment = 2.1, 95 % CI: 1.0–3.6) [290]. Other studies of firefighters observed no increase of all hematologic malignancies combined [291, 292], but did not report on specific types of hematologic cancer.

Occupations to Study Further

Several other occupations have been associated with increased risks of lymphohematopoietic cancers in more than a few studies, including various jobs in the textile industry [160, 161, 263, 293–295], hairdressers, barbers, and cosmetologists [296–299] and welders and solderers [162, 192, 252, 300, 301]. These occupations, among others, should be studied in greater depth to characterize potential risks in relation to specific exposures.

Conclusion

The lymphohematopoietic system appears to be vulnerable to neoplastic changes from a variety of occupational exposures. However, accepted causes of lymphohematopoietic cancers are limited at this time to benzene, 1,3-butadiene, and ionizing radiation for myeloid cell leukemias. Probable causes for at least certain lymphohematopoietic cancer subtypes, that are as yet debated, are formaldehyde, ethylene oxide, certain pesticides, animal exposures, and trichloroethylene and other solvents.

Occupational exposures have been particularly challenging to study, for several reasons. Occupational cohort studies are often ideal in terms of allowing on-site exposure measurements and access to each employee's history of assigned departments, tasks, and shifts. Nevertheless, even very large cohort studies require long follow-up for relatively small numbers of cases for the specific lymphohematopoietic cancer subtypes. For this reason, many cohort studies have only reported on lymphohematopoietic cancers as an overall group, which, as discussed, may mask important associations with specific subtypes. Case-control studies are ideal in that a large number of cases can be selected from the general population, allowing

sufficient statistical power to identify exposure risks, even for rare diseases and disease subtypes. However, only a small proportion of the general population works in any high-risk occupations, thereby limiting statistical power by infrequent exposure. An additional issue with case-control studies, which are usually retrospective, is that exposure assessment relies on participant recall of jobs, specific tasks, exposures, and/or dates, which are subject to biased recall according to case status, as well as faulty recall, in general. Because of the inherent strengths and weaknesses of both study designs, both occupational cohorts and general population-based case-control studies are needed to continue to investigate occupational cancer risks for lymphohematopoietic cancers.

As in any occupational epidemiology research, the usefulness of the data for lymphohematopoietic cancer studies is dependent on the quality and level of detail of the exposure assessment. For many of the exposures discussed, further research on broad exposure groupings (e.g., any solvent) or exposure assessment without any distinction of intensity (e.g., ever exposed to trichloroethylene) will not be useful for clarifying suggested associations. Semiquantitative assessment of specific exposures is needed to support causal inference for observed associations and to promote regulation of exposures in the workplace. For suspected high-risk jobs (e.g., healthcare workers), future research should focus on semiquantitative or quantitative exposure assessment (e.g., by on-site measurements or biomarkers) of specific exposures of interest (e.g., antibodies to certain viruses or trace residues of antineoplastic drugs in different departments in which nurses are employed) in order to move the state of knowledge forward and to target areas for intervention.

References

1. GLOBOCAN 2008. World Health Organization.
2. Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Res. 1992;52:5432s–40.
3. Rabkin CS, Devesa SS, Zahm SH, Gail MH. Increasing incidence of non-Hodgkin's lymphoma. Semin Hematol. 1993;30:286–96.
4. Hartge P, Devesa SS. Quantification of the impact of known risk factors on time trends in non-Hodgkin's lymphoma incidence. Cancer Res. 1992;52:5566s–9.
5. Surveillance, Epidemiology, and End Results (SEER) Program. www.seer.cancer.gov. SEER*Stat Database: incidence – SEER 9 Regs research data, Nov 2009 sub (1973–2007) <Katrina/Rita Population Adjustment> – linked to county attributes – total U.S., 1969–2007 counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the Nov 2009 submission; 2010.
6. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November, 1997. Ann Oncol. 1999;10:1419–32.
7. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, editors. International classification of diseases for oncology. 3rd ed. Geneva: World Health Organization; 2000.
8. Baris D, Zahm SH. Epidemiology of lymphomas. Curr Opin Oncol. 2000;12:383–94.
9. Hoover RN. Lymphoma risks in populations with altered immunity – a search for mechanism. Cancer Res. 1992;52:5477s–8.
10. Birkeland SA, Storm HH, Lamm LU, Barlow L, Blohme I, Forsberg B, Eklund B, Fjeldborg O, Friedberg M, Frodin L. Cancer risk after renal transplantation in the Nordic countries, 1964–1986. Int J Cancer. 1995;60:183–9.
11. Baker GL, Kahl LE, Zee BC, Stolzer BL, Agarwal AK, Medsger Jr TA. Malignancy following treatment of rheumatoid arthritis with cyclophosphamide. Long-term case-control follow-up study. Am J Med. 1987;83:1–9.
12. Ekstrom K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekbom A, Askling J. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum. 2003;48:963–70.
13. Gridley G, McLaughlin JK, Ekbom A, Klareskog L, Adami HO, Hacker DG, Hoover R, Fraumeni Jr JF. Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst. 1993;85:307–11.
14. Hakulinen T, Isomaki H, Knekt P. Rheumatoid arthritis and cancer studies based on linking nationwide registries in Finland. Am J Med. 1985;78:29–32.
15. Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH. Rheumatoid arthritis and cancer risk. Eur J Cancer. 1996;32A:1753–7.
16. Kassan SS, Thomas TL, Moutsopoulos HM, Hoover R, Kimberly RP, Budman DR, Costa J, Decker JL, Chused TM. Increased risk of lymphoma in sicca syndrome. Ann Intern Med. 1978;89:888–92.
17. Pertovaara M, Pukkala E, Laippala P, Miettinen A, Pasternack A. A longitudinal cohort study of Finnish patients with primary Sjogren's syndrome: clinical, immunological, and epidemiological aspects. Ann Rheum Dis. 2001;60:467–72.
18. Tennis P, Andrews E, Bombardier C, Wang Y, Strand L, West R, Tilson H, Doi P. Record linkage to conduct an epidemiologic study on the association of rheumatoid arthritis and lymphoma in the Province of Saskatchewan, Canada. J Clin Epidemiol. 1993;46:685–95.
19. Engels EA, Cerhan JR, Linet MS, Cozen W, Colt JS, Davis S, Gridley G, Severson RK, Hartge P. Immune-related conditions and immune-modulating medications as risk factors for non-Hodgkin's lymphoma: a case-control study. Am J Epidemiol. 2005;162:1153–61.
20. Soderberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. Eur J Cancer. 2006;42:3028–33.
21. Abu-Shakra M, Gladman DD, Urowitz MB. Malignancy in systemic lupus erythematosus. Arthritis Rheum. 1996;39:1050–4.
22. Bjornadal L, Lofstrom B, Yin L, Lundberg IE, Ekbom A. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol. 2002;31:66–71.
23. Pettersson T, Pukkala E, Teppo L, Friman C. Increased risk of cancer in patients with systemic lupus erythematosus. Ann Rheum Dis. 1992;51:437–9.
24. Hannuksela-Svahn A, Pukkala E, Laara E, Poikolainen K, Karvonen J. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. J Invest Dermatol. 2000;114:587–90.
25. Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from

a population-based cohort study in the United Kingdom. Arch Dermatol. 2003;139:1425–9.
26. Kroll ME, Murphy F, Pirie K, Reeves GK, Green J, Beral V. Alcohol drinking, tobacco smoking and subtypes of haematological malignancy in the UK Million Women Study. Br J Cancer. 2012;107:879–87.
27. Ma X, Lim U, Park Y, Mayne ST, Wang R, Hartge P, Hollenbeck AR, Schatzkin A. Obesity, lifestyle factors, and risk of myelodysplastic syndromes in a large US cohort. Am J Epidemiol. 2009;169:1492–9.
28. Musselman JR, Blair CK, Cerhan JR, Nguyen P, Hirsch B, Ross JA. Risk of adult acute and chronic myeloid leukemia with cigarette smoking and cessation. Cancer Epidemiol. 2013;37(4):410–6.
29. Kabat GC, Wu JW, Moore SC, Morton LM, Park Y, Hollenbeck AR, Rohan TE. Lifestyle and dietary factors in relation to risk of chronic myeloid leukemia in the NIH-AARP Diet and Health Study. Cancer Epidemiol Biomarkers Prev. 2013;22:848–54.
30. Lichtman MA. Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. Oncologist. 2010;15: 1083–101.
31. Larsson SC, Wolk A. Obesity and risk of non-Hodgkin's lymphoma: a meta-analysis. Int J Cancer. 2007;121:1564–70.
32. Willett EV, Morton LM, Hartge P, Becker N, Bernstein L, Boffetta P, Bracci P, Cerhan J, Chiu BC, Cocco P, Dal Maso L, Davis S, De Sanjose S, Smedby KE, Ennas MG, Foretova L, Holly EA, La Vecchia C, Matsuo K, Maynadie M, Melbye M, Negri E, Nieters A, Severson R, Slager SL, Spinelli JJ, Staines A, Talamini R, Vornanen M, Weisenburger DD, Roman E. Non-Hodgkin lymphoma and obesity: a pooled analysis from the InterLymph Consortium. Int J Cancer. 2008;122:2062–70.
33. Lu Y, Wang SS, Reynolds P, Chang ET, Ma H, Sullivan-Halley J, Clarke CA, Bernstein L. Cigarette smoking, passive smoking, and non-Hodgkin lymphoma risk: evidence from the California Teachers Study. Am J Epidemiol. 2011;174:563–73.
34. Diver WR, Patel AV, Thun MJ, Teras LR, Gapstur SM. The association between cigarette smoking and non-Hodgkin lymphoid neoplasms in a large US cohort study. Cancer Causes Control. 2012;23:1231–40.
35. Morton LM, Zheng T, Holford TR, Holly EA, Chiu BC, Costantini AS, Stagnaro E, Willett EV, Dal Maso L, Serraino D, Chang ET, Cozen W, Davis S, Severson RK, Bernstein L, Mayne ST, Dee FR, Cerhan JR, Hartge P. Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. Lancet Oncol. 2005;6:469–76.
36. Descatha A, Jenabian A, Conso F, Ameille J. Occupational exposures and haematological malignancies: overview on human recent data. Cancer Causes Control. 2005;16:939–53.
37. Hartge P, Wang SS, Bracci PM, Devesa SS, Holly EA. Non-Hodgkin lymphoma. In: Schottenfeld D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 2006. p. 898–918.
38. Blair A, Freeman LB. Epidemiologic studies in agricultural populations: observations and future directions. J Agromedicine. 2009;14:125–31.
39. Blair A, Zahm SH, Pearce NE, Heineman EF, Fraumeni JFJ. Clues to cancer etiology from studies of farmers. Scand J Work Environ Health. 1992;18:209–15.
40. Keller-Byrne JE, Khuder SA, Schaub EA. Meta-analysis of leukemia and farming. Environ Res. 1995;71:1–10.
41. Khuder SA, Mutgi AB. Meta-analyses of multiple myeloma and farming. Am J Ind Med. 1997;32:510–6.
42. Acquavella J, Olsen G, Cole P, Ireland B, Kaneene J, Schuman S, Holden L. Cancer among farmers: a meta-analysis. Ann Epidemiol. 1998;8:64–74.
43. Khuder SA, Schaub EA, Keller-Byrne JE. Meta-analyses of non-Hodgkin's lymphoma and farming. Scand J Work Environ Health. 1998;24:255–61.
44. Khuder SA, Mutgi AB, Schaub EA, Tano BD. Meta-analysis of Hodgkin's disease among farmers. Scand J Work Environ Health. 1999;25:436–41.
45. Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, Gamet-Payrastre L. Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. Cancer Causes Control. 2007;18:1209–26.
46. Van Maele-Fabry G, Duhayon S, Mertens C, Lison D. Risk of leukaemia among pesticide manufacturing workers: a review and meta-analysis of cohort studies. Environ Res. 2008;106:121–37.
47. Van Maele-Fabry G, Duhayon S, Lison D. A systematic review of myeloid leukemias and occupational pesticide exposure. Cancer Causes Control. 2007;18:457–78.
48. McDuffie HH, Pahwa P, Spinelli JJ, McLaughlin JR, Fincham S, Robson D, Dosman JA, Hu J. Canadian male farm residents, pesticide safety handling practices, exposure to animals and non-Hodgkin's lymphoma (NHL). Am J Ind Med. 2002;Suppl 2:54–61.
49. Hardell L, Eriksson M, Nordstrom M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma. 2002;43:1043–9.
50. De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med. 2003;60:E11.
51. Miligi L, Costantini AS, Veraldi A, Benvenuti A, Vineis P. Cancer and pesticides: an overview and some results of the Italian multicenter case-control study on hematolymphopoietic malignancies. Ann N Y Acad Sci. 2006;1076:366–77.
52. Miligi L, Costantini AS, Bolejack V, Veraldi A, Benvenuti A, Nanni O, Ramazzotti V, Tumino R, Stagnaro E, Rodella S, Fontana A, Vindigni C, Vineis P. Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study. Am J Ind Med. 2003;44:627–36.
53. Fritschi L, Benke G, Hughes AM, Kricker A, Turner J, Vajdic CM, Grulich A, Milliken S, Kaldor J, Armstrong BK. Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma. Am J Epidemiol. 2005;162:849–57.
54. Mills PK, Yang R, Riordan D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988–2001. Cancer Causes Control. 2005;16:823–30.
55. Eriksson M, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer. 2008;123:1657–63.
56. Orsi L, Delabre L, Monnereau A, Delval P, Berthou C, Fenaux P, Marit G, Soubeyran P, Huguet F, Milpied N, Leporrier M, Hemon D, Troussard X, Clavel J. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med. 2009;66:291–8.
57. Koutros S, Alavanja MCR, Lubin JH, Sandler DP, Hoppin JA, Lynch CF, Knott C, Blair A, Freeman LEB. An update of cancer incidence in the Agricultural Health Study. J Occup Environ Med. 2010;52:1098–105.
58. Beane Freeman LE, Rusiecki JA, Hoppin JA, Lubin JH, Koutros S, Andreotti G, Zahm SH, Hines CJ, Coble JB, Barone-Adesi F, Sloan J, Sandler DP, Blair A, Alavanja MC. Atrazine and cancer incidence among pesticide applicators in the Agricultural Health Study (1994-2007). Environ Health Perspect. 2011;119(9):1253–9.
59. Bonner MR, Lee WJ, Sandler DP, Hoppin JA, Dosemeci M, Alavanja MC. Occupational exposure to carbofuran and the incidence of cancer in the Agricultural Health Study. Environ Health Perspect. 2005;113:285–9.
60. Bonner MR, Coble J, Blair A, Beane Freeman LE, Hoppin JA, Sandler DP, Alavanja MC. Malathion exposure and the incidence of cancer in the Agricultural Health Study. Am J Epidemiol. 2007;166:1023–34.

61. Bonner MR, Williams BA, Rusiecki JA, Blair A, Beane Freeman LE, Hoppin JA, Dosemeci M, Lubin J, Sandler DP, Alavanja MC. Occupational exposure to terbufos and the incidence of cancer in the Agricultural Health Study. Cancer Causes Control. 2010;21:871–7.
62. Christensen CH, Platz EA, Andreotti G, Blair A, Hoppin JA, Koutros S, Lynch CF, Sandler DP, Alavanja MC. Coumaphos exposure and incident cancer among male participants in the Agricultural Health Study (AHS). Environ Health Perspect. 2010;118:92–6.
63. De Roos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, Sandler DP, Alavanja MC. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect. 2005;113:49–54.
64. Delancey JO, Alavanja MC, Coble J, Blair A, Hoppin JA, Austin HD, Beane Freeman LE. Occupational exposure to metribuzin and the incidence of cancer in the Agricultural Health Study. Ann Epidemiol. 2009;19:388–95.
65. Hou L, Lee WJ, Rusiecki J, Hoppin JA, Blair A, Bonner MR, Lubin JH, Samanic C, Sandler DP, Dosemeci M, Alavanja MC. Pendimethalin exposure and cancer incidence among pesticide applicators. Epidemiology. 2006;17:302–7.
66. Kang D, Park SK, Beane-Freeman L, Lynch CF, Knott CE, Sandler DP, Hoppin JA, Dosemeci M, Coble J, Lubin J, Blair A, Alavanja M. Cancer incidence among pesticide applicators exposed to trifluralin in the Agricultural Health Study. Environ Res. 2008;107:271–6.
67. Koutros S, Mahajan R, Zheng T, Hoppin JA, Ma X, Lynch CF, Blair A, Alavanja MC. Dichlorvos exposure and human cancer risk: results from the Agricultural Health Study. Cancer Causes Control. 2008;19:59–65.
68. Lee WJ, Blair A, Hoppin JA, Lubin JH, Rusiecki JA, Sandler DP, Dosemeci M, Alavanja MC. Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. J Natl Cancer Inst. 2004;96:1781–9.
69. Lee WJ, Hoppin JA, Blair A, Lubin JH, Dosemeci M, Sandler DP, Alavanja MC. Cancer incidence among pesticide applicators exposed to alachlor in the Agricultural Health Study. Am J Epidemiol. 2004;159:373–80.
70. Lee WJ, Alavanja MC, Hoppin JA, Rusiecki JA, Kamel F, Blair A, Sandler DP. Mortality among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. Environ Health Perspect. 2007;115:528–34.
71. Lynch SM, Rusiecki JA, Blair A, Dosemeci M, Lubin J, Sandler D, Hoppin JA, Lynch CF, Alavanja MC. Cancer incidence among pesticide applicators exposed to cyanazine in the Agricultural Health Study. Environ Health Perspect. 2006;114:1248–52.
72. Lynch SM, Mahajan R, Beane Freeman LE, Hoppin JA, Alavanja MC. Cancer incidence among pesticide applicators exposed to butylate in the Agricultural Health Study (AHS). Environ Res. 2009;109:860–8.
73. Mahajan R, Blair A, Lynch CF, Schroeder P, Hoppin JA, Sandler DP, Alavanja MC. Fonofos exposure and cancer incidence in the Agricultural Health Study. Environ Health Perspect. 2006;114:1838–42.
74. Mahajan R, Bonner MR, Hoppin JA, Alavanja MC. Phorate exposure and incidence of cancer in the Agricultural Health Study. Environ Health Perspect. 2006;114:1205–9.
75. Mahajan R, Blair A, Coble J, Lynch CF, Hoppin JA, Sandler DP, Alavanja MC. Carbaryl exposure and incident cancer in the Agricultural Health Study. Int J Cancer. 2007;121:1799–805.
76. Mozzachio AM, Rusiecki JA, Hoppin JA, Mahajan R, Patel R, Beane-Freeman L, Alavanja MC. Chlorothalonil exposure and cancer incidence among pesticide applicator participants in the Agricultural Health Study. Environ Res. 2008;108:400–3.
77. Park SK, Kang D, Beane-Freeman L, Blair A, Hoppin JA, Sandler DP, Lynch CF, Knott C, Gwak J, Alavanja M. Cancer incidence among paraquat exposed applicators in the Agricultural Health Study: prospective cohort study. Int J Occup Environ Health. 2009;15:274–81.
78. Purdue MP, Hoppin JA, Blair A, Dosemeci M, Alavanja MC. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. Int J Cancer. 2007;120:642–9.
79. Rusiecki JA, Hou L, Lee WJ, Blair A, Dosemeci M, Lubin JH, Bonner M, Samanic C, Hoppin JA, Sandler DP, Alavanja MC. Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study. Int J Cancer. 2006;118:3118–23.
80. Rusiecki JA, Patel R, Koutros S, Beane-Freeman L, Landgren O, Bonner MR, Coble J, Lubin J, Blair A, Hoppin JA, Alavanja MC. Cancer incidence among pesticide applicators exposed to permethrin in the Agricultural Health Study. Environ Health Perspect. 2009;117:581–6.
81. Samanic C, Rusiecki J, Dosemeci M, Hou L, Hoppin JA, Sandler DP, Lubin J, Blair A, Alavanja MC. Cancer incidence among pesticide applicators exposed to dicamba in the Agricultural Health Study. Environ Health Perspect. 2006;114:1521–6.
82. van Bemmel DM, Visvanathan K, Beane Freeman LE, Coble J, Hoppin JA, Alavanja MC. S-ethyl-N, N-dipropylthiocarbamate exposure and cancer incidence among male pesticide applicators in the Agricultural Health Study: a prospective cohort. Environ Health Perspect. 2008;116:1541–6.
83. Barry KH, Koutros S, Lubin JH, Coble JB, Barone-Adesi F, Beane Freeman LE, Sandler DP, Hoppin JA, Ma X, Zheng T, Alavanja MC. Methyl bromide exposure and cancer risk in the Agricultural Health Study. Cancer Causes Control. 2012;23:807–18.
84. Leon ME, Beane Freeman LE, Douwes J, Hoppin JA, Kromhout H, Lebailly P, Nordby KC, Schenker M, Schuz J, Waring SC, Alavanja MC, Annesi-Maesano I, Baldi I, Dalvie MA, Ferro G, Fervers B, Langseth H, London L, Lynch CF, McLaughlin J, Merchant JA, Pahwa P, Sigsgaard T, Stayner L, Wesseling C, Yoo KY, Zahm SH, Straif K, Blair A. AGRICOH: a consortium of agricultural cohorts. Int J Environ Res Public Health. 2011;8:1341–57.
85. Weng WK, Levy S. Hepatitis C virus (HCV) and lymphomagenesis. Leuk Lymphoma. 2003;44:1113–20.
86. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross- Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev. 2001;10:1155–63.
87. Eriksson M, Karlsson M. Occupational and other environmental factors and multiple myeloma: a population based case-control study. Br J Ind Med. 1992;49:95–103.
88. Persson B, Fredrikson M. Some risk factors for non-Hodgkin's lymphoma. Int J Occup Med Environ Health. 1999;12:135–42.
89. Rusiecki JA, De Roos A, Lee WJ, Dosemeci M, Lubin JH, Hoppin JA, Blair A, Alavanja MC. Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. J Natl Cancer Inst. 2004;96:1375–82.
90. Trejo O, Ramos-Casals M, Lopez-Guillermo A, Garcia-Carrasco M, Yague J, Cervera R, Font J, Ingelmo M. Hematologic malignancies in patients with cryoglobulinemia: association with autoimmune and chronic viral diseases. Semin Arthritis Rheum. 2003;33:19–28.
91. Nanni O, Amadori D, Lugaresi C, Falcini F, Scarpi E, Saragoni A, Buiatti E. Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case- control study based on a priori exposure matrices. Occup Environ Med. 1996;53:652–7.
92. Beane Freeman LE, Bonner MR, Blair A, Hoppin JA, Sandler DP, Lubin JH, Dosemeci M, Lynch CF, Knott C, Alavanja MCR.

Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort exposed to diazinon. Am J Epidemiol. 2005;162:1070–9.
93. Blair A, Cantor KP, Zahm SH. Non-Hodgkin's lymphoma and agricultural use of the insecticide lindane. Am J Ind Med. 1998;33:82–7.
94. De Roos AJ, Hartge P, Lubin JH, Colt JS, Davis S, Cerhan JR, Severson RK, Cozen W, Patterson Jr DG, Needham LL, Rothman N. Persistent organochlorine chemicals in plasma and risk of non-Hodgkin's lymphoma. Cancer Res. 2005;65:11214–26.
95. Rothman N, Cantor KP, Blair A, Bush D, Brock JW, Helzlsouer K, Zahm SH, Needham LL, Pearson GR, Hoover RN, Comstock GW, Strickland PT. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. Lancet. 1997;350:240–4.
96. Engel LS, Laden F, Andersen A, Strickland PT, Blair A, Needham LL, Barr DB, Wolff MS, Helzlsouer K, Hunter DJ, Lan Q, Cantor KP, Comstock GW, Brock JW, Bush D, Hoover RN, Rothman N. Polychlorinated biphenyl levels in peripheral blood and non-Hodgkin's lymphoma: a report from three cohorts. Cancer Res. 2007;67:5545–52.
97. Spinelli JJ, Ng CH, Weber JP, Connors JM, Gascoyne RD, Lai AS, Brooks-Wilson AR, Le ND, Berry BR, Gallagher RP. Organochlorines and risk of non-Hodgkin lymphoma. Int J Cancer. 2007;121:2767–75.
98. Cocco P, Brennan P, Ibba A, de Sanjose LS, Maynadie M, Nieters A, Becker N, Ennas MG, Tocco MG, Boffetta P. Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. Occup Environ Med. 2008;65:132–40.
99. Bertrand KA, Spiegelman D, Aster JC, Altshul LM, Korrick SA, Rodig SJ, Zhang SM, Kurth T, Laden F. Plasma organochlorine levels and risk of non-Hodgkin lymphoma in a cohort of men. Epidemiology. 2010;21:172–80.
100. Hardell E, Eriksson M, Lindstrom G, Van Bavel B, Linde A, Carlberg M, Liljegren G. Case-control study on concentrations of organohalogen compounds and titers of antibodies to Epstein-Barr virus antigens in the etiology of non-Hodgkin lymphoma. Leuk Lymphoma. 2001;42:619–29.
101. Quintana PJ, Delfino RJ, Korrick S, Ziogas A, Kutz FW, Jones EL, Laden F, Garshick E. Adipose tissue levels of organochlorine pesticides and polychlorinated biphenyls and risk of non-Hodgkin's lymphoma. Environ Health Perspect. 2004;112:854–61.
102. Hardell K, Carlberg M, Hardell L, Bjornfoth H, Ericson JI, Eriksson M, Van BB, Lindstrom G. Concentrations of organohalogen compounds and titres of antibodies to Epstein-Barr virus antigens and the risk for non-Hodgkin lymphoma. Oncol Rep. 2009;21:1567–76.
103. Pradier C, Carrieri MP, Piche M, Rosenthal E, Dellamonica P, Serraino D. Hepatitis C virus infection and cancer risk among HIV-infected individuals. Infection. 2003;31:194–6.
104. Hardell L, Eriksson M, Degerman A. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non- Hodgkin's lymphoma. Cancer Res. 1994;54:2386–9.
105. Collins JJ, Bodner K, Aylward LL, Wilken M, Swaen G, Budinsky R, Rowlands C, Bodnar CM. Mortality rates among workers exposed to dioxins in the manufacture of pentachlorophenol. J Occup Environ Med. 2009;51:1212–9.
106. Demers PA, Davies HW, Friesen MC, Hertzman C, Ostry A, Hershler R, Teschke K. Cancer and occupational exposure to pentachlorophenol and tetrachlorophenol (Canada). Cancer Causes Control. 2006;17:749–58.
107. Ruder AM, Yiin JH. Mortality of US pentachlorophenol production workers through 2005. Chemosphere. 2011;83:851–61.
108. Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, Bueno-de-Mesquita HB, Coggon D, Green L, Johnson E, Littorin M. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. Epidemiology. 1995;6:396–402.
109. Cooper GS, Jones S. Pentachlorophenol and cancer risk: focusing the lens on specific chlorophenols and contaminants. Environ Health Perspect. 2008;116:1001–8.
110. Richardson DB, Terschüren C, Hoffmann W. Occupational risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Northern Germany. Am J Ind Med. 2008;51:258–68.
111. Flodin U, Fredriksson M, Persson B. Multiple myeloma and engine exhausts, fresh wood, and creosote: a case-referent study. Am J Ind Med. 1987;12:519–29.
112. Chiu BC, Dave BJ, Blair A, Gapstur SM, Zahm SH, Weisenburger DD. Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. Blood. 2006;108:1363–9.
113. Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR, Yount B, Cerhan JR, Lynch CF, Schuman LM, Tolbert PE, Rothman N, Cantor KP, Blair A. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. Epidemiology. 2001;12:701–9.
114. Svec MA, Ward MH, Dosemeci M, Checkoway H, De Roos AJ. Risk of lymphatic or haematopoietic cancer mortality with occupational exposure to animals or the public. Occup Environ Med. 2005;62:726–35.
115. Cano MI, Pollan M. Non-Hodgkin's lymphomas and occupation in Sweden. Int Arch Occup Environ Health. 2001;74:443–9.
116. Fritschi L, Johnson KC, Kliewer EV, Fry R. Animal-related occupations and the risk of leukemia, myeloma, and non- Hodgkin's lymphoma in Canada. Cancer Causes Control. 2002;13:563–71.
117. Tranah GJ, Bracci PM, Holly EA. Domestic and farm-animal exposures and risk of non-Hodgkin's lymphoma in a population-based study in the San Francisco Bay Area. Cancer Epidemiol Biomarkers Prev. 2008;17:2382–7.
118. Pearce NE, Sheppard RA, Howard JK, Fraser J, Lilley BM. Leukemia among New Zealand agricultural workers. A cancer registry-based study. Am J Epidemiol. 1986;124:402–9.
119. Pearce NE, Smith AH, Howard JK, Sheppard RA, Giles HJ, Teague CA. Case-control study of multiple myeloma and farming. Br J Cancer. 1986;54:493–500.
120. Nordstrom M, Hardell L, Magnuson A, Hagberg H, Rask-Andersen A. Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study. Br J Cancer. 1998;77:2048–52.
121. Clavel J, Mandereau L, Cordier S, Legoaster C, Hemon D, Conso F, Flandrin G. Hairy-cell leukemia, occupation, and smoking. Br J Haematol. 1995;91:154–61.
122. Becker N, Deeg E, Nieters A. Population-based study of lymphoma in Germany: rationale, study design and first results. Leuk Res. 2004;28:713–24.
123. Pearce NE, Smith AH, Fisher DO. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand Cancer Registry-based study. Am J Epidemiol. 1985;121:225–37.
124. Baris D, Silverman DT, Brown LM, Swanson GM, Hayes RB, Schwartz AG, Liff JM, Schoenberg JB, Pottern LM, Greenberg RS, Stewart PA. Occupation, pesticide exposure and risk of multiple myeloma. Scand J Work Environ Health. 2004;30:215–22.
125. Pahwa P, McDuffie HH, Dosman JA, Robson D, McLaughlin JR, Spinelli JJ, Fincham S. Exposure to animals and selected risk factors among Canadian farm residents with Hodgkin's disease, multiple myeloma, or soft tissue sarcoma. J Occup Environ Med. 2003;45:857–68.
126. Johnson ES, Shorter C, Rider B, Jiles R. Mortality from cancer and other diseases in poultry slaughtering/processing plants. Int J Epidemiol. 1997;26:1142–50.

127. Bethwaite P, McLean D, Kennedy J, Pearce N. Adult-onset acute leukemia and employment in the meat industry: a New Zealand case-control study. Cancer Causes Control. 2001;12:635–43.
128. Metayer C, Johnson ES, Rice JC. Nested case-control study of tumors of the hematopoietic and lymphatic systems among workers in the meat industry. Am J Epidemiol. 1998;147:727–38.
129. Neasham D, Sifi A, Nielsen KR, Overvad K, Raaschou-Nielsen O, Tjonneland A, Barricarte A, Gonzalez CA, Navarro C, Rodriguez SL, Travis RC, Key T, Linseisen J, Kaaks R, Crosignani P, Berrino F, Rosso S, Mattiello A, Vermeulen RC, Bueno-de-Mesquita HB, Berglund G, Manjer J, Zackrisson S, Hallmans G, Malmer B, Bingham S, Khaw KT, Bergmann MM, Boeing H, Trichopoulou A, Masala G, Tumino R, Lund E, Slimani N, Ferrari P, Boffetta P, Vineis P, Riboli E. Occupation and risk of lymphoma: a multicentre prospective cohort study (EPIC). Occup Environ Med. 2011;68:77–81.
130. Tatham L, Tolbert P, Kjeldsberg C. Occupational risk factors for subgroups of non-Hodgkin's lymphoma. Epidemiology. 1997;8:551–8.
131. Blair A, Hayes Jr HM. Mortality patterns among US veterinarians, 1947–1977: an expanded study. Int J Epidemiol. 1982;11:391–7.
132. Kinlen LJ. Mortality among British veterinary surgeons. Br Med J (Clin Res Ed). 1983;287:1017–9.
133. Sjodin A, Jones RS, Focant JF, Lapeza C, Wang RY, McGahee III EE, Zhang Y, Turner WE, Slazyk B, Needham LL, Patterson Jr DG. Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States. Environ Health Perspect. 2004;112:654–8.
134. Patterson Jr DG, Wong LY, Turner WE, Caudill SP, Dipietro ES, McClure PC, Cash TP, Osterloh JD, Pirkle JL, Sampson EJ, Needham LL. Levels in the U.S. population of those persistent organic pollutants (2003–2004) included in the Stockholm Convention or in other long range transboundary air pollution agreements. Environ Sci Technol. 2009;43:1211–8.
135. Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals. Department of Health and Human Services, 2009.
136. Moysich KB, Ambrosone CB, Vena JE, Shields PG, Mendola P, Kostyniak P, Greizerstein H, Graham S, Marshall JR, Schisterman EF, Freudenheim JL. Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev. 1998;7:181–8.
137. Agudo A, Goni F, Etxeandia A, Vives A, Millan E, Lopez R, Amiano P, Ardanaz E, Barricarte A, Chirlaque MD, Dorronsoro M, Jakszyn P, Larranaga N, Martinez C, Navarro C, Rodriguez L, Sanchez MJ, Tormo MJ, Gonzalez CA. Polychlorinated biphenyls in Spanish adults: determinants of serum concentrations. Environ Res. 2009;109:620–8.
138. Cerna M, Maly M, Grabic R, Batariova A, Smid J, Benes B. Serum concentrations of indicator PCB congeners in the Czech adult population. Chemosphere. 2008;72:1124–31.
139. IARC Working Group on the evaluation of carcinogenic risks to humans: polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. Lyon, France, 4–11 February 1997. IARC Monogr Eval Carcinog Risks Hum 1997;69:1–631.
140. Baan R, Grosse Y, Straif K, Secretan B, El GF, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens–Part F: chemical agents and related occupations. Lancet Oncol. 2009;10:1143–4.
141. Consonni D, Pesatori AC, Zocchetti C, Sindaco R, D'Oro LC, Rubagotti M, Bertazzi PA. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. Am J Epidemiol. 2008;167:847–58.
142. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Saracci R. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epidemiol. 1997;145:1061–75.
143. Viel JF, Arveux P, Baverel J, Cahn JY. Soft-tissue sarcoma and non-Hodgkin's lymphoma clusters around a municipal solid waste incinerator with high dioxin emission levels. Am J Epidemiol. 2000;152:13–9.
144. Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, Giesy JP, Hanberg A, Hasegawa R, Kennedy SW, Kubiak T, Larsen JC, van Leeuwen FX, Liem AK, Nolt C, Peterson RE, Poellinger L, Safe S, Schrenk D, Tillitt D, Tysklind M, Younes M, Waern F, Zacharewski T. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect. 1998;106:775–92.
145. Ballschmiter K, Zell M. Baseline studies of the global pollution. I. Occurrence of organohalogens in pristine European and antarctic aquatic environments. Int J Environ Anal Chem. 1980;8:15–35.
146. Safe S. Toxicology, structure-function relationship, and human and environmental health impacts of polychlorinated biphenyls: progress and problems. Environ Health Perspect. 1993;100:259–68.
147. Laden F, Bertrand KA, Altshul L, Aster JC, Korrick SA, Sagiv SK. Plasma organochlorine levels and risk of non-Hodgkin lymphoma in the Nurses' Health Study. Cancer Epidemiol Biomarkers Prev. 2010;19:1381–4.
148. Brauner EV, Sorensen M, Gaudreau E, Leblanc A, Eriksen KT, Tjonneland A, Overvad K, Raaschou-Nielsen O. A prospective study of organochlorines in adipose tissue and risk of nonHodgkin lymphoma. Environ Health Perspect. 2012;120:105–11.
149. Bosetti C, Negri E, Fattore E, La Vecchia C. Occupational exposure to polychlorinated biphenyls and cancer risk. Eur J Cancer Prev. 2003;12:251–5.
150. Massoudi BL, Talbott EO, Day RD, Swerdlow SH, Marsh GM, Kuller LH. A case-control study of hematopoietic and lymphoid neoplasms: the role of work in the chemical industry. Am J Ind Med. 1997;31:21–7.
151. Orsi L, Troussard X, Monnereau A, Berthou C, Fenaux P, Marit G, Soubeyran P, Huguet F, Milpied N, Leporrier M, Hemon D, Clavel J. Occupation and lymphoid malignancies: results from a French case-control study. J Occup Environ Med. 2007;49:1339–50.
152. Gold LS, Stewart PA, Milliken K, Purdue M, Severson R, Seixas N, Blair A, Hartge P, Davis S, De Roos AJ. The relationship between multiple myeloma and occupational exposure to six chlorinated solvents. Occup Environ Med. 2011;68(6):391–9.
153. Karunanayake CP, McDuffie HH, Dosman JA, Spinelli JJ, Pahwa P. Occupational exposures and non-Hodgkin's lymphoma: Canadian case-control study. Environ Health. 2008;7:44.
154. Lee WJ, Baris D, Jarvholm B, Silverman DT, Bergdahl IA, Blair A. Multiple myeloma and diesel and other occupational exposures in Swedish construction workers. Int J Cancer. 2003;107:134–8.
155. Mester B, Nieters A, Deeg E, Elsner G, Becker N, Seidler A. Occupation and malignant lymphoma: a population based case control study in Germany. Occup Environ Med. 2006;63:17–26.
156. Scherr PA, Hutchison GB, Neiman RS. Non-Hodgkin's lymphoma and occupational exposure. Cancer Res. 1992;52:5503s–9.
157. Demers PA, Vaughan TL, Koepsell TD, Lyon JL, Swanson GM, Greenberg RS, Weiss NS. A case-control study of multiple myeloma and occupation. Am J Ind Med. 1993;23:629–39.
158. Bethwaite PB, Pearce N, Fraser J. Cancer risks in painters: study based on the New Zealand Cancer Registry. Br J Ind Med. 1990;47:742–6.
159. Lundberg I, Milatou-Smith R. Mortality and cancer incidence among Swedish paint industry workers with long-term exposure to organic solvents. Scand J Work Environ Health. 1998;24:270–5.

160. Costantini AS, Miligi L, Kriebel D, Ramazzotti V, Rodella S, Scarpi E, Stagnaro E, Tumino R, Fontana A, Masala G, Vigano C, Vindigni C, Crosignani P, Benvenuti A, Vineis P. A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. Epidemiology. 2001;12:78–87.
161. Morton W, Marjanovic D. Leukemia incidence by occupation in the Portland-Vancouver metropolitan area. Am J Ind Med. 1984;6:185–205.
162. Zheng T, Blair A, Zhang Y, Weisenburger DD, Zahm SH. Occupation and risk of non-Hodgkin's lymphoma and chronic lymphocytic leukemia. J Occup Environ Med. 2002;44:469–74.
163. Motohashi N, Nagashima H, Molnar J. Trichloroethylene. II. Mechanism of carcinogenicity of trichloroethylene. In Vivo. 1999;13:215–9.
164. Zhang L, Rothman N, Li G, Guo W, Yang W, Hubbard AE, Hayes RB, Yin S, Lu W, Smith MT. Aberrations in chromosomes associated with lymphoma and therapy-related leukemia in benzene-exposed workers. Environ Mol Mutagen. 2007;48:467–74.
165. McHale CM, Lan Q, Corso C, Li G, Zhang L, Vermeulen R, Curry JD, Shen M, Turakulov R, Higuchi R, Germer S, Yin S, Rothman N, Smith MT. Chromosome translocations in workers exposed to benzene. J Natl Cancer Inst Monogr. 2008;39:74–7.
166. Tao L, Li Y, Kramer PM, Wang W, Pereira MA. Hypomethylation of DNA and the insulin-like growth factor-II gene in dichloroacetic and trichloroacetic acid-promoted mouse liver tumors. Toxicology. 2004;196:127–36.
167. Griffin JM, Gilbert KM, Lamps LW, Pumford NR. CD4(+) T-cell activation and induction of autoimmune hepatitis following trichloroethylene treatment in MRL+/+ mice. Toxicol Sci. 2000;57:345–52.
168. Blossom SJ, Gilbert KM. Exposure to a metabolite of the environmental toxicant, trichloroethylene, attenuates CD4+ T cell activation-induced cell death by metalloproteinase-dependent FasL shedding. Toxicol Sci. 2006;92:103–14.
169. Andrys C, Hanovcova I, Chylkova V, Tejral J, Eminger S, Prochazkova J. Immunological monitoring of dry-cleaning shop workers–exposure to tetrachloroethylene. Cent Eur J Public Health. 1997;5:136–42.
170. Golding BT, Watson WP. Possible mechanisms of carcinogenesis after exposure to benzene. IARC Sci Publ. 1999;150:75–88.
171. Lan Q, Zhang L, Li G, Vermeulen R, Weinberg RS, Dosemeci M, Rappaport SM, Shen M, Alter BP, Wu Y, Kopp W, Waidyanatha S, Rabkin C, Guo W, Chanock S, Hayes RB, Linet M, Kim S, Yin S, Rothman N, Smith MT. Hematotoxicity in workers exposed to low levels of benzene. Science. 2004;306:1774–6.
172. Khalade A, Jaakkola MS, Pukkala E, Jaakkola JJ. Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. Environ Health. 2010;9:31.
173. Schnatter AR, Glass DC, Tang G, Irons RD, Rushton L. Myelodysplastic syndrome and benzene exposure among petroleum workers: an international pooled analysis. J Natl Cancer Inst. 2012;104:1724–37.
174. Weed DL. Meta-analysis and causal inference: a case study of benzene and non-Hodgkin lymphoma. Ann Epidemiol. 2010;20:347–55.
175. Snyder CA, Goldstein BD, Sellakumar AR, Bromberg I, Laskin S, Albert RE. The inhalation toxicology of benzene: incidence of hematopoietic neoplasms and hematotoxicity in ARK/J and C57BL/6J mice. Toxicol Appl Pharmacol. 1980;54:323–31.
176. Cronkite EP. Benzene hematotoxicity and leukemogenesis. Blood Cells. 1986;12:129–37.
177. Huff JE, Haseman JK, DeMarini DM, Eustis S, Maronpot RR, Peters AC, Persing RL, Chrisp CE, Jacobs AC. Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F1 mice. Environ Health Perspect. 1989;82:125–63.
178. Maltoni C, Ciliberti A, Cotti G, Conti B, Belpoggi F. Benzene, an experimental multipotential carcinogen: results of the long-term bioassays performed at the Bologna Institute of Oncology. Environ Health Perspect. 1989;82:109–24.
179. Farris GM, Everitt JI, Irons RD, Popp JA. Carcinogenicity of inhaled benzene in CBA mice. Fundam Appl Toxicol. 1993;20:503–7.
180. Kawasaki Y, Hirabayashi Y, Kaneko T, Kanno J, Kodama Y, Matsushima Y, Ogawa Y, Saitoh M, Sekita K, Uchida O, Umemura T, Yoon BI, Inoue T. Benzene-induced hematopoietic neoplasms including myeloid leukemia in Trp53-deficient C57BL/6 and C3H/He mice. Toxicol Sci. 2009;110:293–306.
181. Forni A. Chromosome changes and benzene exposure. A review. Rev Environ Health. 1979;3:5–17.
182. Zhang L, Eastmond DA, Smith MT. The nature of chromosomal aberrations detected in humans exposed to benzene. Crit Rev Toxicol. 2002;32:1–42.
183. Sul D, Lee D, Im H, Oh E, Kim J, Lee E. Single strand DNA breaks in T- and B-lymphocytes and granulocytes in workers exposed to benzene. Toxicol Lett. 2002;134:87–95.
184. Alexander DD, Wagner ME. Benzene exposure and non-Hodgkin lymphoma: a meta-analysis of epidemiologic studies. J Occup Environ Med. 2010;52:169–89.
185. Vlaanderen J, Lan Q, Kromhout H, Rothman N, Vermeulen R. Occupational benzene exposure and the risk of lymphoma subtypes: a meta-analysis of cohort studies incorporating three study quality dimensions. Environ Health Perspect. 2011;119:159–67.
186. Infante PF. Benzene exposure and multiple myeloma: a detailed meta-analysis of benzene cohort studies. Ann N Y Acad Sci. 2006;1076:90–109.
187. Wong O, Raabe GK. Multiple myeloma and benzene exposure in a multinational cohort of more than 250,000 petroleum workers. Regul Toxicol Pharmacol. 1997;26:188–99.
188. Miligi L, Costantini AS, Benvenuti A, Kriebel D, Bolejack V, Tumino R, Ramazzotti V, Rodella S, Stagnaro E, Crosignani P, Amadori D, Mirabelli D, Sommani L, Belletti I, Troschel L, Romeo L, Miceli G, Tozzi GA, Mendico I, Vineis P. Occupational exposure to solvents and the risk of lymphomas. Epidemiology. 2006;17:552–61.
189. Costantini AS, Benvenuti A, Vineis P, Kriebel D, Tumino R, Ramazzotti V, Rodella S, Stagnaro E, Crosignani P, Amadori D, Mirabelli D, Sommani L, Belletti I, Troschel L, Romeo L, Miceli G, Tozzi GA, Mendico I, Maltoni SA, Miligi L. Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: evidence from the Italian Multicenter Case-control study. Am J Ind Med. 2008;51:803–11.
190. Cocco P, t'Mannetje A, Fadda D, Melis M, Becker N, de SS, Foretova L, Mareckova J, Staines A, Kleefeld S, Maynadie M, Nieters A, Brennan P, Boffetta P. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. Occup Environ Med. 2010;67:341–7.
191. Orsi L, Monnereau A, Dananche B, Berthou C, Fenaux P, Marit G, Soubeyran P, Huguet F, Milpied N, Leporrier M, Hemon D, Troussard X, Clavel J. Occupational exposure to organic solvents and lymphoid neoplasms in men: results of a French case-control study. Occup Environ Med. 2010;67:664–72.
192. Fabbro-Peray P, Daures JP, Rossi JF. Environmental risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. Cancer Causes Control. 2001;12:201–12.
193. Fritschi L, Benke G, Hughes AM, Kricker A, Vajdic CM, Grulich A, Turner J, Milliken S, Kaldor J, Armstrong BK. Risk of non-Hodgkin lymphoma associated with occupational exposure to solvents, metals, organic dusts and PCBs (Australia). Cancer Causes Control. 2005;16:599–607.
194. Seidler A, Mohner M, Berger J, Mester B, Deeg E, Elsner G, Nieters A, Becker N. Solvent exposure and malignant lymphoma: a population-based case-control study in Germany. J Occup Med Toxicol. 2007;2:2.

195. Tranah GJ, Holly EA, Bracci PM. Solvent exposure and non-Hodgkin lymphoma: no risk in a population-based study in the San Francisco Bay Area. Cancer Epidemiol Biomarkers Prev. 2009;18:3130–2.
196. Wang R, Zhang Y, Lan Q, Holford TR, Leaderer B, Zahm SH, Boyle P, Dosemeci M, Rothman N, Zhu Y, Qin Q, Zheng T. Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. Am J Epidemiol. 2009;169:176–85.
197. Wong O, Harris F, Armstrong TW, Hua F. A hospital-based case-control study of non-Hodgkin lymphoid neoplasms in Shanghai: analysis of environmental and occupational risk factors by subtypes of the WHO classification. Chem Biol Interact. 2010;184:129–46.
198. Purdue MP, Bakke B, Stewart P, De Roos AJ, Schenk M, Lynch CF, Bernstein L, Morton LM, Cerhan JR, Severson RK, Cozen W, Davis S, Rothman N, Hartge P, Colt JS. A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma. Environ Health Perspect. 2011;119:232–8.
199. Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Travis LB, Li CY, Rothman N, Hoover RN, Linet MS. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine–National Cancer Institute Benzene Study Group [see comments]. J Natl Cancer Inst. 1997;89:1065–71.
200. Bond GG, Bodner KM, Olsen GW, Cook RR. Mortality among workers engaged in the development or manufacture of styrene-based products–an update. Scand J Work Environ Health. 1992;18:145–54.
201. Bakke B, Stewart PA, Waters MA. Uses of and exposure to trichloroethylene in U.S. industry: a systematic literature review. J Occup Environ Hyg. 2007;4:375–90.
202. McGregor DB, Heseltine E, Moller H. Dry cleaning, some solvents used in dry cleaning and other industrial chemicals. IARC meeting, Lyon, 7–14 February 1995. Scand J Work Environ Health. 1995;21:310–2.
203. Ward EM, Schulte PA, Straif K, Hopf NB, Caldwell JC, Carreon T, DeMarini DM, Fowler BA, Goldstein BD, Hemminki K, Hines CJ, Pursiainen KH, Kuempel E, Lewtas J, Lunn RM, Lynge E, McElvenny DM, Muhle H, Nakajima T, Robertson LW, Rothman N, Ruder AM, Schubauer-Berigan MK, Siemiatycki J, Silverman D, Smith MT, Sorahan T, Steenland K, Stevens RG, Vineis P, Zahm SH, Zeise L, Cogliano VJ. Research recommendations for selected IARC-classified agents. Environ Health Perspect. 2010;118:1355–62.
204. Lan Q, Zhang L, Tang X, Shen M, Smith MT, Qiu C, Ge Y, Ji Z, Xiong J, He J, Reiss B, Hao Z, Liu S, Xie Y, Guo W, Purdue MP, Galvan N, Xin KX, Hu W, Beane Freeman LE, Blair AE, Li L, Rothman N, Vermeulen R, Huang H. Occupational exposure to trichloroethylene is associated with a decline in lymphocyte subsets and soluble CD27 and CD30 markers. Carcinogenesis. 2010;31:1592–6.
205. Scott CS, Jinot J. Trichloroethylene and cancer: systematic and quantitative review of epidemiologic evidence for identifying hazards. Int J Environ Res Public Health. 2011;8:4238–72.
206. Hansen J, Raaschou-Nielsen O, Christensen JM, Johansen I, McLaughlin JK, Lipworth L, Blot WJ, Olsen JH. Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med. 2001;43:133–9.
207. Axelson O, Selden A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. J Occup Med. 1994;36:556–62.
208. Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med. 1995;37:797–806.
209. Raaschou-Nielsen O, Hansen J, McLaughlin JK, Kolstad H, Christensen JM, Tarone RE, Olsen JH. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Am J Epidemiol. 2003;158:1182–92.
210. Barry DM, Carpenter C, Yager C, Golik B, Barry KJ, Shen H, Mikse O, Eggert LS, Schulz DJ, Garcia ML. Variation of the neurofilament medium KSP repeat sub-domain across mammalian species: implications for altering axonal structure. J Exp Biol. 2010;213:128–36.
211. Deng Q, Zheng T, Lan Q, Lan Y, Holford T, Chen Y, Dai M, Leaderer B, Boyle P, Chanock SJ, Rothman N, Zhang Y. Occupational solvent exposure, genetic variation in immune genes, and the risk for non-Hodgkin lymphoma. Eur J Cancer Prev. 2013;22:77–82.
212. Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, Spinelli JJ, Willett E, De Sanjose S, Cocco P, Berndt SI, Brennan P, Brooks-Wilson A, Wacholder S, Becker N, Hartge P, Zheng T, Roman E, Holly EA, Boffetta P, Armstrong B, Cozen W, Linet M, Bosch FX, Ennas MG, Holford TR, Gallagher RP, Rollinson S, Bracci PM, Cerhan JR, Whitby D, Moore PS, Leaderer B, Lai A, Spink C, Davis S, Bosch R, Scarpa A, Zhang Y, Severson RK, Yeager M, Chanock S, Nieters A. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006;7:27–38.
213. Jiao J, Zheng T, Lan Q, Chen Y, Deng Q, Bi X, Kim C, Holford T, Leaderer B, Boyle P, Ba Y, Xia Z, Chanock SJ, Rothman N, Zhang Y. Occupational solvent exposure, genetic variation of DNA repair genes, and the risk of non-Hodgkin's lymphoma. Eur J Cancer Prev. 2012;21:580–4.
214. Hansen ES. A follow-up study on the mortality of truck drivers. Am J Ind Med. 1993;23:811–21.
215. Heineman EF, Olsen JH, Pottern LM, Gomez M, Raffn E, Blair A. Occupational risk factors for multiple myeloma among Danish men. Cancer Causes Control. 1992;3:555–68.
216. Boffetta P, Stellman SD, Garfinkel L. A case-control study of multiple myeloma nested in the American Cancer Society prospective study. Int J Cancer. 1989;43:554–9.
217. Howe GR, Lindsay JP. A follow-up study of a ten-percent sample of the Canadian labor force. I. Cancer mortality in males, 1965–73. J Natl Cancer Inst. 1983;70:37–44.
218. Blair A, Zheng T, Linos A, Stewart PA, Zhang YW, Cantor KP. Occupation and leukemia: a population-based case-control study in Iowa and Minnesota. Am J Ind Med. 2001;40:3–14.
219. Holly EA, Lele C. Non-Hodgkin's lymphoma in HIV-positive and HIV-negative homosexual men in the San Francisco Bay Area: allergies, prior medication use, and sexual practices. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;15:211–22.
220. Van den Eeden SK, Friedman GD. Exposure to engine exhaust and risk of subsequent cancer. J Occup Med. 1993;35:307–11.
221. Sonoda T, Nagata Y, Mori M, Ishida T, Imai K. Meta-analysis of multiple myeloma and benzene exposure. J Epidemiol. 2001;11:249–54.
222. Flodin U, Fredriksson M, Persson B, Axelson O. Chronic lymphatic leukaemia and engine exhausts, fresh wood, and DDT: a case-referent study. Br J Ind Med. 1988;45:33–8.
223. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. J Natl Cancer Inst. 2003;95:1615–23.
224. Beane Freeman LE, Blair A, Lubin JH, Stewart PA, Hayes RB, Hoover RN, Hauptmann M. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. J Natl Cancer Inst. 2009;101:751–61.
225. Hauptmann M, Stewart PA, Lubin JH, Beane Freeman LE, Hornung RW, Herrick RF, Hoover RN, Fraumeni Jr JF, Blair A, Hayes RB. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. J Natl Cancer Inst. 2009;101:1696–708.

226. Stroup NE, Blair A, Erikson GE. Brain cancer and other causes of death in anatomists. J Natl Cancer Inst. 1986;77:1217–24.
227. Hall A, Harrington JM, Aw TC. Mortality study of British pathologists. Am J Ind Med. 1991;20:83–9.
228. Schwilk E, Zhang L, Smith MT, Smith AH, Steinmaus C. Formaldehyde and leukemia: an updated meta-analysis and evaluation of bias. J Occup Environ Med. 2010;52:878–86.
229. Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. Mutat Res. 2009;681:150–68.
230. Zhang L, Tang X, Rothman N, Vermeulen R, Ji Z, Shen M, Qiu C, Guo W, Liu S, Reiss B, Freeman LB, Ge Y, Hubbard AE, Hua M, Blair A, Galvan N, Ruan X, Alter BP, Xin KX, Li S, Moore LE, Kim S, Xie Y, Hayes RB, Azuma M, Hauptmann M, Xiong J, Stewart P, Li L, Rappaport SM, Huang H, Fraumeni Jr JF, Smith MT, Lan Q. Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells. Cancer Epidemiol Biomarkers Prev. 2010;19:80–8.
231. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation NRC. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. Washington, D.C.: The National Academies Press; 2006.
232. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T, Matsui T. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res. 1994;137:S68–97.
233. Richardson D, Sugiyama H, Nishi N, Sakata R, Shimizu Y, Grant EJ, Soda M, Hsu WL, Suyama A, Kodama K, Kasagi F. Ionizing radiation and leukemia mortality among Japanese atomic bomb survivors, 1950–2000. Radiat Res. 2009;172:368–82.
234. Iwanaga M, Hsu WL, Soda M, Takasaki Y, Tawara M, Joh T, Amenomori T, Yamamura M, Yoshida Y, Koba T, Miyazaki Y, Matsuo T, Preston DL, Suyama A, Kodama K, Tomonaga M. Risk of myelodysplastic syndromes in people exposed to ionizing radiation: a retrospective cohort study of Nagasaki atomic bomb survivors. J Clin Oncol. 2011;29:428–34.
235. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn YO, Amoros E, Ashmore P, Auvinen A, Bae JM, Solano JB, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklof M, Engels H, Engholm G, Gulis G, Habib R, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ (Clin Res Ed). 2005;331:77.
236. Daniels RD, Schubauer-Berigan MK. A meta-analysis of leukaemia risk from protracted exposure to low-dose gamma radiation. Occup Environ Med. 2011;68(6):457–64.
237. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn YO, Amoros E, Ashmore P, Auvinen A, Bae JM, Bernar J, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklöf M, Engels H, Engholm G, Gulis G, Habib RR, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiat Res. 2007;167:396–416.
238. Vrijheid M, Cardis E, Ashmore P, Auvinen A, Gilbert E, Habib RR, Malker H, Muirhead CR, Richardson DB, Rogel A, Schubauer-Berigan M, Tardy HÃ, Telle-Lamberton M. Ionizing radiation and risk of chronic lymphocytic leukemia in the 15-country study of nuclear industry workers. Radiat Res. 2008;170:661–5.
239. Berrington A, Darby SC, Weiss HA, Doll R. 100 years of observation on British radiologists: mortality from cancer and other causes 1897–1997. Br J Radiol. 2001;74:507–19.
240. Linet MS, Freedman DM, Mohan AK, Doody MM, Ron E, Mabuchi K, Alexander BH, Sigurdson A, Hauptmann M. Incidence of haematopoietic malignancies in US radiologic technologists. Occup Environ Med. 2005;62:861–7.
241. Kheifets L, Renew D, Sias G, Swanson J. Extremely low frequency electric fields and cancer: assessing the evidence. Bioelectromagnetics. 2010;31:89–101.
242. Swanson J, Kheifets L. Biophysical mechanisms: a component in the weight of evidence for health effects of power-frequency electric and magnetic fields. Radiat Res. 2006;165:470–8.
243. Kheifets L, Monroe J, Vergara X, Mezei G, Afifi AA. Occupational electromagnetic fields and leukemia and brain cancer: an update to two meta-analyses. J Occup Environ Med. 2008;50:677–88.
244. Kheifets LI, Afifi AA, Buffler PA, Zhang ZW, Matkin CC. Occupational electric and magnetic field exposure and leukemia. A meta-analysis. J Occup Environ Med. 1997;39:1074–91.
245. Guenel P, Nicolau J, Imbernon E, Chevalier A, Goldberg M. Exposure to 50-Hz electric field and incidence of leukemia, brain tumors, and other cancers among French electric utility workers. Am J Epidemiol. 1996;144:1107–21.
246. Miller AB, To T, Agnew DA, Wall C, Green LM. Leukemia following occupational exposure to 60-Hz electric and magnetic fields among Ontario electric utility workers. Am J Epidemiol. 1996;144:150–60.
247. Karipidis K, Benke G, Sim M, Fritschi L, Yost M, Armstrong B, Hughes AM, Grulich A, Vajdic CM, Kaldor J, Kricker A. Occupational exposure to power frequency magnetic fields and risk of non-Hodgkin lymphoma. Occup Environ Med. 2007;64:25–9.
248. Sahl JD, Kelsh MA, Greenland S. Cohort and nested case-control studies of hematopoietic cancers and brain cancer among electric utility workers. Epidemiology. 1993;4:104–14.
249. Schroeder JC, Savitz DA. Lymphoma and multiple myeloma mortality in relation to magnetic field exposure among electric utility workers. Am J Ind Med. 1997;32:392–402.
250. Theriault G, Goldberg M, Miller AB, Armstrong B, Guénel P, Deadman J, Imbernon E, To T, Chevalier A, Cyr D. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France: 1970–1989. Am J Epidemiol. 1994;139:550–72.
251. Villeneuve PJ, Agnew DA, Miller AB, Corey PN. Non-Hodgkin's lymphoma among electric utility workers in Ontario: the evaluation of alternate indices of exposure to 60 Hz electric and magnetic fields. Occup Environ Med. 2000;57:249–57.
252. Hakansson N, Floderus B, Gustavsson P, Johansen C, Olsen JH. Cancer incidence and magnetic field exposure in industries using resistance welding in Sweden. Occup Environ Med. 2002;59:481–6.
253. Milham SJ. Mortality in workers exposed to electromagnetic fields. Environ Health Perspect. 1985;62:297–300.
254. Roosli M, Lortscher M, Egger M, Pfluger D, Schreier N, Lortscher E, Locher P, Spoerri A, Minder C. Leukaemia, brain tumours and exposure to extremely low frequency magnetic fields: cohort study of Swiss railway employees. Occup Environ Med. 2007;64:553–9.
255. Tynes T, Haldorsen T. Residential and occupational exposure to 50 Hz magnetic fields and hematological cancers in Norway. Cancer Causes Control. 2003;14:715–20.
256. Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting. IARC Monogr Eval Carcinog Risks Hum. 1989;47:1–442.
257. Kato I, Koenig KL, Watanabe-Meserve H, Baptiste MS, Lillquist PP, Frizzera G, Burke JS, Moseson M, Shore RE. Personal and

occupational exposure to organic solvents and risk of non-Hodgkin's lymphoma (NHL) in women (United States). Cancer Causes Control. 2005;16:1215–24.
258. McLaughlin JK, Malker HS, Linet MS, Ericsson J, Stone BJ, Weiner J, Blot WJ, Fraumeni JFJ. Multiple myeloma and occupation in Sweden. Arch Environ Health. 1988;43:7–10.
259. Andersen A, Barlow L, Engeland A, Kjaerheim K, Lynge E, Pukkala E. Work-related cancer in the Nordic countries. Scand J Work Environ Health. 1999;25 Suppl 2:1–116.
260. Steenland K, Palu S. Cohort mortality study of 57,000 painters and other union members: a 15 year update. Occup Environ Med. 1999;56:315–21.
261. Brown LM, Moradi T, Gridley G, Plato N, Dosemeci M, Fraumeni Jr JF. Exposures in the painting trades and paint manufacturing industry and risk of cancer among men and women in Sweden. J Occup Environ Med. 2002;44:258–64.
262. Chen R, Seaton A. A meta-analysis of painting exposure and cancer mortality. Cancer Detect Prev. 1998;22:533–9.
263. Blair A, Linos A, Stewart PA, Burmeister LF, Gibson R, Everett G, Schuman L, Cantor KP. Evaluation of risks for non-Hodgkin's lymphoma by occupation and industry exposures from a case-control study. Am J Ind Med. 1993;23:301–12.
264. Dryver E, Brandt L, Kauppinen T, Olsson H. Occupational exposures and non-Hodgkin's lymphoma in Southern Sweden. Int J Occup Environ Health. 2004;10:13–21.
265. Cuzick J, De Stavola B. Multiple myeloma–a case-control study. Br J Cancer. 1988;57:516–20.
266. Friedman GD. Multiple myeloma: relation to propoxyphene and other drugs, radiation and occupation. Int J Epidemiol. 1986;15:424–6.
267. Morris PD, Koepsell TD, Daling JR, Taylor JW, Lyon JL, Swanson GM, Child M, Weiss NS. Toxic substance exposure and multiple myeloma: a case-control study. J Natl Cancer Inst. 1986;76:987–94.
268. Pasqualetti P, Casale R, Collacciani A, Colantonio D. Work activities and the risk of multiple myeloma. A case-control study. Med Lav. 1990;81:308–19.
269. Pearce NE, Howard JK. Occupation, social class and male cancer mortality in New Zealand, 1974–78. Int J Epidemiol. 1986;15:456–62.
270. Mele A, Szklo M, Visani G, Stazi MA, Castelli G, Pasquini P, Mandelli F. Hair dye use and other risk factors for leukemia and pre-leukemia: a case-control study. Italian Leukemia Study Group. Am J Epidemiol. 1994;139:609–19.
271. Delzell E, Sathiakumar N, Graff J, Macaluso M, Maldonado G, Matthews R. An updated study of mortality among North American synthetic rubber industry workers. Res Rep Health Eff Inst. 2006;132:1–63.
272. Andjelkovich D, Taulbee J, Symons M, Williams T. Mortality of rubber workers with reference to work experience. J Occup Med. 1977;19:397–405.
273. Wilczynska U, Szadkowska-Stanczyk I, Szeszenia-Dabrowska N, Sobala W, Strzelecka A. Cancer mortality in rubber tire workers in Poland. Int J Occup Med Environ Health. 2001;14:115–25.
274. Dost A, Straughan J, Sorahan T. A cohort mortality and cancer incidence survey of recent entrants (1982–91) to the UK rubber industry: findings for 1983–2004. Occup Med (Lond). 2007;57:186–90.
275. Sorahan T, Parkes HG, Veys CA, Waterhouse JA, Straughan JK, Nutt A. Mortality in the British rubber industry 1946–85. Br J Ind Med. 1989;46:1–10.
276. Gustavsson P, Hogstedt C, Holmberg B. Mortality and incidence of cancer among Swedish rubber workers, 1952–1981. Scand J Work Environ Health. 1986;12:538–44.
277. McMichael AJ, Andjelkovic DA, Tyroler HA. Cancer mortality among rubber workers: an epidemiologic study. Ann N Y Acad Sci. 1976;271:125–37.
278. Steenland K, Stayner L, Deddens J. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med. 2004;61:2–7.
279. Coggon D, Harris EC, Poole J, Palmer KT. Mortality of workers exposed to ethylene oxide: extended follow up of a British cohort. Occup Environ Med. 2004;61:358–62.
280. King AS, Threlfall WJ, Band PR, Gallagher RP. Mortality among female registered nurses and school teachers in British Columbia. Am J Ind Med. 1994;26:125–32.
281. Rix BA, Lynge E. Cancer incidence in Danish health care workers. Scand J Soc Med. 1996;24:114–20.
282. Skov T, Maarup B, Olsen J, Rorth M, Winthereik H, Lynge E. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. Br J Ind Med. 1992;49:855–61.
283. Petralia SA, Dosemeci M, Adams EE, Zahm SH. Cancer mortality among women employed in health care occupations in 24 U.S. states, 1984–1993. Am J Ind Med. 1999;36:159–65.
284. Williams RR, Stegens NL, Goldsmith JR. Associations of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. J Natl Cancer Inst. 1977;59:1147–85.
285. Miligi L, Seniori CA, Crosignani P, Fontana A, Masala G, Nanni O, Ramazzotti V, Rodella S, Stagnaro E, Tumino R, Vigano C, Vindigni C, Vineis P. Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women. Am J Ind Med. 1999;36:60–9.
286. Baker P, Inskip H, Coggon D. Lymphatic and hematopoietic cancer in teachers. Scand J Work Environ Health. 1999;25:5–17.
287. Guidotti TL. Evaluating causality for occupational cancers: the example of firefighters. Occup Med (Lond). 2007;57:466–71.
288. Howe GR, Burch JD. Fire fighters and risk of cancer: an assessment and overview of the epidemiologic evidence. Am J Epidemiol. 1990;132:1039–50.
289. Baris D, Garrity T, Telles JL, Heineman EF, Olshan A, Zahm SH. A cohort mortality study of Philadelphia firefighters. Am J Ind Med. 2001;39:463–76.
290. Demers PA, Heyer NJ, Rosenstock L. Mortality among firefighters from three northwestern United States cities. Br J Ind Med. 1992;49:664–70.
291. Beaumont JJ, Chu GS, Jones JR, Schenker MB, Singleton JA, Piantanida LG, Reiterman M. An epidemiologic study of cancer and other causes of mortality in San Francisco firefighters. Am J Ind Med. 1991;19:357–72.
292. Vena JE, Fiedler RC. Mortality of a municipal-worker cohort: IV. Fire fighters. Am J Ind Med. 1987;11:671–84.
293. Delzell E, Grufferman S. Cancer and other causes of death among female textile workers, 1976–78. J Natl Cancer Inst. 1983;71:735–40.
294. Fritschi L, Siemiatycki J. Lymphoma, myeloma and occupation: Results of a case-control study. Int J Cancer. 1996;67:498–503.
295. Linet MS, McLaughlin JK, Malker HS, Chow WH, Weiner JA, Stone BJ, Ericsson JL, Fraumeni JFJ. Occupation and hematopoietic and lymphoproliferative malignancies among women: a linked registry study. J Occup Med. 1994;36:1187–98.
296. Spinelli JJ, Gallagher RP, Band PR, Threlfall WJ. Multiple myeloma, leukemia, and cancer of the ovary in cosmetologists and hairdressers. Am J Ind Med. 1984;6:97–102.
297. Boffetta P, Andersen A, Lynge E, Barlow L, Pukkala E. Employment as hairdresser and risk of ovarian cancer and non-Hodgkin's lymphomas among women. J Occup Med. 1994;36:61–5.
298. Takkouche B, Regueira-Mendez C, Montes-Martinez A. Risk of cancer among hairdressers and related workers: a meta-analysis. Int J Epidemiol. 2009;38:1512–31.
299. Robinson CF, Walker JT. Cancer mortality among women employed in fast-growing U.S. occupations. Am J Ind Med. 1999;36:186–92.
300. Preston-Martin S, Peters JM. Prior employment as a welder associated with the development of chronic myeloid leukaemia. Br J Cancer. 1988;58:105–8.
301. Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. Some occupational exposures as risk factors for malignant lymphomas. Cancer. 1993;72:1773–8.

Occupational Cancer Burden

29

Lesley Rushton, Sally J. Hutchings, and Kurt Straif

Keywords
Occupational cancer • Burden of occupational cancer • Attributable cancer burden

Introduction

Exposures encountered in the general environment and at work and the potential adverse health effects arising from them are topics of a large body of multidisciplinary research and of public concern. Investigation involves both knowledge of the source and nature of the hazard and an understanding of the relationship of the exposure to the disease. Epidemiological studies of industrial workforces have played an important role in the identification of carcinogens and the understanding of the etiology of cancer. The working environment should not be a place where there is a risk of disease or injury, yet many thousands of workers worldwide are exposed to hazardous substances at work every day. Although substances related to occupational cancer are often associated with chemical exposures, especially man-made [1], a wider definition is needed to encompass all patterns of working.

The International Agency for Research on Cancer (IARC) classifies substances into four groups according to the strength of evidence for both human and animal carcinogenicity. For human data, sufficient evidence is defined as the establishment of a causal relationship between exposure to the agent and human cancer. Limited evidence is defined as the observation of a positive association between exposure to the agent and human cancer, for which a causal interpretation is considered credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.

The results from studies of occupational groups have many uses, for example, in carrying out risk assessments for standard setting and for decisions regarding compensation. In addition, estimation of attributable burden of disease, that is, the proportion or percentage of disease attributable to a specific exposure, has become widely used generally [2] and for cancer [3, 4] as a public health tool particularly for identification of major risk factors and high-risk populations; burden estimations facilitate decisions on priority actions for risk reduction and provide an understanding of important contributions to health inequalities. There have been several studies estimating the burden of cancer due to occupational exposures for specific countries and using a variety of methods. Burden estimates range between 3 % and 10 % partly due to differences in the numbers of cancers and carcinogens considered [5 –13]. This chapter gives a brief general overview of burden estimation methods, followed by more details of an approach to estimating attributable burden. Important occupational carcinogens and circumstances are described, and burden estimation for these is illustrated for Great Britain. Interpretation of these results is discussed together with extension of the methods to estimating the global burden of disease and to other exposure circumstances and different data availability conditions.

Overview of Burden Estimation Methods

There are a number of approaches useful for calculating the occupation attributable cancer burden. These include:

1. Estimation of the attributable fraction, that is, the proportion of cases that would not have occurred in the absence of an occupational exposure. This involves combining (i)

L. Rushton, PhD, MSc, BA (✉) • S.J. Hutchings, BSc
Epidemiology and Biostatistics, Imperial College London, Norfolk Place, London, W2 1PG, UK
e-mail: l.rushton@imperial.ac.uk

K. Straif, MD, PhD
IARC Monographs Section,
International Agency for Research on Cancer, Lyon, France

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_29, © Springer-Verlag London 2014

a risk estimate of the cancer type of interest associated with exposure to the carcinogen of concern with (ii) an estimate of the proportion of the population exposed to the carcinogen at work. Two main approaches to obtaining these data are to use:
   (a) Risk estimates from epidemiological studies of specific industries or occupations with proportions exposed from independent sources such as census information, national employment data, or specialist databases
   (b) Risk estimates from population-based case-control studies with estimates of the proportion exposed from the distribution of exposures in the same study, usually among the controls
2. The use of absolute burden measures directly from the literature. These are appropriate for a few cancer sites and exposures for which the attributable burden (fraction) is associated with an occupational exposure that is thought to account for close to 100 % of the risk, for example, mesothelioma uniquely caused by exposure to asbestos [14] and pneumoconiosis associated with the coal industry.
3. The Delphic Principle [15] which uses panels of experts to estimate attributable burden. For example, Landrigan et al. [16] used panels of experts to arrive at estimates using a consensus process of meetings and ballots to estimate environmental attributable burden of disease in US children [16]. This method can be extended by the use of, for example, attributable percentages from countries considered to have similar exposure conditions to numbers of deaths and cancer registrations in another country [15].
4. The use of newly occurring incident cases over a period of time to estimate the percentage caused by occupational exposures. Deschamps et al. [17] collected work histories for all newly diagnosed first cancers occurring over a 3-year period (1995–1998) in a single county in France in those over 16 (excluding housewives or permanently unemployed) and assigned cases as occupational if they were exposed to one of 13 specific occupational agents for at least 5 weeks per year for at least 3 years [17].
5. The use of linkage analysis of census and cancer registry and death certificate data if national databases exist as, for example, in many Scandinavian countries. Standardized mortality or incidence ratios by occupation are estimated for a population-based cohort [18, 19].

Quantifying the Burden of Occupational Cancer: The British Study

Estimation of the Current Burden

The British study utilized an adaptation of the attributable fraction approach (1) described above together with elements of the "Delphic Principle" (2) the overall methodology is described below, and full details of both the methods and the results are available in study publications [20] and technical reports (available at http://www.hse.gov.uk/cancer/) (3) using a panel of experts to assist in the choice of appropriate data, plus disease counts for mesothelioma. The study considered all carcinogenic agents and occupations classified by IARC as a Group 1 (established) or 2A (probable) carcinogen that, for occupational exposures, had either "strong" or "suggestive" evidence of carcinogenicity in humans for the specific cancer site, as defined by Siemiatycki et al. [21] and subsequent evaluations [22–24]. (Table 29.1). The British study estimated burden for 2005 for mortality and 2004 for cancer incidence for all occupational carcinogens classified by IARC generally up to the end of 2008. The most recent IARC evaluations are available at http://monographs.iarc.fr/ENG/Classification/index.php.

For each relevant combination of carcinogen and cancer type, appropriate data were obtained for (i) the relative risk of the cancer associated with the carcinogen and (ii) the proportion of the population ever exposed to each occupationally related carcinogenic agent. Risk estimates were obtained from meta-analyses or pooled studies or where necessary from key studies that either were British or were from populations similar to Britain. The quality of studies was also taken into account, for example, the size, extent of control for potential confounders, accuracy of exposure assessment, and case definition. Where possible we selected risk estimates adjusted for important confounders or non-occupational risk factors, for example, smoking for lung cancer and smoking and alcohol use for laryngeal cancer. Where only a narrative review was available giving a range of risk estimates from several relevant studies, we calculated a combined estimate of the relative risks using appropriate statistical methods. Formal systematic reviews and meta-analyses were carried out to estimate risk estimates for laryngeal and stomach cancers related to asbestos exposure.

Exposure-response estimates were generally not available in the epidemiological literature nor were proportions of those exposed at different levels of exposure over time available for the working population in Britain. However, where possible, risk estimates were obtained for an overall "lower" level and an overall "higher" level of exposure to the agents of concern. A substantial proportion of the excess is likely to occur in the large number of workers with low exposures where risk estimates of average risks are often unreliable. Where no suitable risk estimate for a specific carcinogen could be identified from the literature for low levels of exposure, an estimate was derived by combining the ratios from all other carcinogens where data were available of the risk estimate for high exposure and risk estimate for low exposure.

An important issue concerning chronic diseases such as many cancers is that of latency, that is, the window of time

Table 29.1 Occupational agents, groups of agents, mixtures, and exposure circumstances included in the burden estimate for Britain on the basis of the classification by the International Agency for Research on Cancer (IARC) as Group 1 (definite) and Group 2A (probable) human carcinogens[a]

Agents, mixture, circumstance	Main industry, use	IARC classification[a]	Strength of evidence[a]	Target organs specified by IARC[a]
Agents, groups of agents				
Acrylamide	Chemical industry; water and wastewater treatment; textile, steel, and lumber industries; petroleum refining; mineral processing; sugar production and hospitals	2A	Suggestive	Pancreas
Aflatoxins	Feed production industry, workers loading and unloading cargo, rice and maize processing	1	Strong	Liver[b]
Aromatic amine dyes 4-Aminobipheyl Benzidine 2-Naphthylamine	Production: dyestuffs and pigment manufacture	1	Strong	Bladder
Arsenic and arsenic compounds	Nonferrous metal smelting; production, packaging, and use of arsenic-containing pesticides; sheep dip manufacture; wool fiber production; mining or ores containing arsenic	1	Suggestive Strong Strong	Liver[h] Lung Non-melanoma skin[b]
Asbestos	Mining and milling, by-product manufacture, insulating, shipyard workers, sheet-metal workers, asbestos cement industry	1	Suggestive Strong Strong Suggestive Suggestive	Larynx Lung Mesothelioma GI tract[b] Stomach
Benzene	Production; boot and shoe industry; chemical, pharmaceutical, and rubber industries; printing; petrol additive	1	Strong	Leukemia
Beryllium	Aerospace	1	Strong	Lung
1,3-Butadiene	Chemical and rubber industries	1	Suggestive Suggestive	Leukemia LH
Cadmium	Dye/pigment	1	Strong	Lung
Chromium	Chromate production plants' dyes and pigments, plating and engraving, chromium ferroalloy production, stainless-steel welding, in wood preservatives, leather tanning, water treatment, inks, photography, lithography, drilling muds, synthetic perfumes, pyrotechnics, corrosion resistance	1	Strong Suggestive	Lung Sinonasal
Coal tar and pitches	Production of refined chemicals and coal-tar products (patent fuel), coke production, coal gasification, aluminum production; foundries, road paving and construction (roofers and slaters)	1	Suggestive Suggestive Strong	Bladder[e] Lung[e] Non-melanoma skin
Cobalt metal with tungsten carbide	Production of cemented carbides (hard metal industry), tool grinders, saw filers, diamond polishers	2A	Suggestive	Lung
Creosotes	Brickmaking; wood preserving	2A	Suggestive	Non-melanoma skin [l]
Diesel engine exhaust	Railroad, professional drivers; dock workers; mechanics	2A	Suggestive Suggestive	Bladder Lung
Dioxins/TCDD	Production, use of chlorophenols and chlorophenoxy herbicides, waste incineration, PCB production, pulp and paper bleaching	1	Suggestive Suggestive Suggestive suggestive	Lung Non-Hodgkin's lymphoma STS All cancers combined[b]
Epichlorohydrin	Production and use of resins, glycerin, and propylene-based rubbers; used as a solvent	2A	Suggestive Suggestive	Brain and CNS[f] Lung[g]
Ethylene oxide	Production, chemical industry, sterilizing agent (hospitals, spice fumigation)	1	Strong	Leukemia
Environmental tobacco smoke		2A	Strong	Lung

(continued)

Table 29.1 (continued)

Agents, mixture, circumstance	Main industry, use	IARC classification[a]	Strength of evidence[a]	Target organs specified by IARC[a]
Formaldehyde	Production, pathologists, medical laboratory technicians, plastics, textile industry	1	Suggestive	Leukemia
			Suggestive	Nasopharynx
			Suggestive	Sinonasal
Intermediates in plastics and rubber manufacturing	Production; curing agent for roofing and wood sealing	2A	Suggestive	Bladder[b]
4,4′-Methylene bis(2-chloroaniline)	Production; styrene glycol production; perfume preparation; reactive diluent in epoxy resin formulations; as chemical intermediate for cosmetics, surface coating, and agricultural and biological chemicals; used for treatment of fibers and textiles; in fabricated rubber products			
Styrene-7,8-oxide				
Ionizing radiation	Radiologists, technologists, nuclear workers, radium-dial painters, underground miners, plutonium workers, cleanup workers following nuclear accidents, aircraft crew	1	Strong	Bone
			Strong	Leukemia
			Strong	Liver
			Strong	Lung
			Strong	Thyroid
Lead/inorganic lead	Lead smelters, plumbers, solderers, occupations in battery recycling smelters	2A	Suggestive	Brain
			Suggestive	Lung
			Suggestive	Stomach
Mineral oils, untreated and mildly treated	Production; used as lubricant by metal workers, machinists, and engineers; printing industry (ink formulation); used in cosmetics, medicinal, and pharmaceutical preparations	1	Suggestive	Bladder
			Strong	Lung
			Strong	Non-melanoma skin
			Suggestive	Sinonasal
Mustard gas	Production, used in research laboratories, military personnel	1	Strong	Larynx[f]
			Suggestive	Lung[f]
			Suggestive	Nasopharynx[f]
Nickel	Metallurgy, alloy, catalyst	1	Strong	Lung
			Strong	Sinonasal
Non-arsenical insecticides	Production, pest control and agricultural workers, flour and grain mill workers	2A	Suggestive	Brain
			Suggestive	Leukemia
			Suggestive	Multiple myeloma
			Suggestive	Non-Hodgkin's lymphoma
Polycyclic aromatic hydrocarbons	Work involving combustion of organic matter; foundries; steel mills; firefighters; vehicle mechanics, see also coal-tar pitch, soot, aluminum production, coal gasification and coke production	1	Strong	Bladder
Benzo[a]pyrene			Suggestive	Lung
Benz[a]anthracene			Suggestive	Non-melanoma skin[b]
Dibenz[a,h]anthracene				
Polychlorinated biphenyls	Production – electrical capacitor manufacturing	2A	Suggestive	Liver[b]
Radon		1	Strong	Lung
Shale oils or shale-derived lubricants	Mining and processing, used as fuels or chemical-plant feedstocks, lubricant in cotton textile industry	1	Strong	Non-melanoma skin[m]
Silica	Stone cutting, mining, glass, paper	1	Strong	Lung
Solar radiation	Outdoor workers	1	Strong	Melanoma[j]
			Strong	Non-melanoma skin
Soots	Chimney sweeps, heating unit service personnel, brickmasons and helpers, building demolition workers, insulators, firefighters, metallurgical workers, work involving burning of organic materials	1	Strong	Lung[e]
			Strong	Non-melanoma skin[l]
			Suggestive	Esophagus
Strong inorganic acid mists containing sulfuric acid	Pickling operations, steel industry, petrochemical industry, phosphate acid fertilizer manufacturing	1	Strong	Larynx
			Suggestive	Lung

Table 29.1 (continued)

Agents, mixture, circumstance	Main industry, use	IARC classification[a]	Strength of evidence[a]	Target organs specified by IARC[a]
Tetrachloroethylene	Production, dry cleaning, metal degreasing	2A	Suggestive	Cervix
			Suggestive	Non-Hodgkin's lymphoma
			Suggestive	Esophagus
Trichloroethylene	Production – dry cleaning, metal degreasing	2A	Suggestive	Kidney
			Suggestive	Liver
			Suggestive	Non-Hodgkin's lymphoma
Ultraviolet radiation	Arc welding, industrial photoprocesses, sterilization and disinfection, phototherapy, operating theaters, laboratories, ultraviolet fluorescence in food industry, insect traps	2A	Suggestive	Melanoma[k], including ocular melanoma
Vinyl chloride	Production: production of polyvinyl chloride and copolymers, refrigerant before 1974, extraction solvent, in aerosol propellants	1	Strong	Liver
Wood dust	Logging and sawmill workers, pulp and paper and paperboard industry, woodworking trades (furniture industries, cabinetmaking, carpentry and construction), used as filler in plastic and linoleum production	1	Suggestive	Nasopharynx
			Strong	Sinonasal
Exposure circumstances	**Suspected substance**			
Aluminum production	Pitch volatiles, aromatic amines	1	Strong	Bladder[e]
			Strong	Lung[e]
Auramine manufacture	2-Naphthylamine, auramine, other chemicals		Strong	Bladder[i]
Boot and shoe manufacture and repair	Leather dust, benzene and other solvents	1	Suggestive	Bladder [i]
			Strong	Leukemia [c]
			Strong	Nose
				Paranasal sinuses
Coal gasification	Coal tar, coal-tar fumes, PAHs	1	Strong	Bladder[e]
			Strong	Lung[e]
			Strong	Non-melanoma skin [l]
Coke production	Coal-tar fumes	1	Suggestive	Bladder[e]
			Suggestive	Kidney[b]
			Strong	Lung[e]
			Strong	Non-melanoma skin[l]
Hairdressers and barbers	Dyes (aromatic amines, aminophenols with hydrogen peroxide); solvents, propellants; aerosols	2A	Suggestive	Bladder
			Suggestive	Lymphoma[b]
			Suggestive	Non-Hodgkin's disease
			Suggestive	Ovary
Isopropanol manufacture, strong acid process	Diisopropyl sulfate, isopropyl oils, sulfuric acid	1	Strong	Larynx[g]
			Strong	Paranasal sinuses[b]
			Suggestive	Lung[d]
Magenta manufacture	Magenta, ortho-toluidine, 4,4'-methylene bis(2-methylaniline), ortho-nitrotoluene	1	Strong	Bladder[i]
Painters		1	Suggestive	Bladder
			Strong	Lung
			Suggestive	Stomach
Petroleum refining	PAHs	2A	Suggestive	Brain
			Suggestive	Bladder[e]
			Suggestive	Leukemia[c]
Rubber industry	Aromatic amines, solvents	1	Strong	Bladder
			Suggestive	Larynx
			Suggestive	Leukemia[c]
			Suggestive	Lung[b]
			Suggestive	Stomach

(continued)

Table 29.1 (continued)

Agents, mixture, circumstance	Main industry, use	IARC classification[a]	Strength of evidence[a]	Target organs specified by IARC[a]
Shift work		2A	Suggestive	Breast
Steel foundry work		1	Strong	Lung
Welders		2B	Strong	Lung

[a]Classification of carcinogenicity by IARC generally as of December 2008 (see the series of Technical Reports for the GB cancer burden study by cancer site available at http://www.hse.gov.uk/cancer/research.htm for the specific monograph volumes used), cancer-site-specific evidence as assessed by Siemiatycki et al. [21] and related updates Rousseau et al. [22] or more recent IARC Monograph; most recent classifications are available at http://monographs.iarc.fr/ENG/Classification/index.php
[b]These cancer/agent pairs were excluded from the estimates of GB occupational cancer burden due to insufficient data on exposed numbers or risk estimates
[c]Considered for the GB cancer burden study with benzene
[d]Included for the GB cancer burden study with strong acids/chromium
[e]Included for the GB cancer burden study with PAHs
[f]Excluded due to small exposed numbers
[g]Excluded due to unknown number of workers exposed
[h]Considered with vinyl chloride
[i]Included with aromatic amines
[j]Not calculated because of uncertainties in attributing occupational exposure to solar radiation compared to recreational exposure
[k]Artificial UV radiation predominantly harms the eyes; thus the burden estimate for GB was for melanoma of the eye only
[l]Considered under PAHs (coal tars and pitches)
[m]Considered under mineral oils

during which an exposure to a carcinogen could result in a cancer being diagnosed or appearing in national mortality or cancer registration records decades later. In the British study, the period during which occupational exposure occurred that was relevant to the development of the cancer in the target year 2005 was defined as the risk exposure period (REP). For solid tumors, a latency of 10–50 years was assumed giving a REP of 1956–1995; for hematopoietic neoplasms, 0–20 years' latency was assumed giving a REP of 1986–2005. The proportion of the population ever exposed to each carcinogenic agent or occupation in the REP was obtained from the ratio of the numbers ever exposed to the carcinogens of interest in each relevant industry/occupation within Britain and still alive in the target year over the total number of people ever of working age during the same period. Annual employment turnover for the main industry sectors was taken into account to estimate the numbers ever exposed [25].

For the British study, AFs were estimated across all ages and recruitment between the ages of 15 and 24 was assumed. This approach takes advantage of the trade-off between higher cancer rates that affect greater numbers in older age groups if older recruitment is allowed and age group-specific AFs are estimated and attrition from the exposed and therefore at-risk population by the target year due to reaching ages beyond normal life expectancy as estimated from GB life tables [25]. However, it is also possible to estimate age group-specific AFs by dividing the age group-specific numbers ever exposed by age group-specific estimates of the population ever of working age in the REP and alive in the target year. Occupation attributable numbers are then obtained by applying these age-specific AFs to total disease incidence by age; attributable numbers can then be summed across ages and an estimate of overall (all age) AF obtained by dividing this sum by cancer numbers summed across age groups (as the attributable fractions cannot be summed across the age groups).

National data sources such as the CARcinogen EXposure database (CAREX) [26], the UK Labour Force Survey (LFS) [27], and Census of Employment [28] were used to estimate the proportion of the population exposed to each carcinogen of interest. The numbers of workers ever exposed during the REP were estimated by extrapolating from a point estimate of exposed workers for a single year within the REP. For example, CAREX gives estimates of numbers of the British population exposed to a carcinogen by industry sector for the period 1990 to 1993. For each carcinogen, these industry sectors were allocated to "higher" or "lower" exposure categories assuming distributions of exposure and risk that corresponded broadly to those of the studies from which the risk estimates were selected. The initial allocations were based on the judgment of an experienced industrial scientist; each assessment was then independently peer-reviewed and if necessary, a consensus assessment agreed. Data from CAREX are not differentiated by sex; 1991 Census data by industry and occupation were used to estimate the relative proportions of men and women exposed.

The LFS and Census of Employment data were used to estimate numbers ever employed in specific occupations, for example, welder, painter, etc., and for specific industries for carcinogens not included in CAREX. Where the LFS was used, the first year available and therefore used for the point estimate was 1979 for solid tumors and 1991 for

hematopoietic cancers. If the Census of Employment was used, the point estimate year was 1971 for solid cancers.

When CAREX data were used, adjustment factors were applied to take account of the change in numbers employed in primary and manufacturing industry and service sectors in Britain particularly over the long solid tumor REP.

There are several statistical methods for estimation of the attributable fraction (AF). Levin's method was used if risk estimates came from an industry-based study or a review or meta-analysis together with estimates of the proportion of the population exposed from independent national sources of data [29]:

$$\mathrm{AF} = p(E)\times(\mathrm{RR}-1)/\{1+p(E)\times(\mathrm{RR}-1)\}$$

where $p(E)$ is the proportion of the population exposed.

RR is an estimate of relative risk.

Miettinen's method is appropriate if risk estimates and proportion of cases exposed came from a population-based study [30]:

$$\mathrm{AF} = p(E\mid D)\times(\mathrm{RR}-1)/\mathrm{RR}$$

where $p(E|D)$ is the proportion of cases exposed.

In practice, no such studies were used for the GB risk estimates.

For each attributable fraction, a random error confidence interval was calculated using Monte Carlo simulations [31]. The AFs were applied to total numbers of cancer-specific deaths (2005) and cancer registrations (2004) for ages that could have been exposed during the REP to give attributable numbers. Where risk estimates were only available from mortality studies, AFs derived from these were used for the estimation of attributable registrations and vice versa. Similarly if separate AFs for women could not be estimated, those for men or for men and women combined were used.

Different approaches were used in the British study for estimation of the burden for (i) mesothelioma due to asbestos exposure which was derived directly from several UK mesothelioma studies; (ii) lung cancer due to asbestos exposure, which was estimated using a ratio of 1:1, mesothelioma to lung cancer deaths; and (iii) lung cancer associated with radon exposure from natural sources, for which estimates of rates of lung cancer due to exposure to radon in domestic buildings were applied to estimates of the time employees spend in workplaces where radon exposure occurs [25].

AFs for all the relevant carcinogenic agents and occupational circumstances were combined into a single estimate of AF for each separate cancer. To take account of potential multiple exposures, strategies including partitioning exposed numbers between overlapping exposures or estimating only for the "dominant" carcinogen with the highest risk were used. Where exposure to multiple carcinogens remained, it was assumed that the exposures were independent of one another and that their joint carcinogenic effects were multiplicative. The AFs were then combined to give an overall AF for that cancer using a product sum [32]:

$$\mathrm{AF}_{\mathrm{Combined}} = 1 - P_k\left(1-\mathrm{AF}_k\right) \text{ for } k \text{ exposures}$$

This can be shown to minimize bias that is introduced if the exposures are disjoint (not occurring concurrently) or are not independent [25]. An overall AF for all cancers was estimated by summing the attributable numbers for each and dividing by the total number of cancers in Britain.

Predicting the Future Burden of Occupational Cancer

Estimating the current burden of disease is an important step toward targeting risk reduction strategies. However, models predicting what might happen in the future under different circumstances also facilitate policy decisions. There are two possible approaches to estimating future burden. One is the lifetime risk approach, in which an individual exposed worker's lifetime risk for a particular occupational cancer is the product of the lifetime risk for that cancer in the general population (estimated as disease rate multiplied by future person years at risk obtained from life tables) and the relative risk associated with the worker's level of occupational exposure. Thus for a cohort of workers currently in a particular age category, the difference between the estimates of their lifetime risk assuming no change to current exposures and estimates assuming some change in exposure level occurs in the future will give an indication of the benefit resulting from the change. In particular, the total number of cancer cases attributable to the exposure can be estimated for the birth cohort starting work after the exposure levels have changed, by estimating their lifetime risk of cancer with and without the change. This would indicate the numbers of cancers that could be avoided if, for example, exposure levels dropped.

Using a second, attributable fraction, approach, the British study extended their methodology to estimate the future burden of occupational cancer for the 14 most important carcinogens identified from the current burden research and to forecast the impact of alternative strategies affecting future workplace exposure levels.

Because of the long latency of many cancers, a risk exposure period (REP) that included both past and predicted future exposure was projected forward in time for a series of forecast target years (FTY), that is, 2010, 2020,…2060, and attributable fractions were predicted for these (Fig. 29.1) [33].

Adjustment factors were applied to newly recruited workers (assumed to be aged 15–24 years) in separate 10-year estimation intervals to adjust for changing numbers employed

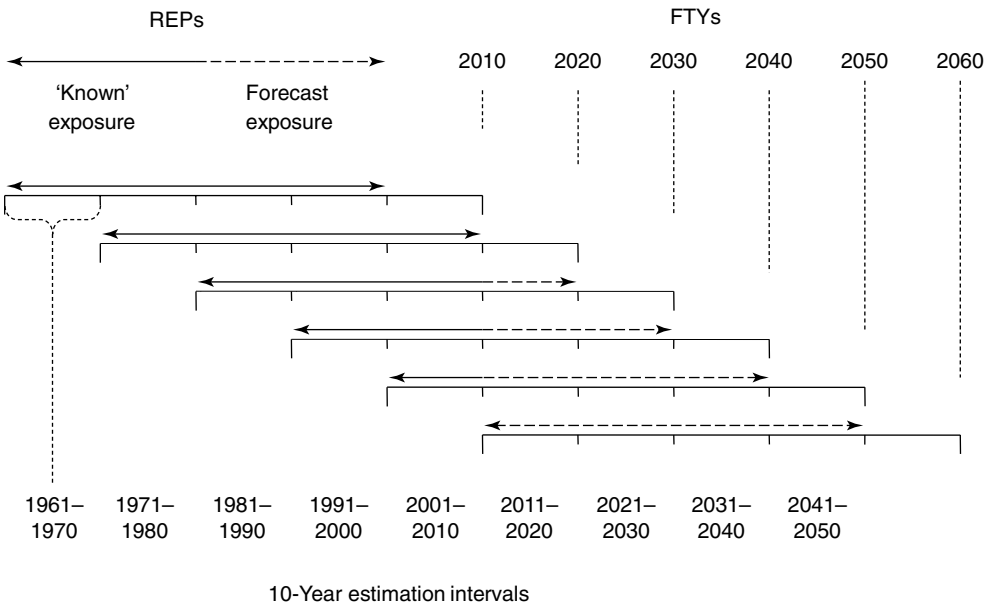


Fig. 29.1 Forecast risk exposure periods for a solid tumor with assumed latency of between 10 and 50 years

in broad industry sectors and, where data were available, to adjust for declining exposure levels. To do this, an average of workers' exposure levels across all exposed industry and a measure of the spread of these data (the estimate's standard deviation), plus an estimate of the annual percentage rate of change (usually decline), are needed. Then the rate of change will determine how the mean of the distribution of exposures, and therefore the estimated boundaries between exposure levels, shifts with time, so that workers are shifted from higher to lower exposure categories. Generally four exposure level categories were used, with appropriate risk estimates, including no excess risk if appropriate for a "background" category.

Where suitable exposure data were not available, risk estimates could be adjusted to represent reduced risk scenarios; for example, for occupational circumstances such as work as a painter or work as a welder, excess risk could be reduced successively by 25 % per decade; alternatively workers could be shifted arbitrarily from higher to lower risk categories, for example, moving shift workers at risk of breast cancer to shorter duration of exposure categories.

Alternative scenarios of change can be based on (i) historic and forecast employment and exposure level trends, (ii) introduction of a range of possible exposure standards or reduction of a current exposure limit if exposure level estimates are available, (iii) improved compliance to an existing exposure standard, or (iv) a planned intervention such as engineering controls or introduction of personal protective equipment or industry closure. A fall in relative risk where only a single exposure level risk estimate is available can also be used. All interventions could be adapted for introduction in any forecast year (2010, 2020, etc.) and for variable compliance levels according to workplace size (e.g., self-employed, small, medium, large). To assess their relative impact, the intervention scenario results are compared to a baseline scenario of historic trends only or incorporating projected exposure trends such as (i) above.

Using Burden Results to Inform Decision Making

Selected results from the British study are presented and their use for informing decision making is discussed.

Results from the British Study: Current Burden Estimation

These are reported in more detail elsewhere [20]. Table 29.2 gives the attributable fraction and attributable number of deaths and cancer registrations (newly occurring incident cancers) for those cancer sites with 20 or more total cancer registrations. The AFs by cancer site range from less than 0.01 % to 95 % overall, the most important cancer sites for occupational attribution being, for men, mesothelioma (97 %), sinonasal (46 %), lung (21.1 %), bladder (7.1 %), and non-melanoma skin cancer (NMSC) (7.1 %) and, for women, mesothelioma (83 %), sinonasal (20.1 %), lung (5.3 %), breast (4.6%), and nasopharynx (2.5%). Occupation also contributes 2 % or more overall to cancers of the larynx, esophagus, and stomach and soft tissue sarcoma (STS), with in addition for men melanoma of the eye (due to welding) and non-Hodgkin's lymphoma (NHL).

Figure 29.2 shows for each carcinogen with >20 total registrations the total number of cancer registrations by cancer

Table 29.2 Estimated attributable fractions, deaths (in 2005), and registrations by cancer site (in 2005) for the British study for cancer sites with a total of >20 cancer registrations

Cancer site[a]		Attributable fraction (%) (95 % confidence interval)			Attributable numbers (95 % confidence interval)					
					Deaths (2005)			Registrations (2004)		
	ICD-10 code	Male	Female	Total (based on deaths)	Male	Female	Total	Male	Female	Total
Bladder	C67	7.1 (4.6, 9.7)	1.9 (1.3, 3.9)	5.3 (3.4, 7.7)	215 (139, 296)	30 (21, 62)	245 (159, 358)	496 (321, 684)	54 (37, 110)	550 (357, 795)
Breast	C50		4.6 (3.3, 6.0)	4.6 (3.3, 6.0)		555 (397, 727)	555 (397, 727)		1969 (1,407, 2,579)	1969 (1,407, 2,579)
Larynx	C32	2.9 (1.4, 5.7)	1.6 (0.6, 3.5)	2.6 (1.2, 5.2)	17 (8, 34)	3 (1, 6)	20 (9, 40)	50 (24, 99)	6 (2, 13)	56 (26, 112)
Leukemia[b]	C91-C95	0.9 (0.2, 3.5)	0.5 (0.1, 4.5)	0.7 (0.1, 4.5)	18 (4, 71)	5 (1, 49)	23 (5, 120)	30 (7, 118)	9 (1, 80)	38 (8, 198)
Lung	C33-C34	21.1 (19.2, 24.7)	5.3 (4.3, 6.9)	14.5 (13.0, 17.2)	4,020 (3,659, 4,696)	725 (592, 946)	4,745 (4,251, 5,643)	4,627 (4,212, 5,406)	815 (666, 1,063)	5,442 (4,877, 6,469)
Mesothelioma[c]	C45	97.0 (96.0, 98.0)	82.5 (75.0, 90.0)	94.9 (93.0, 96.9)	1,699 (1,681, 1,717)	238 (216, 260)	1,937 (1,898, 1,976)	1,699 (1,681, 1,717)[d]	238 (216, 260)[d]	1,937 (1,898, 1,976)[d]
NHL	C82-C85	2.1 (0, 6.9)	1.1 (0.1, 2.9)	1.7 (0, 5.4)	43 (0, 138)	14 (1, 37)	57 (1, 176)	102 (0, 328)	39 (3, 101)	140 (3, 430)
NMSC[e]	C44	6.9 (1.3, 15.0)	1.1 (0.0, 2.9)	4.5 (0.8, 9.9)	20 (4, 44)	2 (0, 6)	23 (4, 50)	2,513 (478, 5,447)	349 (0, 899)	2,862 (478, 6,346)
Esophagus	C15	3.3 (1.5, 7.5)	1.1 (0.3, 2.8)	2.5 (1.1, 5.9)	156 (70, 358)	28 (8, 70)	184 (78, 429)	159 (71, 365)	29 (9, 74)	188 (80, 439)
Ovary	C56		0.5 (0, 1.2)	0.5 (0, 1.2)		23 (0, 52)	23 (0, 52)		33 (0, 76)	33 (0, 76)
Sinonasal	C30-C31	43.3 (27.3, 74.0)	19.8 (14.4, 31.6)	32.7 (21.5, 54.8)	27 (17, 47)	10 (8, 16)	38 (25, 63)	95 (60, 162)	31 (23, 50)	126 (83, 212)
STS	C49	3.4 (0, 11.4)	1.1 (0, 3.8)	2.4 (0, 8.1)	11 (0, 36)	3 (0, 9)	13 (0, 45)	22 (0, 75)	4 (0, 15)	27 (0, 90)
Stomach	C16	3.0 (1.5, 5.1)	0.3 (0.1, 0.5)	1.9 (1.0, 3.4)	101 (52, 176)	6 (3, 11)	108 (55, 187)	149 (77, 258)	9 (4, 15)	157 (81, 274)
Total:	C00-C97									
Based on deaths		**8.2 (7.2, 9.9)**	**2.3 (1.7, 3.2)**	**5.3 (4.6, 6.6)**	**6,355 (5,640, 7,690)**	**1,655 (1,249, 2,287)**	**8,010 (6,888, 9,977)**			
Based on registrations		**5.7 (4.0, 8.4)**	**2.1 (1.4, 3.2)**	**4.0 (2.7, 5.9)**				**9,988 (6,938, 14,794)**	**3,611 (2,370, 5,412)**	**13,598 (9,308, 20,206)**
Total cancers in GB in ages 15+					**77,912**	**72,212**	**150,124**	**175,399**	**168,184**	**343,583**

CIs were not estimated for bone and thyroid cancers and other cancers attributed to ionizing radiation, as CI estimates are not yet available for the excess relative risk models used (ref UNSCEAR report)

Abbreviations: *ICD* International Classification of Diseases, *NHL* non-Hodgkin's lymphoma, *NMSC* non-melanoma skin cancer, *STS* soft tissue sarcoma

[a]There were an additional 40 deaths (11 brain, 7 cervix, 1 kidney, 5 liver, 1 melanoma of the eye, 6 multiple myeloma, 8 nasopharynx, 1 pancreas) and 74 registrations (14 brain, 18 cervix, 3 kidney, 5 liver, 1 total lymphohematopoietic system, 6 melanoma of the eye, 10 multiple myeloma, 15 nasopharynx, 1 pancreas, 1 thyroid)

[b]AF applicable to all leukemias

[c]Includes cases described as due to para-occupational or environmental exposure to asbestos

[d]Taken as equal to attributable deaths for this short survival cancer

[e]Based on registrations

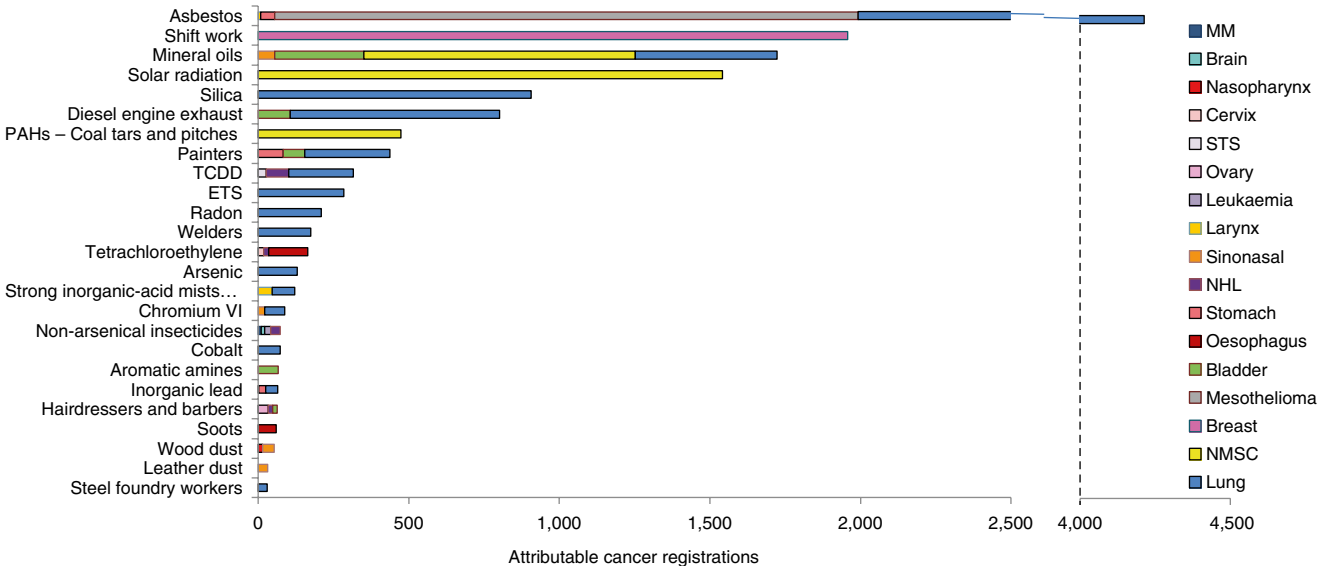


Fig. 29.2 Total numbers of cancer registrations (2004) by carcinogen and cancer site

site. The contributions of the carcinogens to the total attributable burden are (figures given as attributable burden %, attributable number of deaths, attributable number of registrations) asbestos (total 2.6%, 3,909, 4,216; laryngeal cancer 0.37 %, 3, 8; lung cancer 5.91 %, 1,937, 2,223; mesothelioma 95.09 %, 1,937, 1,937; stomach cancer 0.58 %, 32, 47), silica (0.53 %, 789, 907), diesel engine exhaust (DEE) (0.43 %, 652, 801), mineral oils (0.38 %, 563, 1,722), shift work (0.37 %, 552, 1,957), work as a painter (0.22 %, 334, 437), environmental tobacco smoke (ETS) (0.17 %, 249, 284), TCDD (dioxins) (0.15 %, 231, 316), naturally occurring radon (0.12%, 184, 209), and work as a welder (0.10%, 152, 175) (see References for more details). Figure 29.2 demonstrates that many carcinogenic exposures in the workplace affect multiple cancer sites.

The British study, unlike many other previous studies, estimated burden within industry sectors. The top ten industry sectors/occupational circumstances contributing to the total burden differ between deaths and registrations, for deaths being construction, shift work, personal and household services (this sector includes repair trades, laundries and dry cleaning, domestic services, hairdressing, and beauty), land transport, metal workers, painters and decorators in the construction industry, printing and publishing, mining, wholesale and retail trades, and manufacture of transport equipment and for registrations being construction, shift work, metal work, personal and household services, land transport, roofers and road repairs, painters and decorators in the construction industry, mining, printing and publishing, and public administration and defense. The difference occurs because of the increased numbers of cancer registrations compared to deaths for longer survival cancers such as NMSC.

Twenty-one industry sectors have 100 or more total attributable registrations (Table 29.3). The majority of industry sectors involve exposure to several carcinogens (many over 10) with construction and many of the manufacturing sectors involving potential exposure to between 15 and 20 carcinogens. In addition, the potential occurrence of several exposures in what might be thought as less traditionally exposed sectors, for example, dry cleaning, hairdressing, and beauty, is highlighted. There are several key exposures which give rise to substantial numbers of registrations across multiple industry sectors. Of note is the contribution of exposure to (i) asbestos, DEE, silica, and solar radiation in the construction industry; (ii) asbestos, DEE, ETS (nonsmokers), soots, and tetrachloroethylene in personal and household services; (iii) asbestos and DEE in land transport (railway, road, pipeline); (iv) asbestos, DEE, silica, and solar radiation in mining; (v) ETS (nonsmokers) and solar radiation in public administration and defense; (vi) asbestos, ETS (nonsmokers), and radon in the wholesale and retail trade, restaurants, and hotels; and (vii) dioxins, non-arsenical insecticides, and solar radiation in farming.

In addition to the contribution of multiple carcinogens in many industry sectors, there are several types of cancer affecting some industry sectors. For example, there are seven for farming (brain, leukemia, lung, multiple myeloma, non-Hodgkin's lymphoma, NMSC, soft tissue sarcoma), nine for construction (bladder, brain, larynx, lung, mesothelioma, NMSC, esophagus, sinonasal, and stomach), and 12 for personal and household services (bladder, cervix, kidney, leukemia, lung, mesothelioma, non-Hodgkin's lymphoma, esophagus, ovary, sinonasal, stomach).

The results from studies as detailed as the British study provide a wealth of data for policy makers to consider as part

of their decision making process for risk reduction. How they are used very much depends on the focus of any proposed intervention. For example, a focus on prevention of deaths might target rapidly fatal cancers such as lung cancer and mesothelioma. A focus on incidence might target cancers such as non-melanoma skin cancer which is very common but rarely fatal. Certain cancer sites might be of concern. Focus might be on targeting those cancers where occupational exposures cause large numbers of deaths and registrations such as lung cancer or those such as sinonasal cancer, which is a relatively rare disease with small numbers occurring each year, but where most of this burden is attributable to occupation. Some policy makers might want to start by targeting those carcinogens with both a high risk and high levels of exposures. Others may want to focus on more ubiquitous carcinogens where, although levels of exposure may be low, large numbers of workers are exposed, for example, in service industries. Where many carcinogenic exposures and multiple cancer sites are involved an industry sector approach could be considered such as targeting dusts and fumes as a whole in the construction industry.

Results from the British Study: Future Burden Prediction

The current burden results from the British study identified priority carcinogens and industry sectors of concern. Some results from the prediction element of the project are now presented using respirable crystalline silica (RCS) and lung cancer to illustrate how various reduction strategies can be compared and a preferred option chosen. The workplace exposure limit (WEL) for RCS at the time of the study (2011) was 0.1 mg/m^3. Average exposure levels in the construction industry where much of the exposure now occurs were known to be about 0.226 mg/m^3, that is, compliance to the WEL was only about 33%. The interventions tested included (i) different reductions of the WEL in 2010, (ii) delaying reduction of the WEL to 2020 or 2030, (iii) improving compliance to the current WEL, (iv) simultaneously improving compliance and reducing the WEL, and (v) improving compliance in different sizes of workplace. The intervention scenarios tested are described in Table 29.4 together with the attributable fractions, numbers of attributable cancer registrations for forecast year 2060 when historic exposures no longer have an effect, and the reduction in that year is compared with the baseline scenario of no change. Forecast attributable numbers of deaths and cancer registrations have been estimated by applying the predicted attributable fractions to predicted total future numbers of deaths and registrations based on current (2005) cancer rates applied to a population estimate taking account of projected demographic change only. Changes in cancer trends due to non-occupational risk factors, for example, smoking and lung cancer, were not taken into account.

Scenarios 2 and 3 compared with the baseline scenario 1 demonstrate the gradually decreasing numbers of attributable cancers and increasing numbers avoided by introducing reduced WELs even at the current compliance rate of 33 %; over half of the cancers are prevented by reducing the WEL to a quarter of the current standard. However, given the poor compliance to the current standard, policy makers might conclude that this is an impractical option. Scenarios 4 and 5 demonstrate the effect of a delay in reducing the WEL by 10 and 20 years, respectively.

The effectiveness of enforcement compared to lowering the WEL is shown by comparison of scenarios 1–3 with scenarios 6–8 in which compliance is improved to 90 % simultaneously with reduction of the WEL. Retaining the current WEL of 1 mg/m^3 and improving compliance to 90 % (scenario 6) avoids 693 cancers compared with halving the WEL to 0.05 mg/m^3 and keeping compliance at 33 % (scenario 2) for which only 202 cancers are avoided. These six scenarios are illustrated in terms of attributable cancers per year and attributable fractions for each prediction year in Fig. 29.3. Numbers of cancers tend to rise for the baseline scenario due to rising numbers of total projected lung cancers caused by an aging population. An important message from this graph is the lack of any reduction in cancers until after 2030 from any of the interventions due to the long latency of lung cancer.

Scenarios 9–12 represent the introduction of a halved exposure standard (0.05 mg/m^3) in 2010 plus the effect of improving compliance to 90 % in an increasing range of workplaces from only the largest (250+ employees, scenario 9) to all workplaces including the self-employed (scenario 12). Attributable cancers do not disappear totally as low-level exposure still occurs even with this level of compliance, but the improvement on scenario 2, where non-compliance rates are assumed to be the same as were occurring with respect to the existing exposure standard (0.1mg/m^3), is considerable. The great improvement in cancers avoided when workplaces with less than 50 workers have an improved compliance rate (scenario 11) compared to reduction in larger workplaces (scenario 10) highlights the comparative predominance of small enterprises particularly in the construction industry which is the most important industry sector for potential silica exposure.

The future burden associated with the 14 carcinogenic agents and occupational circumstances considered in the British study showed that, without intervention, occupational attributable cancers were forecast to remain at over 10,000 annually by 2060. With modest intervention nearly 2,500 or with stricter interventions over 8,100, cancers could be avoided by 2060 although due to long latency no impact would be seen until at least 10years after intervention. Effectiveinterventions

Table 29.3 Total cancer registrations by industry sector and carcinogenic agent or occupational circumstance for industry sectors with 100 or more attributable cancer registrations and carcinogens with 50 or more attributable cancer registrations

Industry sector/ carcinogenic agent	Asbestos[a]	Aromatic amines	Arsenic	Chromium VI	Cobalt	Diesel engine exhaust	Environmental tobacco smoke	Hairdressers and barbers	Inorganic lead	Mineral oils
Total agricultural, hunting, fishing, and forestry										
Iron and steel basic industries		16		0		0			2	0
Manufacture of industrial chemicals	64	0	3	4	6	1			2	
Manufacture of instruments, photographic and optical goods				0	2	0				203
Manufacture of machinery except electrical				28	5	2				
Manufacture of other chemical products	69			2	10	1			3	
Manufacture of transport equipment	115			18	4	2				
Metal workers										1,252
Mining	192					43			0	
Nonferrous metal basic industries			50	3	6	2			8	
Painters (not construction)										
Printing, publishing and allied industries				0	4	0				267
Welders										
Total manufacturing industry, mining, quarrying, electricity, gas, water	**535**	**48**	**113**	**86**	**67**	**80**			**34**	**1,722**
Construction	2,773		15	0	4	290	36		31	
Painters and decorators (construction)										
Roofers, road surfacers, roadmen, paviors (construction)										
Total construction	**2,773**		**15**	**0**	**4**	**290**	**36**		**31**	
Land transport	133			0		350	3			
Personal and household services	361	18		2		29	22	63		0
Public administration and defense						1	20			
Shift work										
Wholesale and retail trade and restaurants and hotels	66					6	118			
Total service industries	**573**	**18**	**1**	**3**	**2**	**431**	**248**	**63**		**0**
Total[a,b]	**4,216**	**66**	**129**	**89**	**73**	**801**	**284**	**63**	**65**	**1,722**

[a]Asbestos-related cancers by industry exclude mesotheliomas thought to be para-occupational and environmental in origin, which are included in the total
[b]Grouped sector subtotals exclude mesotheliomas thought to be para-occupational and environmental in origin, and industry attributable deaths and registrations do not sum to the totals and subtotals due to the method used to combine attributable fractions across exposures

Non-arsenical pesticides	PAHs – coal tars and pitches	Painters	Radon	Shift work	Silica	Solar radiation	Soots	Strong inorganic acid mists with sulfuric acid	TCDD (dioxins)	Tetrachloroethylene	Welders	Wood dust	Overall[b]
72			**1**			**135**			**55**			**1**	**263**
	4		1			0		3	75	1		0	135
1			2		1			16	11			0	116
			1									0	206
			9		28			13		18		0	111
			2		10			20				0	119
			5		11	5		12		6		0	182
													1,252
			0		29	31							296
			1		4	9		14	50	1		0	156
		102											102
			4			3				2		0	282
											175		181
2	**4**	**102**	**62**		**200**	**163**		**122**	**254**	**60**	**175**	**23**	**3,909**
			9		707	841				11		29	4,668
		334											334
	471												471
	471	**334**	**9**		**707**	**841**				**11**		**29**	**5,439**
			4			6				3		0	498
			6			14	60			89			670
			12			240							273
				1,957									1,957
			42			6			7				246
			137	**1,957**		**402**	**60**	**0**	**7**	**94**		**1**	**4,007**
73	**475**	**437**	**209**	**1,957**	**907**	**1,541**	**60**	**122**	**316**	**164**	**175**	**54**	**13,598**

Table 29.4 Forecast lung cancers for 2060 attributable to occupational exposure to respirable crystalline silica and avoidable numbers for a range of interventions

Intervention scenario		Attributable fraction (%)	Attributable cancer registrations	Cancer registrations avoided
		2010		
	Current burden	2.07	837	
		2060		
Baseline scenario (1)	Current (2005) employment and exposure levels are maintained, WEL = 0.1 mg/m^3, compliance 33 %	1.08	794	
To test introduction of different reduced exposure standards in 2010, overall compliance 33 %				
(2)	Introduce exposure standard = 0.05 mg/m^3	0.80	592	202
(3)	Introduce exposure standard = 0.025 mg/m^3	0.56	409	385
To test different timing of introduction of a reduced exposure standard, overall compliance 33 %				
(4)	Introduce exposure standard = 0.05 mg/m^3 in 2020	0.90	666	128
(5)	Introduce exposure standard = 0.05 mg/m^3 in 2030	1.02	753	42
To test introduction of different reduced exposure standards in 2010, overall compliance 90 %				
(6)	Maintain exposure standard = 0.1 mg/m^3 in 2010	0.14	102	693
(7)	Introduce exposure standard = 0.05 mg/m^3 in 2010	0.07	49	745
(8)	Introduce exposure standard = 0.025 mg/m in 2010	0.03	21	773
To test introduction of a reduced exposure standard of 0.05 mg/m^3 in 2010, with different compliance by workplace size				
(9)	33 % compliance in workplaces employing 0–249, 90 % compliance in workplaces employing 250+	0.68	499	295
(10)	33 % compliance in workplaces employing 0–49, 90 % compliance in workplaces employing 50+	0.61	451	344
(11)	33 % compliance in self-employed, 90 % compliance in other workplaces	0.35	261	533
(12)	90 % compliance in all workplaces	0.07	49	745

assessed in this study include reducing workplace exposure limits and improving compliance with these limits. Cancers associated with asbestos, diesel engine exhaust, polycyclic aromatic hydrocarbons, work as a painter, radon, and solar radiation were forecast to continue (although at much reduced levels in the case of asbestos), with construction remaining the prime industry of concern [34].

Extension to Measures of Lost Quality of Life

The sections above have demonstrated how estimation of numbers of attributable deaths and registrations can inform risk reduction for occupational cancer. However, attributable deaths may underestimate the total burden of disease particularly as survival rates improve; in the case of registrations, no differentiation is made between life-threatening cancers and those for which the prognosis for future quality of life is good. To obtain a better estimate of the relative costs to the individual and society of the occupational cancers that are occurring, one can apply attributable fractions to (i) a measure of lost years of life and (ii) a measure of lost quality of life to the individual. Health-adjusted life years (HALYs) are summary measures of population health that allow the combined impact of death and morbidity to be considered simultaneously. HALYs include disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs). DALYs are disease specific and use disability weights which are based on expert judgment. QALYs tend to be based on the surveyed opinion of patients or the general population and may apply to personal or community health effects. Short survival cancers such as lung cancer and especially those occurring relatively early in life will contribute large numbers of years of life lost (YLLs). Years of life lived with a disability (YLDs) contribute, with YLLs, to the estimation of DALYs, and lost quality of life measures are used to estimate QALYs. Comparison of YLDs and YLLs can aid prioritization of interventions.

QALYs and DALYs were originally developed for different purposes. QALYs were developed by economists, operations researchers, and psychologists to use in the denominator of a cost-effectiveness ratio in cost-utility analyses to measure quality of life for comparison of the outcomes of medical and public health interventions. QALYs for an individual are estimated over their lifetime as the sum of years remaining to death, each year weighted by a health-related quality of life (HRQL) component representing their health state in that year. The HRQL weights for QALYs are based on an individual's assessment of their own health status or that of others in the community, and the weights are therefore culture specific and apply to health states rather than diseases. Health states are measured in terms of symptoms including pain and suffering and of psychological and social factors.

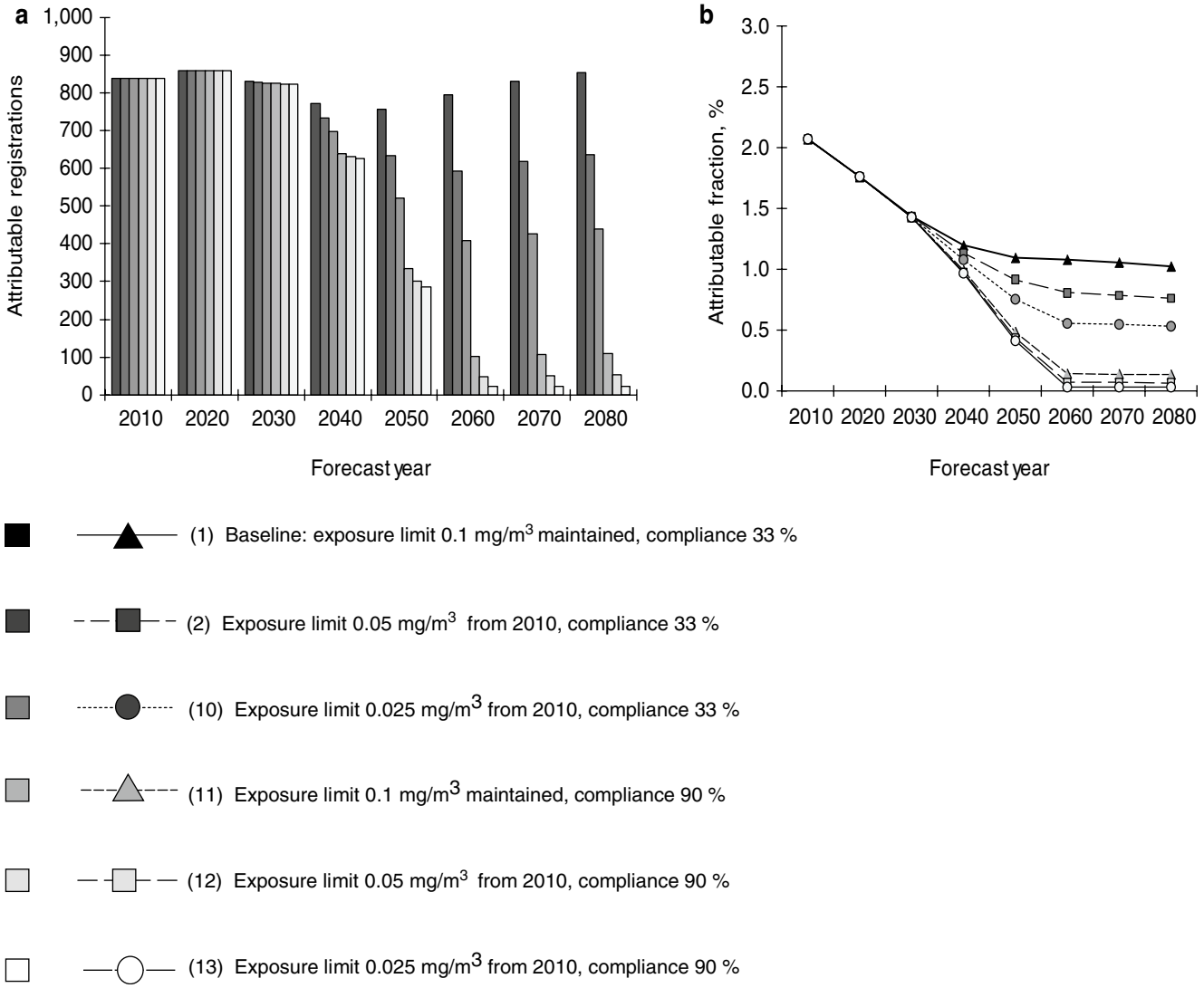


Fig. 29.3 Effect of reducing workplace exposure limits and improving compliance for respirable crystalline silica associated with lung cancer. (**a**) attributable registrations, (**b**) attributable fractions

DALYs were developed by the World Bank and World Health Organization (WHO) for the Global Burden of Disease (GBD) study, to quantify the burden of disease and disability in populations and to set priorities for resource allocation. They are derived from the sum of YLLs plus YLDs and measure the gap between a population's health and a hypothetical ideal for health achievement. One DALY represents a year of healthy life lost be it from mortality or morbidity. The HRQLs (disease-specific disability weights) for DALYs are based on secondary data and expert opinion, placing different conditions along a continuum of disability.

Lost years of life were used originally to compare burden of disease across different causes of death; they measure lifetime lost due to premature mortality for a particular disease. Years of potential life lost (YPLLs, also called years of life lost, YLLs) are obtained by multiplying the number of disease-specific deaths at a given age by a weighting factor for that age, usually average life expectancy for that age, and summing across ages. The WHO uses life expectancies from Japan, which has the longest overall life expectancy for any country. For the British study, British life expectancy data were used.

YLDs are estimated by combining over each age group and each cancer stage the number of incident cases, the proportion of nonfatal or long survival incident cases, a disability weight, and the mean duration of each stage. For the GBD approach, weights were available from the WHO, for grouped ages (15–44, 45–59, 60+) and for four stages of disease: diagnosis/therapy, waiting, metastasis, and terminal. The British study used a modification of the GBD approach adapted for the most recent estimates of burden of disease in Australia, which draws on Dutch weights developed for burden of disease estimation and medical knowledge of disease sequelae and their durations for each cancer. Six main

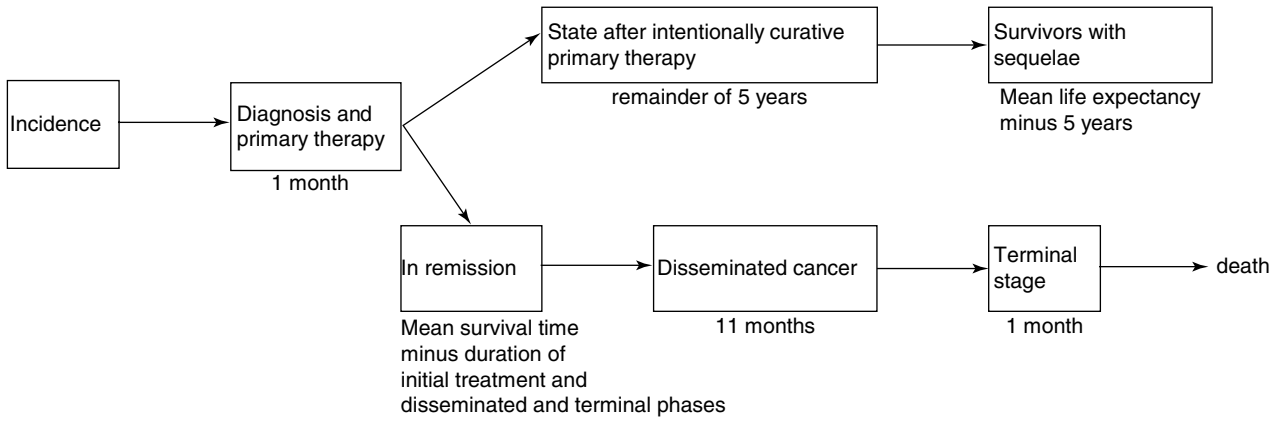


Fig. 29.4 General disease stage model for estimating cancer YLDs

Table 29.5 Years of life lost (*YLLs*), years of life lived with a disability (*YLDs*), disability-adjusted life-years lost (*DALY*) and average (*YLLs*)

Cancer site	Attributable deaths (2005)	YLLs (years)	YLDs (years)	DALYs (years)	Average YLL (years)
Bladder	245	2,543	567	3,110	10.7
Breast	555	9,600	4,196	13,797	17.3
Larynx	20	290	123	414	14.6
Leukemia	23	390	33	423	17.6
Lung	4,745	62,848	3,164	66,012	13.7
Mesothelioma	1,937	26,942	796	27,738	14.0
NHL	57	964	65	1,029	17.4
NMSC	23	203	67	270	8.7
Esophagus	184	2,528	163	2,691	13.5
Ovary	23	383	35	418	16.8
Sinonasal	38	622	181	802	16.8
STS	13	286	38	324	22.5
Stomach	108	1,324	129	1,453	12.4
Total:					
Based on deaths	8,010	109,672			15.1
Based on registrations			9,662	119,334	

stages were identified, "diagnosis and primary therapy," "stage after intentionally curative primary therapy," "survivors with long term sequelae," "remission," "disseminated/preterminal," and "terminal" stages, with some variability for the different cancers. A general model for these disease stages is given in Fig. 29.4.

Example from the British Study

Table 29.5 gives the YLDs, YLLs, and DALYs for the British study for the major cancer sites, together with the mean years of life lost. For poor survival cancers such as mesothelioma and cancers of the brain, lung, esophagus, and stomach, the YLLs are close to the total DALYs with few YLDs. Strategies for prevention of premature mortality might thus focus on cancer sites such as these. Cancer sites with longer and improving survival patterns are breast cancer and laryngeal cancer as seen by the greater proportion of YLDs. Average years of life lost range from about ten (bladder and non-melanoma skin cancer) to about 20 (brain, cervix, soft tissue sarcoma, nasopharynx). Because the top 10–20 carcinogens/occupations have a dominance of cancers such as lung and bladder, the average years of life lost is around about 12–14 for most.

Discussion

The British study has been used in this chapter to illustrate the detail of the results that can be derived using burden estimation methods and their use for prioritization of risk reduction strategies and targeting specific occupational cancers, carcinogens, and industries. Differences between the

estimates for Britain and those from other countries occur for various reasons, including differences in the numbers of agents considered, for example, Steenland et al. [8] considered eight agents in the estimation of current burden of lung cancer, whereas the British study used 21; the occupational situations in which exposures occur; the levels of exposure encountered, for example, higher/lower risk estimates might be appropriate for certain countries and the proportion of workers exposed may also differ; and the methodological approaches used. Burden estimates from other studies range between 3 % and 10 % [5–13]. With the exception of leukemia, the British estimates are greater than those of Doll and Peto [5] whose estimates were used in the UK for many years. The steep rise in asbestos-related deaths from lung cancer and mesothelioma since 1981 has made a major contribution to the increase [35, 36]. More recent estimates of occupational cancer have been made for Australia [37] (5,000 invasive cancers and 34,000 NMSCs) and France [38] (4,335 (2.7 %) cancers for men, 403 (0.3 %) cancers for women) using similar methods to the British study. Parkin (2011) applied the PAFs from the British study to the estimated number of cancers in the UK in 2010 and estimated a total of 11,494 cancers attributable to occupational cancers (7,832 for men, 3,662 for women) [39]; they excluded NMSC primarily because it was thought that, as registration of NMSC in the UK is probably incomplete, including them in the total attributable cancers would be incomplete. Rushton et al. [40] acknowledge this point [40]. Their estimate could be considered as "lower bound" [40] for NMSC from occupational exposure to solar radiation and mineral oils, and they draw attention to the potential for substantial morbidity as disfigurement may be caused from the tendency for lesions to be on the head and neck and as the prevalence is high NMSC can represent a considerable economic burden to health services [41, 42].

There are a number of important issues which affect the results. Some of the biases and uncertainties inherent in burden estimation are shown in Table 29.6 together with an indication of the possible direction of the effect on results. A key decision at the start of any burden estimation is to decide which diseases and exposures are to be included. For cancers the classification developed and implemented by IARC is well respected worldwide. The British study chose to assess only those agents classified by IARC as Group I and 2A carcinogens. Other substances, such as IARC Group 2B carcinogens, many of which may be treated as if they were human carcinogens in regulatory settings, were not included; the estimates could thus be too low. In contrast, those estimating burden may prefer to be even more restrictive and only assess definite human carcinogens (IARC Group1) and cancer sites with sufficient evidence.

The use of the attributable fraction as a measure of burden with its dependence on estimation of risk and proportion exposed also has potential for introduction of uncertainty or bias. This includes the choice of the study for obtaining data for the risk estimates, for example, if the exposures in this study did not reflect those experienced in the country for which estimation is being carried out. Much of the occupational literature is focused on studies of men and mortality necessitating assumptions for estimating burden for women and for cancer incidence. The use of risk estimates derived from studies of men for women and mortality risk estimates for incidence may bias the AFs. Epidemiological studies of occupational groups often result in a "healthy worker effect," that is, a reduced risk estimate compared to the general population. This together with potential misclassification of exposure in epidemiological studies could lead to an underestimation of the true effect and thus an underestimation of the burden.

Ideally, one needs risk estimates from quantitative dose-response analyses. Although these are increasingly available

Table 29.6 Sources of bias in the estimation of occupational cancer burden

Bias affecting the combined AF estimate	Likely direction of bias
Choice of cancer/exposure pairings	↓
Missing unknown exposures	↓
Inadequate data for exposed number estimates:	
Inadequate estimates of number employed	↕
Unknown proportion exposed in workplace	↑
Inadequate definition of exposure levels	↕
Unknown cancer latency range	↕
Inadequate estimates of staff turnover	↕
Wrong assumption about workforce recruitment age range	↑
Choice of relative risk estimates:	
Is risk reversible after exposure withdrawn?	↑
Absence of dose-response data for RR estimate	↔
No risk estimates for low exposure	↓
Incidence, not mortality RRs	↕
Publication bias	↑
Confounding	↑
Exposure misclassification	↕
Non-portability of the relative risks:	
Source-target unmatched confounders/effect modifiers	↕
Source-target unmatched exposures	↑
Use of historic RRs (source-target unmatched RRs)	↕
Wrong estimator bias:	
Levin's formula used with adjusted RR	↑
AF estimator not by age	↕
Combining disjoint or non-independent overlapping AFs	↑

Entries in bold were considered to be the most important potential sources of bias and uncertainty in the British cancer burden study, and the arrows indicate the likely direction of the bias (↔ indicates a wider confidence interval)

in the epidemiological literature, parallel data giving the proportion exposed at certain exposure levels is largely unavailable. The British study addressed this by taking a pragmatic decision to assign industry sectors to qualitative exposure categories such as high or low and using appropriate risk estimates for these categories. Implicit assumptions were thus made regarding the similarity of durations and intensities of exposure between the studies used for the risk estimates and the British national populations.

In most occupational epidemiological studies, very short-term workers, for example, those employed for less than a year, are excluded. Another key decision is thus whether to exclude workers with less than 1-year employment in the estimation of turnover over the risk exposure period, as carried out in the British study. The overall effect of including these short-term workers would be to increase the AFs and attributable numbers.

There is a general lack of information on the latency of cancer, particularly in relation to specific occupational exposures. The British study in estimating current burden made pragmatic decisions of between 10 and 50 years before the estimation year for solid tumors and for up to 20years before the estimation year for lymphohematopoietic malignancies. Changes to these assumptions, for example, different latencies for different cancer sites, would affect the results.

The results shown for the British study highlighted the potential for multiple concurrent exposures to occur; one exposure could lead to multiple cancer types and/or two or more exposures experienced in a single job could cause the same cancer. The latter issue is important when considering how to combine attributable fractions for different risk factors to give an estimate of overall burden. In addition, there may be unidentifiable risk factors in certain occupations; for example, IARC has considered risk within hairdressing as a whole. This approach was used for some occupational circumstances in the British study. To take account of potential multiple exposures to carcinogenic agents, strategies can include partitioning exposed numbers between overlapping exposures or carrying out estimation only for what is considered to be the dominant carcinogen with the highest risk. If it can be assumed that the exposures are independent of one another and that their joint carcinogenic effects are multiplicative, then they can be combined using a product sum [24]. However, bias can arise if independence has been incorrectly assumed. This methodological bias like that associated with the use of Levin's equation with adjusted risk estimates can be quantified unlike many of the other effects of uncertainty.

Many past exposures will have been at much higher levels than those existing today. However, although trends vary depending on the substance and source of data, there is a tendency for exposures to many occupational carcinogens to be gradually decreasing. For example, analyses of exposure measurement data held in the UK National Exposure Database (NEDB) and from UK Health and Safety Executive inspection surveys and other surveys showed downward trends of 11 % per year for toluene between 1985 and 2002 based on inspection surveys, but follow-up surveys of eight companies using toluene-containing compounds show an average decrease of only 1 % per year in toluene concentrations [43]. Although respirable dust exposure in the quarry industry declined by 6 % each year from 1984 to 2003, there was no clear change in exposure over time for respirable quartz exposure.

Other exposures have all but disappeared due to the decline of the industry or the substitution of hazardous substances by other noncarcinogenic agents. Other carcinogens such as naturally occurring radon could also easily be eliminated from workplaces. However, the long latency of some cancers means that numbers of deaths and registrations due to past high exposures will continue to be substantial in the near future (particularly asbestos-related cancers).

The British estimation of the future burden of occupational cancers has attempted to capture the nature of these changes in exposure. Uncertainties such as those described above will, however, also be applicable to future burden estimation. The results demonstrated the considerable reductions in occupational cancer burden that could potentially be achieved. However, they also highlight the fact that whatever the choice of intervention little reduction is achieved in the short term due to the long latency of many cancers and the legacy of high exposures in the past. The results also demonstrate that for Britain, even with stringent risk reduction measures, some carcinogens such as asbestos, polycyclic aromatic hydrocarbons in coal tars and pitches, and solar radiation are likely to continue to cause occupationally related cancers in the future. The contribution to the future total burden of large numbers of workers exposed at low levels within several service industries was highlighted in this study, rather than the current more highly exposed manufacturing industry sectors.

Only limited intervention options were tested in the British study, for example, reducing workplace limits and improving compliance with these limits. The methodology has the potential to be extended to assess other interventions such as improving technology, increasing awareness, and changing attitudes and behaviors which are important in exposure control and risk reduction. It is important to note that interventions to reduce exposure to carcinogens may often also lead to reductions in other health-related conditions in the working and living environment, for example, reduction of silica exposure will not only reduce lung cancer but will affect respiratory function and other nonmalignant respiratory diseases.

In summary, this chapter has outlined different methods for estimating the burden of occupational cancer and focused

on the estimation of attributable burden using a British study as illustration. The methods described have the potential to be adapted for use in other countries and extended to include social and economic impact evaluation. For example, the methods from the British study have been utilized to inform a project to assess the socioeconomic impact of and make recommendations for revised Occupational Exposure Limits for the European Union for 25 recognized carcinogens; the methods have also been extended to calculate attributable fractions by age for estimating the contribution of occupational disease in the current Global Burden of Disease update [44]. Estimation of attributable numbers and fractions makes an important contribution to the knowledge base on which to inform prioritization for health and safety strategic planning and for research to fill information gaps. Highlighting the impact of occupational exposures on population cancer morbidity and mortality, together with the occupational circumstances and industrial areas where exposures to these agents occurred in the past, can also provide a comparison with the impact of other causes of cancer.

References

1. Higginson J. Environmental carcinogenesis. Cancer. 1993;72:971–7.
2. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006;367:1747–57.
3. Brown ML, Lipscomb J, Snyder C. The burden of illness of cancer: economic cost and quality of life. Annu Rev Public Health. 2001;22:91–113.
4. Danaeii G, Vander Hoorn S, Lopez AD, Murray CJL, Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366:1784–93.
5. Doll R, Peto R. The cause of cancer. Oxford: Oxford University Press; 1981.
6. Dreyer L, Andersen A, Pukkala E. Avoidable cancers in the Nordic countries. Occupation. APMIS. 1997;76(Supplement):68–79.
7. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. Am J Ind Med. 2005;48:419–31.
8. Steenland K, Burnett C, Lalich N, Ward E, Hurrell J. Dying for work: the magnitude of US mortality from selected causes of death associated with occupation. Am J Ind Med. 2003;43:461–82.
9. Nurminen MM, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. Scand J Work Environ Health. 2001;27:161–213.
10. Vineis P, Simonato L. Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach. Arch Environ Health. 1991;46:6–15.
11. Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Jarup L, Scheele P. Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden. Am J Epidemiol. 2000;152:32–40.
12. Landrigan PJ, Markowitz S. Current magnitude of occupational disease in the United States: estimates for New York. In: Landrigan PJ, Selikoff IJ, editors. Occupational health in the 1990s. Developing a platform for disease prevention. NewYork: Annals of New York Academy of Science; 1989. p. 27–45.
13. Leigh JP, Markowitz SB, Fahs M, Shin C, Landrigan PJ. Occupational injury and illness in the United States. Arch Intern Med. 1997;157:1557–68.
14. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg. 2000;44:565–601.
15. Morrell S, Kerr C, Driscoll T, Taylor R, Salkeld G, Corbett S. Best estimate of the magnitude of mortality due to occupational exposure to hazardous substances. Occup Environ Med. 1998;55:634–41.
16. Landrigan PL, Schechter CB, Lipton JM, Fahs MC, Schwartz J. Environmental pollutants and disease in American children: estimates of morbidity, mortality and costs for lead poisoning, asthma, cancer, and developmental disabilities. Environ Health Perspect. 2002;110:721–8.
17. Deschamps F, Barouh M, Deslee G, Prevost A, Munck J.Estimates of work-related cancers in workers exposed to carcinogens. Occup Med. 2006;56:204–9.
18. Andersen A, Barlow L, Engeland A, Kjaerheim K, Lynge E, Pukkala E. Work-related cancer in the Nordic countries. Scand J Work Environ Health. 1999;25 Suppl 2:1–116.
19. Kjaerheim K, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparen P, Tryggvadottir L, et al. Effects of occupation on risks of avoidable cancer in the Nordic countries. Eur J Cancer. 2010;46:2545–54.
20. Rushton L, Evans G, editors. The burden of occupational cancer in Britain. Br J Cancer. 2012;107:S1–108.
21. Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al. Listing occupational carcinogens. Environ Health Perspect. 2004;112:1447–59.
22. Rousseau M-C, Straif K, Siemiatycki J. IARC Carcinogen update. Environ Health Perspect. 2005;113(9):A58.
23. Straif K, Baan R, Grosse Y, Secretan B, Ghissassi FE, Cogliano V. Carcinogenicity of polycyclic aromatic hydrocarbons. Lancet Oncol. 2005;6:931.
24. Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of shift-work, painting and firefighting. Lancet Oncol. 2007;8(12):1065–6.
25. Hutchings SJ, Rushton L. The burden of occupational cancer in Britain. Statistical methodology. Br J Cancer. 2012;107:S8–17.
26. Kauppinen T, Toikkanen J, Pedersen D, Young R, Kogevinas M, Ahrens W, et al. Carex. Occupational exposure to carcinogens in the European Union in 1990–93. Helsinki: Finnish Institute of Occupational Health; 1998. http://www.ttl.fi/en/chemical_safety/carex/Documents/1_description_and_summary_of_results.pdf.
27. Labour Force Survey (2009) Available at:http://www.statistics.gov.uk/
28. ONS (2009) Census of employment. Available at: https://www.nomisweb.co.uk/
29. Levin M. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum. 1953;9:531–41.
30. Miettinen O. Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol. 1974;99:325–32.
31. Greenland S. Interval estimation by simulation as an alternative to and extension of confidence intervals. Int J Epidemiol. 2004;33:1389–97.
32. Steenland K, Armstrong B. An overview of methods for calculating the burden of disease due to specific risk factors. Epidemiology. 2006;17:512–9.
33. Hutchings SJ, Rushton L. Towards risk reduction: predicting the future burden of occupational cancer. Am J Epidemiol. 2011;173(9):1069–77.
34. Hutchings SJ, Cherrie JW, Van Tongeren M, Rushton L. Intervening to reduce the future burden of occupationally-related cancers in Britain: what could work? Cancer Prev Res. 2012;5:1213–22.

35. Darnton AJ, McElvenny DM, Hodgson JT. Estimating the number of asbestos-related lung cancer deaths in Great Britain from 1980 to 2000. Ann Occup Hyg. 2006;50:29–38.
36. Hodgson JT, McElvenny DM, Darnton AJ, Price M, Peto J. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2005. Br J Cancer. 2005;93:587–93.
37. Fritschi L, Driscoll T. Cancer due to occupation in Australia. Aust N Z J Public Health. 2006;30(3):213–9.
38. Boffetta P, Autier P, Boniol M, Boyle P, Hill C, Aurengo A, et al. An estimate of cancers attributable to occupational exposures in France. J Occup Environ Med. 2010;52(4):399–406.
39. Parkin DM. Cancers attributable to occupational exposures in the UK in 2010. Br J Cancer. 2011;105:S70–2.
40. Rushton L, Bagga S, Bevan R, Brown TP, Cherrie JW, Fortunato L, Holmes P, Slack R, Van Tongeren M, Young C, Hutchings SJ. Occupation and cancer in Britain. Br J Cancer. 2010;102:1428–37.
41. Trakatelli M, Ulrich C, del Marmol V, Eudvard S, Stockfleth E, Abeni D. Epidemiology of Nonmelanoma Skin Cancer (NMSC) in Europe: accurate and comparable data are needed for effective public health monitoring and interventions. Br J Dermatol. 2007;156 Suppl 3:1–7.
42. Houseman TS, Feldman SR, Williford PM, Fleischer AB, Goldman ND, Acostamadiedo JM, Chen GJ. Skin cancer is among the most costly of all cancers to treat for the Medicare population. J Am Acad Dermatol. 2003;48:425–9.
43. Cherrie JW, Van Tongeren M, Semple S. Exposure to occupational carcinogens in Great Britain. Ann Occup Hyg. 2007;51(8):653–64.
44. Lim S, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease study 2010. Lancet. 2012;380: 2224–60.

Occupational Carcinogens and Cancer in Children

30

Mana Mann and Philip J. Landrigan

Keywords
Occupational cancer • Children • Maternal occupational exposure • Paternal occupational exposure • Childhood hematolymphoid malignancies • Childhood brain tumors • Neuroblastoma • Germ cell tumors

Introduction

This chapter reviews two aspects of the literature relating childhood cancer to occupational exposures. First, we review published reports that examine associations between childhood cancer and parental exposures to carcinogens in the workplace. In the first portion of this chapter, we consider maternal as well as paternal exposures to occupational carcinogens in several different windows of time – preconception (more than 1 year prior to birth), periconception (3 months before and after conception), during pregnancy, and postnatally. Then in the second portion of this chapter, we examine the emerging literature on the health consequences of child workers' occupational exposures to carcinogens in the workplace. Here we consider carcinogenic hazards confronting youth workers in the United States (US) as well as those confronting child laborers in developing countries.

This chapter draws from peer-reviewed English language publications and government reports up to May 2011 identified through PubMed searches. Search strategies included using keywords for various combinations of childhood cancers and parental occupational exposures. The PubMed "related articles" option was utilized to identify articles not found in initial keyword searches. Review of other relevant publications by authors initially identified by keyword searches was performed. Reports included in this chapter were limited to original epidemiologic studies as well as recent literature reviews, meta-analyses, and pooled analyses.

Parental Exposure to Occupational Carcinogens on Childhood Cancer Risk

Elucidation of the role of parental occupations on the risk for childhood cancer has become an important area of current study. Because certain cancers typically present in early childhood, it is hypothesized that risk factors very early in life, during pregnancy, or potentially even before conception may play a role in cancer causation [1]. Earlier studies in the field had focused on understanding the role of paternal exposures on childhood cancer risk without taking into account the timing of the exposures. Subsequently, studies have assessed the role of both paternal and maternal occupational exposures at various time periods in child development as risk factors for childhood cancer [2].

Children are at risk of exposures to occupational carcinogens via several pathways and mechanisms. One mechanism is entry of the carcinogen into the parent's body to cause mutagenic changes in the mother's ovum or the father's sperm before conception. A second pathway involves the parent bringing the carcinogenic material home – "take-home exposure" – on clothing leading to transplacental exposure of the fetus and direct exposure of the child. Breastfeeding is a third possible pathway of exposure for the child. Direct exposure to carcinogenic substances used in the home (e.g., pesticides for pest control) is another route of exposure [3, 4]. Multiple

M. Mann, MD, MPH (✉) • P.J. Landrigan, MD, MSc
Department of Preventive Medicine,
Mount Sinai School of Medicine,
One Gustave L. Levy Place, New York, NY 10029, USA
e-mail: philip.landrigan@mssm.edu

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_30, © Springer-Verlag London 2014

pathways of exposure to carcinogenic substances at different times of child development may together have a cumulative effect on the child's risk for cancer.

Hematologic and Lymphoid Malignancies

Maternal Occupational Exposures

A systematic review identified a number of maternal occupational exposures as potential risk factors in the development of childhood leukemia, including pesticide use and employment in personal service and textiles industries, as well as occupational exposure to metals [5].

Pesticides

Childhood leukemia has been shown to be associated with maternal occupational exposure to pesticides in the prenatal time period. In a meta-analysis evaluating pesticide exposure and childhood cancers, the summary odds ratio (OR) of prenatal maternal occupational exposures to any pesticides was 2.09, 95 % confidence interval (CI) 1.51–2.88 and to unspecified pesticides was 2.16, 95 % CI 1.51–3.08. Specifically, childhood leukemia risk was significantly elevated with prenatal maternal occupational exposure to broad pesticide classes of insecticides (summary OR 2.72, 95 % CI 1.47–5.05) and herbicides (summary OR 3.62, 95 % CI 1.28–10.3). Two limitations of this meta-analysis were that the studies included exposure status that was determined after the child's diagnosis, potentially introducing recall bias, and the studies did not uniformly evaluate pesticide exposure frequency [6]. Further support for the role of maternal pesticide exposure and childhood leukemia was provided by a large case-control study in Montreal which showed an exposure–risk relationship between childhood acute lymphatic leukemia and maternal prenatal use of herbicides, plant insecticides, or tree pesticides in or around the home. The study also suggested that this association was stronger among the subset of cases with the m1 or m2 polymorphisms of CYP1A1 [7, 8]. These findings led to the suggestion that maternal prenatal pesticide exposure played a more important role than paternal exposure in the development of childhood leukemia [9].

Personal Service

Significant associations between maternal occupations involving personal services, metals, and textiles and childhood leukemia have previously been shown. These associations were found to be significant before birth but not during the postnatal phase [5]. In the studies focusing on the personal service industry, there was no consistent definition of the occupation [5]. Because of variability in this definition, it is difficult to assess whether multiple exposures to different occupational materials or one specific material played a greater role in the development of childhood leukemia.

Textiles

Mothers' occupational exposure in the textile industry was another identified risk factor for childhood leukemia [5]. In addition, McKinney et al. found in the UK Childhood Cancer Study, a large case-control study, that maternal exposures during the periconception period to textile dust were associated with an increased rate of Hodgkin's disease in their children; there were seven cases of Hodgkin's disease (HD) in the children of exposed case mothers, which over represented this malignancy (15.6 %, 7/45) compared to the distribution in the entire set of cases (8 %, 117/1414). The majority of mothers of exposed cases (76 %) and controls (67 %) were classed as sewing machinists, menders, darners, and embroiderers [10]. No specific cause for this observation was presented.

Metals

Maternal exposure to metals in a wide range of occupational groups has been implicated as a risk factor for both acute lymphoblastic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL). McKinney et al. showed in the UK Childhood Cancer Study that for children born to mothers exposed to metals at periconception, sometimes in combination with oil mists in metalworking operations, the risks for childhood leukemia and ALL were threefold higher than in the children of unexposed mothers (leukemia: OR 3.68, 95 % CI 1.59–8.55; ALL: OR 3.91, 95 % CI 1.64–9.32). The risks associated with maternal occupations with metals at the time of the child's diagnosis were not significant (leukemia: OR 2.54, 95 % CI 0.46–13.93; ALL: OR 1.58, 95 % CI 0.18–14.27). Seven out of ten case mothers in this category were "machine tool, press stamping, and automatic machine operatives" [10]. Two other case-control studies found excess risks of ANLL among children whose mothers were exposed occupationally to metals [11, 12].

Solvents

Maternal exposure to solvents has been shown to be a potential risk factor for childhood leukemia, but the evidence has been inconsistent. Solvents are especially concerning in their association with childhood leukemia because benzene is a well-established risk factor implicated in adult leukemia and other solvents are suspected carcinogens [13]. A study of the Children's Cancer Group, a large-scale case-control study which examined the association of self-reported occupational exposure to various hydrocarbons, found elevated ORs for childhood ALL with maternal exposure to the following: solvents (OR 1.8, 95 % CI 1.3–2.5) and paints or thinners (OR 1.6, 95 % CI 1.2–2.2) during the preconception period, maternal exposure to solvents (OR 1.6, 95 % CI 1.1–2.3) and

paints or thinners (OR 1.7, 95 % CI 1.2–2.3) during pregnancy, and to plastic materials during the postnatal period (OR 2.2, 95 % CI 1.0–4.7) [2]. Similar findings were published from results of a case-control study of childhood leukemia in the Netherlands which found a significant association between maternal occupational exposure to chemicals (paint, petroleum products, and unspecified chemicals) during pregnancy and childhood leukemia (relative risk (RR) = 2.4, 95 % CI = 1.2–4.6) [14].

These studies were partially supported by a pooled analysis of three German case-control studies conducted from 1992 to 1997 looking at parental occupational exposure to different chemicals and industrial dusts or fumes. The authors found that maternal exposure to paints or lacquers during the preconception period (OR 1.6, 95 % CI 1.1–2.4) and during the index pregnancy (OR 2.0, 95 % CI 1.2–3.3) was associated with an elevated risk of childhood ALL. Unlike the results of the Children's Cancer Group, a significant association was not found between the risk of ALL and maternal exposure to solvents and parental exposure to plastic materials [15].

Maternal exposure to solvents in the periconception period has been shown to be significantly associated with childhood leukemia. A case-control study by Sung et al. reported an increased odds ratio between childhood leukemia and maternal employment in factories where there was exposure to organic solvents in the periconception period (RR 3.83, 95 % CI 1.17–12.55) [16]. A twofold increase in childhood leukemia and ALL among mothers with dermal exposure to hydrocarbons at periconception (leukemia: OR 2.20, 95 % CI 1.23–3.95, ALL 2.16, 95 % CI 1.16–4.02) has also been found. For maternal exposures at the time of the child's cancer diagnosis, however, an increased risk for child leukemia and ALL was not seen [10].

Other case-control studies of maternal solvent exposure and childhood ALL have not found an association. A population-based, case-control study, for example, reported the odds ratio for any maternal exposure to solvents with childhood leukemia to be 1.11 (95 % CI, 0.88–1.40) in the period from 2 years before pregnancy to birth. Increased risks for specific solvent exposures, such as to 1,1,1-trichloroethane (OR 7.55, 95 % CI 0.92–61.97), toluene (OR 1.88, 95 % CI 1.01–3.47), and mineral spirits (OR 1.82, 95 % CI 1.05–3.14) were reported. Maternal exposure to alkanes (OR 1.78, 95 % CI, 1.11–2.86) and mononuclear aromatic hydrocarbons (OR 1.64, 95 % CI 1.12–2.41) with childhood leukemia had moderately increased risks. Results were generally similar for the period ranging from 2 years before pregnancy up to birth and for the pregnancy period alone [17]. These studies suggest that maternal occupational exposure to hydrocarbons on child leukemia risk may depend on both the type of hydrocarbon and the timing of the exposure.

The International Agency for Research on Cancer (IARC) has concluded that "There is limited evidence in humans, based primarily on studies of maternal exposure, that painting is associated with childhood leukaemia" [18].

Electromagnetic Field Exposure (EMF)

Inconsistent findings have been reported on the role of maternal occupational electromagnetic field exposure (EMF) and childhood leukemia. In two case-control studies, an association was found between preconception EMF exposure and childhood leukemia [19], while in four other case-control studies no significant association was found [20–23]. A potential explanation for these differing results is that the majority of women have low level of exposures resulting in only small numbers of children with mothers who have high level of exposures. As a result of this skewed distribution of exposures, risk estimates could be unstable.

Ionizing Radiation

Children, especially during the prenatal period, appear considerably more sensitive than adults to the carcinogenic effects of ionizing radiation. The first evidence for this enhanced sensitivity comes from Alice Stewart's classic epidemiologic studies in Oxford, UK, which found increased risk for childhood leukemia among children prenatally exposed through maternal abdominal x-rays [24, 25]. These findings have been confirmed in studies of cancer risks in the children of female radiation workers [26]. A large matched case-control study in Germany of leukemia cases, non-Hodgkin's lymphomas, and solid tumors found that maternal occupational exposure to ionizing radiation during pregnancy increased the risk for childhood lymphomas (OR 3.87, 95 % CI 1.54–9.75) but not for leukemia or solid tumors [26].

Paternal Occupational Exposures

Epidemiologic studies have identified a number of potential paternal exposures that may be associated with childhood leukemia. Studies have found an increased risk of childhood leukemia associated with paternal exposure to solvents, paints and pigments, motor vehicles, ionizing radiation, woodwork, and extremely low-frequency magnetic fields (ELF-MFs) [3, 12, 27–29].

Solvents

In one of the earliest studies examining the role of parental occupation on childhood leukemia risk, Fabia and Thuy reported a significant relationship between paternal hydrocarbon exposure and childhood leukemia [30]. In their systematic review, Colt and Blair found multiple studies

demonstrating significant associations between childhood leukemia and paternal exposure to solvents; the relative risks between paternal solvent exposure and childhood leukemia were greater than 3.0 in the setting of small numbers of exposed cases in many of the studies [5]. The significant exposures were solvents in general [12], chlorinated solvents [27], and benzene, carbon tetrachloride, and trichloroethylene (TCE) [28]. Paternal exposure to solvents during the periods of preconception and pregnancy were found to have a significant association with childhood leukemia [10, 12]. Lowengart et al. found a significant relationship between paternal exposure to chlorinated solvents and childhood leukemia when the exposure was after birth of the child [27]. Take-home exposure was the postulated route of exposure, and the authors considered the possibility that children could be exposed to solvent vapor in workers' exhaled breath. It was noted further that studies published since 1998 did not support an association between childhood leukemia/lymphoma and paternal occupational solvent exposure [31].

Paints and Pigments

In regard to paternal exposures to paints and pigments, a majority of studies reported elevated ORs for childhood leukemia of 1.5 or greater with two of these studies reaching statistical significance during prenatal exposure as well as exposure at any time period [5]. The reviews by Colt et al. [5] and Savitz et al. [32] concluded that paternal exposure to paints and pigments yielded a relatively consistent positive association with childhood leukemia. There have been subsequent studies, however, that have not supported this association [3].

Motor Vehicles

A majority of studies have found an association between childhood leukemia and paternal employment in occupations related to motor vehicles or involving exposure to exhaust gases. Specifically, significant associations have been found with paternal work as motor vehicle or lorry drivers, mechanics, and gas station attendants, as well as broader groups of motor-vehicle-related occupations [5]. It has been previously suggested that the association between motor-vehicle occupations and adult leukemia is connected to benzene and other engine exhausts [5].

A UK-based case-control study found that children of fathers exposed to exhaust fumes, driving, and inhaled particulate hydrocarbons at periconception had a small but statistically significant increased risk for childhood leukemia and ALL [10]. Also, paternal exposure to exhaust fumes at the time of the child's diagnosis increased the child's risk of leukemia (OR 1.23, 95 % CI 1.00–1.52), but neither occupation involving driving nor exposure to hydrocarbons were found to be statistically significant. The authors highlighted the importance of a cautious interpretation of these findings because the data were self-reported, the exposure assessment had the potential to lack precision, and the large number of comparisons made could have resulted in some statistically significant associations arising by chance [10].

Ionizing Radiation

The relationship between paternal exposure to ionizing radiation and childhood risk of leukemia/lymphoma has not been consistently defined; there is limited evidence that preconception paternal ionizing radiation exposure is a risk factor. Although initial studies reported no significant association, Gardner et al. found that the risk of childhood leukemia in West Cumbria, England, was significantly associated with paternal employment in the Sellafield nuclear fuel reprocessing plant, especially for fathers with high radiation dose recordings before their child's conception [33]. Colt et al. pointed out that the results were specific to workers in the village of Seascale and were not seen among the children of other Sellafield workers with similar preconception exposure [5]. Studying a population which overlapped with Gardner's population, McKinney et al. found significantly increased risks for childhood leukemia among children with paternal exposure to ionizing radiation [5, 28]. Other studies have not supported these findings [5, 10].

Woodwork

Paternal woodwork has also been implicated as a risk factor for childhood leukemia. Paternal employment as building finishers and other related workers (OR 4.08, 95 % CI 1.12–14.8) as well as wood treaters (OR 12.17, 95 % CI 1.36–109.2) in the preconception period was associated with increased risk for childhood leukemia among their children [34]. In the perinatal period, Ali et al. found elevated odds ratios for childhood leukemia among children whose fathers were employed as wood treaters (OR 13.08, 95 % CI 1.36–125.5) and as building finishers and related trade workers (OR 4.51, 95 % CI 1.04–19.6) [34]. These results were supported by a Swedish cohort study that found an increased risk ratio of childhood leukemia of 2.18 (95 % CI: 1.26–3.78) among children with fathers employed in woodwork in the preconception period (from 2 to 26 months before the child was born) [3].

Extremely Low-Frequency Magnetic Fields (ELF-MFs)

Studies have suggested a potential role for paternal exposures to ELF-MFs (50 or 60 Hz) either in the preconception

time period or during pregnancy as a risk factor for childhood cancer. The potential causal pathways are uncertain. One hypothesis suggests that exposure to magnetic fields induces mutagenesis in sperm, increasing the cancer susceptibility of the child [20, 35]. Confounding by "take-home" effects due to other preconceptual and lifetime occupations may, however, impact the observed association between paternal occupation in electrical-related jobs and childhood cancer [35].

The risk for leukemia in a Swedish cohort significantly doubled among children with fathers occupationally exposed to magnetic field levels above 0.3 μT in the 2–26 months before the child's birth [20]. A case-control study from the North of England found that children of electricians had a significant 1.6-fold risk of acute lymphoblastic leukemia [35]. Similarly, another study reported that children of fathers employed as electronic equipment assemblers and as "other assemblers" during the preconception time period had increased odds ratios for leukemia, ORs of 4.56 (95 % CI 1.05–19.9) and 10.24 (95 % CI 1.02–102.6), respectively [34]. An association between childhood leukemia and paternal exposure to magnetic field levels above 0.2 μT in the preconception period, however, was not found to be significant in a population-based case-control study in Germany. Children whose fathers were exposed to magnetic fields above 1 μT also did not have increased odds ratios for leukemia or non-Hodgkin's lymphoma [23].

Pesticides

Childhood leukemia has been shown to be associated with paternal and maternal use of pesticides in the home and garden but not with paternal occupation [27]. In a review and meta-analysis by Wigle et al., the authors found that neither ALL nor AML was associated with preconception paternal occupational exposure to any either specified or unspecified pesticide (OR 1.09 (0.88–1.34) and OR 1.12 (0.60–2.13), respectively). Paternal exposure to the broad class of insecticide, however, was significantly associated with an OR of 1.43 (1.06–1.92). Use of neither herbicide (OR 1.25 (0.94–1.66)) nor fungicides (OR 1.66 (0.87–3.17)) was associated with childhood leukemia [6].

Several studies have observed increased risk estimates with paternal agricultural exposures and childhood leukemia while others have not [6, 27]. A US prospective cohort study of children of licensed agricultural pesticide applicators found an increased risk of childhood cancer compared to the general population and a greater risk among children whose fathers did not use protective gloves. This study found a higher number of cases of lymphoma (Hodgkin's, Burkitt's, and non-Hodgkin's) among participants [36]. Several recent epidemiologic studies have supported the association between childhood leukemia and lymphoma and paternal occupational pesticide exposure [31].

Childhood Nervous System Tumors

Maternal Occupational Exposures

The epidemiologic studies assessing the role of maternal occupation and childhood brain tumors have found increased risk among mothers employed in the following industries: textile/garment [34], electronic [34], chemical, motor vehicle, health services, and food [37].

Textile Industry

Children born to mothers employed in the textile/garment industry whose employment extended across all early developmental periods – (preconception, perinatal, postnatal) – had significantly increased ORs for childhood brain tumors. The odds ratios for childhood brain tumor for mothers employed during any of these periods in textile/garment industry were 13.78 (95 % CI 1.47–129.0). ORs remained elevated although there were few cases [34].

Cordier et al. supported these findings in their assessment of childhood brain tumors in seven developed countries (Israel, Australia, Canada, the United States, France, Italy, and Spain). The authors found significantly elevated ORs of brain cancer in children with mothers employed as textile workers (OR 1.7, 95 % CI 1.1–2.7). The highest odds ratio was seen among mothers employed as textile workers in the prenatal period (1.8, 95 % CI 0.9–3.5) [37].

Electronics Industry

Children of mothers who worked in the electronic parts and components manufacturing industries during all periods (preconception, perinatal, postnatal) also had significantly increased ORs for childhood brain tumors. The odds ratio for childhood brain tumor among children with mothers employed during any of these periods in electronic and components manufacturing was 13.1 (95 % CI 1.38–125.5) [34].

Chemical Industry

Mothers working in the chemical industries before pregnancy had elevated odds of having children with CNS tumors (OR 1.9, 95 % CI 1.0–3.9) [37]. A case-control study in California and Washington State, USA, found evidence further strengthening this association. The authors reported that parents who worked in the chemical industry 5 years prior to their child's birth were at increased risk of having children with astroglial tumors (mothers' OR 3.3, 95 % CI 1.4–7.7). No trend was seen by duration of maternal employment [38].

Solvents

A population-based case-control study from three European centers (Milan, Italy; Paris, France; and Valencia, Spain), evaluating the role of parental occupational exposure to solvents and polycyclic aromatic hydrocarbons (PAHs) during

the 5-year period before birth, found that high levels of maternal exposure to solvents were associated with an increased risk of both astroglial tumors (OR 2.3, 95 % CI 0.9–5.8) and primitive neuroectodermal tumors (OR 3.2, 95 % CI 1.0–10.3) in their children [39].

Pesticides

Van Winjgaarden et al. assessed the risk of childhood brain cancer in relation to parental exposure to various classes of pesticides among 154 children diagnosed with astrocytoma and 158 children diagnosed with primitive neuroectodermal tumors (PNETs) in the United States and Canada between 1986 and 1989. The odds ratios for astrocytoma were elevated (but not statistically significant) for children with maternal exposures to insecticides, herbicides, and nonagricultural fungicides (OR = 1.3–1.6) but not for children with maternal exposures to agricultural fungicides (OR = 1.0) [40].

Motor Vehicle, Health Service, and Food Industries

Mothers with the following activities also had increased odds of having children with brain tumors: motor-vehicle-related work during pregnancy (OR 2.0, 95 % CI 1.0–4.0), health services work before pregnancy (OR 1.7, 95 % CI 1.1–2.4), and food industry during pregnancy (OR 2.0, 95 % CI 1.0–4.1) [37].

Electromagnetic Fields

Studies assessing maternal occupational exposure to electromagnetic fields have not suggested an increased risk of childhood brain tumors [20, 21].

Paternal Occupational Exposures

The role of paternal occupational exposures and childhood nervous system tumors has been extensively studied, with the majority of studies focusing on brain tumors. Multiple investigations have found a significant relationship between childhood nervous system tumors and paternal occupational exposure to electromagnetic fields, paints and pigments, solvents, motor-vehicle-related occupations, and pesticides [5]. Since the late 1990s, however, further studies have not supported these earlier findings.

Electromagnetic Fields

Paternal work in electrical assembly/installation/repair occupations, as electricians, construction electricians, electrical repair workers, workers in electronics manufacturing industries, or employment at electronic components manufacturing plant has been reported as risk factors for childhood nervous system tumors [5]. McKean-Coudin et al. found children of fathers employed as electrical workers 5 years prior to the birth of their child were at increased risk of developing brain tumors of any histologic type (OR = 2.3; 95 % CI 1.3–4.0) [38], but Hug et al. did not find any evidence of an association between paternal occupation exposure to EMF fields either above 0.2 μT or 1 μT [23].

Paints and Pigments

Paternal exposure to paints and/or inks as a risk factor for childhood nervous system cancers has been reported. The relative risks were statistically significant with some risks reported to be greater than 5. Studies have also found that brain cancer risk was elevated among children of fathers whose employment exposed them to certain aromatic amines that have been used in some dyes and pigments [5]. An increased risk of nervous system tumors was found among children of father employed as painters in the preconception period (OR 3.65, 95 % CI 1.71–7.8) [3].

Solvents

One of the earliest studies of paternal occupation and childhood cancer found a threefold increase in childhood deaths from nervous system cancers among children born to men whose occupations exposed them to hydrocarbons [30]. Fathers with preconception occupations that involved probable exposures to solvents also had increased risk of having children with nervous system tumors (OR 2.48, 95 % CI 1.29–4.76) [3]. While these findings have been supported by some studies, multiple other studies have not found evidence for this relationship [5]. This inconsistent pattern likely reflects limitations in exposure assessment with fathers potentially being exposed to numerous chemicals at different exposure levels [5].

Motor-Vehicle-Related Occupations

Fathers employed as mechanical engineers and technicians during the preconception time period have a higher risk of having children with nervous system tumors with an OR of 1.93, 95 % CI 1.04–3.57 [3]. Fathers working as motor-vehicle drivers in the preconception period had increased odds of other types of glial cancers (OR 1.3, 95 % CI 1–1.8). Paternal activity with petroleum in the preconception period also increased a child's risk for astroglial tumor, with an odds ratio of 3.4 (95 % CI 1.4–8.2) [37].

Population-based case-control studies carried out in seven countries as part of the SEARCH Program compared data for 1,218 cases of childhood brain tumors and 2,223 controls (1976–1994) looking at parental occupational exposure to polyaromatic hydrocarbons (PAHs), one component of diesel exhaust, during the 5-year period before birth. The study found that paternal preconception occupational exposure to PAH was associated with increased risks of all childhood brain tumors (OR 1.3, 95 % CI 1.1–1.6) and astroglial tumors (OR 1.4, 95 % CI 1.1–1.7) [41].

Previous studies, however, have not found an association with relative risks typically less than 1.0 [5].

Pesticides

An increased risk of childhood brain tumors has been found to be related to paternal agricultural work or residence on a farm; these studies have primarily focused on the time prior to conception or during pregnancy [42, 43]. Feychting et al. found an increased risk of nervous system tumors related to paternal occupational exposure in the preconception period to pesticides with an OR of 2.36 (95 % CI 1.27–4.39) [3]. Cordier et al. also found that a father working in agriculture in the preconception period had a 1.8-fold increased odds of his child having other types of glial cancers [37]. Elevated risks of astrocytoma have been reported among children with paternal exposure to all four classes of pesticides (insecticides, herbicides, agricultural fungicides, and nonagricultural fungicides) (OR 1.4–1.6). An increased risk of PNET was observed for only herbicides (OR 1.5) [40].

Neuroblastoma

Maternal Occupational Exposures

There are a limited number of epidemiologic studies characterizing the role of maternal occupational exposure and childhood neuroblastoma. The Children's Cancer Group and the Pediatric Oncology Group found an elevated odds ratios for neuroblastoma among children with mothers employed as farmers and farm workers (OR 2.2, 95 % CI 0.6–8.8), florists and garden store workers (OR 2.4, 95 % CI 0.6–9.9), hairdressers and barbers (OR 2.8, CI 1.2–6.3), electric power installers and power plant operators, and sailors, fishers, and railroad workers (with the latter five occupations listed without an odds ratio) [44].

A case-control study among residents of New York State between 1976 and 1987 found that the odds ratios for childhood neuroblastoma were significantly elevated for maternal occupation in the service and retail industries, respectively (OR 2.0, 95 % CI 1.0–4.1 and OR 2.0, 95 % CI 1.1–3.7). Odds ratios between maternal occupational exposures and childhood neuroblastoma were increased in exposures to acetone (OR 3.1, 95 % CI 1.7–5.6), insecticides (OR 2.3, 95 % CI 1.4–3.7), lead (OR 4.7, 95 % CI 1.3–18.2), and petroleum (OR 3.0, 95 % CI 1.5–6.1) [45]. A multicenter case-control study, however, did not find an association between maternal exposures to chemicals and childhood neuroblastoma [46].

A case-control study by Hug et al. found an elevated risk between maternal exposure levels of EMF above 0.2 μT and childhood neuroblastoma (OR 1.26, 95 % CI 0.66, 2.43) [23].

Paternal Occupational Exposures

While some studies have found an association between paternal occupational exposures to EMF and childhood risk for neuroblastoma, subsequent studies that focus on both intracranial brain tumors and neuroblastomas have reported mixed results [5, 23]. Of four studies limited to ELF-MF exposures with risk estimates given for different levels of exposure, none of the results found a significant association between paternal exposure and childhood cancers of the nervous system [23].

A large, population-based, case-control study of subjects diagnosed with childhood tumors in Great Britain over 30 years found a statistically significant relationship between paternal occupational exposure to leather with neuroblastoma (OR 5.00, 95 % CI 1.07–46.93), but this association became nonsignificant on correction for multiple testing [47]. McKinney et al. found that there were elevated risks among men working with leather at periconception (OR 4.02, 95 % CI 1.39–11.63) and diagnosis (OR 5.50, 95 % CI 1.10–27.38) for neuroblastoma. These men were employed as "shoe repairers, leather cutters and sewers, footwear lasters, makers and finishers, other leather making and repairing." This study was limited by small numbers of exposed participants [10].

Paternal exposures to hydrocarbons such as diesel fuel (OR 1.5; 95 % CI 0.8–2.6), lacquer thinner (OR 3.5, 95 % CI 1.6–7.8), and turpentine (OR 10.4; 95 % CI 2.4–44.8) were found to be associated with neuroblastoma, as were exposures to wood dust (OR 1.5, 95 % CI 0.8–2.8) and solders (OR 2.6, 95 % CI: 0.9–7.1) [46]. Odds ratios for childhood neuroblastoma were also elevated for paternal exposure to creosote (OR 2.1, 95 % CI 1.1–4.3), dioxin (OR 6.9, 95 % CI 1.3–68.4), lead (OR 2.4, 95 % CI 1.2–4.8), and petroleum (OR 1.8, 95 % CI 1.1–2.8) [45].

Urinary System Malignancies

Pediatric malignancies of the urinary tract are predominantly Wilms tumors. Of 181 pediatric urinary tract malignancies reviewed by the Danish Cancer Registry, 175 were Wilms tumor cases and the other six were "other and unspecified cancers" [48].

Maternal Occupational Exposures

An association between childhood Wilms tumor and maternal exposure to aromatic amines has previously been reported [5]. Additionally, an association between childhood renal cancers and maternal employment in education, health and welfare, health departments, and dentistry has also been found [5].

Maternal EMF exposure above 0.2 μT was associated with a slightly raised nonsignificant risk with Wilms tumors (OR 1.53, 95 % CI 0.88–2.66)[23]. A hospital-based, multicenter, case-control investigation from Brazil found an association between maternal exposure to farm work involving frequent use of pesticides for 6 months before the pregnancy with elevated risks for childhood Wilms tumor (OR 128.6, 95 % CI 6.4–2,569) [49].

Paternal Occupational Exposures

Significant associations have been identified between renal cancers and paternal employment in general manufacturing, the wood and furniture industry, manufacturing of iron and metal structures, and electrical contracting firms. Studies have consistently found elevated risk from paternal hydrocarbon exposure, some reaching statistical significance [5].

McKinney et al. reported that there were raised risks for Wilms tumor in children of men working with leather at periconception (OR 4.02, 95 % CI 1.39–11.63) and diagnosis (OR 5.50, 95 % CI 1.10–27.38). Among the six case fathers classified as working with leather at periconception, three had children diagnosed with neuroblastoma, one with Wilms tumor, one with retinoblastoma, and one with rhabdomyosarcoma [10].

A hospital-based, multicenter, case-control study from Brazil reported an increased odds ratio for Wilms tumor among children with fathers employed in farm work involving frequent use of pesticides 6 months prior to pregnancy or during pregnancy (OR = 3.24, 95 % CI 1.2–9.0), with risk elevations (ORs >4) restricted to Wilms tumor diagnosed after 2 years of age [46].

Fear et al. examined the relationship between paternal occupational exposures and Wilms tumor using birth registration data for cases from the National Registry of Childhood Tumours (NRCT) based in Great Britain and found ORs approaching unity with no statistically significant associations reported [50]. The lack of detailed paternal exposure information may have contributed to these null results.

Bone Tumors

Osteosarcoma and Ewing's sarcoma are the two predominant forms of childhood bone cancer. Of 146 malignant bone tumor cases included in the Danish Cancer Registry, 66 were osteosarcoma, 65 Ewing's sarcoma, 4 chondrosarcoma, and 11 "other and unspecified" [48].

Maternal Occupational Exposures

Epidemiologic studies have implicated maternal exposure to farming as a risk factor for Ewing's sarcoma (ES) [51]. An analysis of three case-control studies found an elevated pooled odds ratio for Ewing's sarcoma among children with mothers who farmed during the gestation period (OR 3.9, 95 % CI 1.6–9.9) and in the postnatal period (OR 2.1, 95 % CI 1–4.3). In addition, there was a 3.5-fold increased risk for children with both parents who farmed and a twofold higher risk for those with at least one parent who farmed. The studies were limited by the small number of exposed participants as well as the rarity of the malignancy [52].

Moore et al., using data from the Intergroup Ewing's Sarcoma Study from 64 institutions throughout the United States, found that the risk of ES was increased with probable maternal or paternal exposure to wood dusts during their usual occupation post pregnancy (OR 3.2, 95 % CI 1.1–9.2). The authors hypothesized that earlier reports of associations of ES with parental farm employment may have been capturing risks associated with organic dusts encountered when working on a farm, rather than agricultural exposures or other farming-related exposures [51].

A case-control study from the Ontario Cancer Registry, with data collected from parents through the use of a mailed self-administered questionnaire, found the risk of Ewing's sarcoma was significantly high among children with mothers employed in teaching (OR 3.1, 95 % CI 1.1–8.7) or farming (OR 7.8, 95 % CI 1.9–31.7). Osteosarcoma risk was increased (but not significantly) for mothers in managerial and administrative work (OR 2.3, 95 % CI 0.6–8.1), and product fabricating, assembling, and repairing (OR 2.0, 95 % CI 0.6–7.2) [53].

Paternal Occupational Exposures

Paternal occupation on a farm has been found to be associated with ES [51]. Holly et al. reported an elevated risk for childhood ES among children born to fathers with agricultural employment from 6 months before conception until the time of diagnosis and a significantly elevated risk ratio in children whose fathers were exposed to herbicides, pesticides, or fertilizers during any time of their occupations [54]. Children of fathers employed in farming occupations during the time of pregnancy had an approximately twofold risk of ES compared to children whose fathers had other occupations [55]. In a pooled analysis of three case-control studies, the pooled odds ratio for Ewing's sarcoma was elevated for paternal employment in farming during the paternal periconception and postnatal exposure periods with odds ratios of 2.3 (95 % CI = 1.3–4.1) and 1.7 (1–2.7), respectively [52].

Results from the Ontario Cancer Registry found the risk of Ewing's sarcoma was significantly elevated among children with fathers in social sciences (OR 6.2, 95 % CI 1.6–24.5) [53]. Osteosarcoma risk was also reported to be increased among children with fathers who farmed (OR 2.1, 95 % CI 0.8–5.7) [53].

Germ Cell Tumors

Testicular cancer is the most common solid malignancy affecting males between the ages of 15 and 35, accounting for about 1 % of all cancers in men [56]. Epidemiologic studies suggest that testicular cancer incidence has been increasing since the early 1900s. Data from the Surveillance Epidemiology and End Results (SEER) database of the US National Cancer Institute found that the overall incidence of testicular germ cell tumors among American men rose 44 % (from 3.35 to 4.84 per 100,000 men between 1973–1978 and 1994–1998). The incidence of seminomas increased by 62 %, while the incidence of nonseminomatous germ cell tumors (GCTs) increased by 24 % [57].

The factors resulting in increased testicular cancer incidence are not fully understood. Known risk factors for testicular malignancies are cryptorchidism, a personal or family history of testicular cancer, and infertility or subfertility [58–60]. Multiple hypotheses for the recently observed increased incidence have included in utero exposure to diethylstilbestrol (DES), early exposure to viruses or other environmental agents, and testicular trauma [61, 62]. IARC has concluded that there is "limited evidence" for an association between DES exposure in utero and testicular cancer. These factors, however, do not completely account for the rise in testicular cancer.

Studies have examined the role of parental occupation as a potential explanation for the increased rates of testicular cancer. A case-control study to assess the role of parental occupation, especially during the 12-month period before birth, with testicular cancer in young men found that among all histologic types of testicular cancer combined, no significant associations were identified for specific occupations nor for the broad occupational categories of professional, other white-collar, or blue-collar workers. For cases with seminomas, however, excess risks were found for parents employed in the following occupations: mothers in health-related occupations (OR 4.6, 95 % CI 1.1–19.1) and fathers working in automobile service stations (OR 4.0, 95 % CI 0.6–24.5), manufacturing industries (OR 2.2, 95 % CI 1.0–4.2), and aircraft production and maintenance (OR 5.3, 95 % CI 0.7–24.1) [63]. In another study, significantly elevated polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), and *cis*- and *trans*-nonachlor levels were found in mothers of children diagnosed with testicular cancer relative to those found in controls [64].

Parental exposure to endocrine disruptors as a risk factor for testicular cancer in their sons has also been studied. An endocrine disruptor is an exogenous substance that causes adverse health effects secondary to alterations in endocrine function. Maternal urinary levels of some phthalate metabolites during pregnancy were found to be associated with crude measures of reproductive tract development and testes descent, which are risk factors for the development of testicular cancer [65, 66].

Congenital cryptorchidism has been found to be associated with low concentrations of persistent organochlorine pesticides in breast milk [67]. In addition, mothers who were employed in greenhouses and who were exposed to above average levels of pesticides had sons with a threefold increased rate of cryptorchidism at 3 months of age in comparison to the control group. Additionally, the boys had smaller genitalia and lower serum concentrations of testosterone and inhibin B [68]. Another group of chemicals that have been implicated in a male's increased risk of cryptorchidism is polybrominated diphenyl ethers (PBDEs), used as flame retardants. The concentration of certain PBDE congeners was found to be elevated in breast milk from mothers who gave birth to boys with cryptorchidism [69, 70].

Parental occupational exposures and childhood risk for other types of germ cell tumors (germinoma, dysgerminoma, seminoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, immature teratoma, and mixed germ cell tumor) have also been studied. The results of the Children's Oncology Group, a case-control study from 1993 to 2001, found that the odds ratios for childhood germ cell tumors associated with maternal occupational exposure to pesticides before pregnancy, during pregnancy, and after the birth of the index child were 1.0, 95 % CI 0.8–1.4, 1.1, 95 % CI 0.7–1.6, and 1.3, 95 % CI 0.9–1.8, respectively. Paternal occupational exposures before pregnancy, during pregnancy, and after the birth of the index child were not related to risk for childhood germ cell tumors. Subgroup analyses showed a positive association between maternal exposure to herbicides during the postnatal period and risk of germ cell tumors in girls (OR 2.3, 95 % CI 1.0–5.2), while an inverse association between paternal exposure to pesticides during the index pregnancy and germ cell tumors in boys (OR 0.2, 95 % CI 0.1–1.0) was reported [71].

Conclusions on Parental Exposures and Childhood Cancer

Epidemiologic studies have found that certain parental occupational exposures potentially increase the risk for childhood cancers. The evidence for associations between parental occupational exposures and pediatric cancer is different between maternal and paternal exposures, as well as for different pediatric malignancies, and is dependent on the timing of exposure in relation to conception, pregnancy, and early childhood development.

Childhood Leukemia

For childhood leukemia, maternal occupational exposures to pesticides and metals and employment in personal service as well as textiles industries have been identified as risk factors [5]. Studies of the timing of exposures suggest that exposures

in both the prenatal and periconception periods are important, but further studies, especially better assessments of exposures, are needed to support these findings and to characterize the levels of exposure involved and the mechanisms of action that link maternal occupational exposures to childhood cancers [5, 6, 9–12]. Because of the large percentage of women working in the textile industry worldwide, Colt et al. suggest that further studies are especially needed in this occupational sector [5].

Studies of childhood leukemia in relation to paternal occupational exposures find significant links between childhood leukemia and paternal exposures to solvents, paints and pigments, motor vehicles, ionizing radiation, woodwork, and extremely low-frequency magnetic fields (ELF-MFs). Significant associations have been noted in relation to paternal exposures in the preconception, periconception, pregnancy, and perinatal periods [3, 10, 12, 27–29, 34]. The single strongest association reported in this literature is between paternal occupational exposure to solvents and risk for pediatric leukemia [5]. Solvent exposure may explain the consistent association observed between childhood leukemia and paternal employment in the painting and printing trades [5].

Childhood Nervous System Tumors

For childhood brain tumors, epidemiologic studies have found that children of mothers employed in textile/garment, electronic, chemical, motor vehicle, health services, and food industries are at increased risk [34, 37]. For mothers working in the textile and the electronics industries, significant associations were reported during the preconception, perinatal, and postnatal periods. For mothers working in the chemical industries, occupational exposure 5 years prior to pregnancy was significant [34, 37, 38].

Studies of associations between pediatric nervous system tumors and paternal occupational exposures to electromagnetic fields, hydrocarbons, and motor-vehicle-related occupations produce mixed results. The most consistently positive associations are reported in relation to paternal occupational exposures to paints, pigments, and pesticides. The developmental periods identified as most significant for associations are 5 years prior to birth of the child and the preconception period [3, 5, 30, 37].

Limitations in the Data

Inadequate assessment of exposure with poor specification of chemical exposures and insufficient documentation of levels of exposure is a pervasive limitation in virtually all of the studies that attempt to link parental occupational exposures with childhood cancer. The exposure classification used in most studies is relatively crude and often focuses solely on duration of employment without including any information regarding the frequency or intensity of exposure, or to other variables such as the use of personal protective equipment. Some studies use the parent's stated occupation as a surrogate indicator of exposure to particular chemicals – for example, work in agriculture as a surrogate for exposure to pesticides [72]. Such relatively imprecise approaches to exposure assessment tend to bias findings towards the null and reduce the likelihood of detecting biologically significant associations even if they are present.

Shortcomings in exposure assessment are further compounded by the fact that most of the published studies are case-control investigations, where recall and reporting bias in parental exposure assessments between cases and the controls may occur. Confounders in the relationship between parental occupational exposure and childhood cancers have not been well-defined, and the use of different controls in studies (population-based versus hospital-based) can also lead to inconsistent results [72]. Most studies also do not account for the child's own exposure to the material in question in the home and other settings as a risk factor for cancer [6].

A second limitation is that some studies obtain information from secondary sources (e.g., birth records). Small sample size is a third limitation in many of these studies.

Future Prospects

The best data on associations between parental occupational exposures and childhood cancer will be obtained in the years ahead through large, prospective birth cohort studies that measure parental exposures before and during pregnancy in real time as those exposures are actually occurring. The prospective study design permits relatively unbiased assessment of exposures months or years before the onset of disease. Currently, large epidemiologic studies are underway to understand exposures during childhood and risk for disease. The US National Children's Study (NCS) is a large prospective epidemiologic study jointly developed by the National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, the US Environmental Protection Agency (EPA), and the Centers for Diseases Control and Prevention to understand the impact of environmental, behavioral, and socioeconomic factors on child and adult health. This prospective epidemiologic birth cohort is currently enrolling women in pregnancy. The study will measure environmental exposures during pregnancy and then follow the children longitudinally [73]. Similar studies are underway in Japan, China, Denmark, and the United Kingdom.

The formation of the International Childhood Cancer Cohort Consortium (IC4) under the auspices of IARC and the World Health Organization (WHO) is an especially promising development. IC4 is a global multicenter epidemiologic project that will gather data on associations between prenatal exposures and childhood cancer from all of the many prospective studies now proceeding around the world and to pool the data as a strategy for substantially increasing statistical power [74, 75].

Effects of Childhood Exposure to Occupational Carcinogens

Introduction

This section will discuss the cancer risks that are the consequence of children's occupational exposures. The first description of occupational cancer among working children was published in 1775 by the English surgeon, Sir Percivall Pott, who described an epidemic of scrotal cancer among adolescent chimney sweeps in London and identified soot as the causative agent. Since that time, child labor in dangerous occupations has declined in developed countries, but still remains a major problem in developing countries [76].

The International Labour Office, a United Nations (UN) agency responsible for drawing up and overseeing international labor standards, published a report in 2010 showing that the global number of child laborers was 215 million, a 3 % decrease from 2004 to 2008. Child laborers are defined as "either under the minimum age for work or above that age and engaged in work that poses a threat to their health, safety or morals, or are subject to conditions of forced labour." The number of boy laborers increased by eight million or 7 %, and the number of child laborers between the ages of 15 and 17 increased by 20 %, from 52 to 62 million from the previous 4 years [77]. In the developing world, child employment is concentrated in agriculture, service, small enterprises, family trades, and the informal sectors [78].

The United States Department of Labor, using the results of the National Longitudinal Survey of Youth 1997 (NLSY97), a nationally representative sample of 9,022 young men and women who were between the ages of 12 and 17 at the time of the first interview, found that 57 % of interviewed youths reported having held some type of job while they were aged 14. Eighteen percent of 14-year-olds worked either during the school year only or during both school year and summer weeks. The large majority – 66 % at age 14 and 76 % at age 15 – was employed in the retail or services industries. Many of those employed in this industry worked in eating and drinking establishments, entertainment and recreation services, and industries and construction. Landscape and horticultural services, livestock production, and automotive repair were more common in male workers [79].

Data from the Current Population Survey (CPS), a monthly labor force survey of 50,000 households with information on persons aged 15 or older, found that 2.9 million youths aged 15–17 worked during school months, and 4.0 million worked during the summer months from 1996 to 1998. Nine percent of 15-year-olds were employed in an average month, compared with 26 % of 16-year-olds and 39 % of 17-year-olds. These young workers worked more in the summer, during which employment rates increased to 18, 36, and 48 % at each age, respectively. The majority of youths aged 15–17 who were employed during the school months of the 1996–1998 worked in retail trade. Among males aged 15–17 years, 17 % worked either in agriculture, or goods-producing industries such as mining, construction, and manufacturing [80].

Health Effects

Exposure to occupational carcinogens during childhood and adolescence can have more severe effects than similar exposures in adult life, because children are biologically more vulnerable than adults as a consequence of their rapid growth and development. In comparison to adults, children's metabolic rates are higher relative to size, they breathe at a faster rate, and they consume more food and water per pound of body weight. Also children have a longer anticipated future life span than most adults and therefore have more years in which to develop cancers of long latency that may be initiated by environmental and occupational exposures in early life [81, 82].

There is limited information on the incidence and prevalence of work-related diseases and occupational cancer in children [78]. The greater risk is likely for adult cancers initiated by exposures in childhood or adolescence.

Exposures

Children can be exposed to occupational carcinogens through cleaning with solvents, using wood-impregnated products, working on small painting jobs or with adhesives, directly applying pesticide or handling flags to guide pesticide spray airplanes, and mixing, loading, and applying pesticides. Protective equipment is rarely used. In addition, in developing countries, children can also be involved in textile manufacture, carpet weaving, leather production, wood processing, ceramics, glass, brickmaking, slate-making, painting, metalwork, toy making (with exposure to plastics, paints, and dyes), precious stone and gem production, auto repair, and petrol distribution [83].

Asbestos

Asbestos, a known human carcinogen, has been established by IARC and national regulatory bodies in countries around the world as a risk factor for lung, laryngeal, and ovarian

cancers, as well as for mesothelioma and probably for colorectal cancer [84]. It is estimated that about 125 million people worldwide are exposed to asbestos in their work environments [85]. Children who are exposed to asbestos either directly through their labor or indirectly through parental take-home exposures are at increased risk of developing lung cancer, malignant mesothelioma, and other asbestos-related diseases decades later. Any exposure to asbestos involves some risk of malignancy, with higher and more chronic levels resulting in greater risk [86].

Agriculture

Children employed in agriculture are exposed to both pesticides and sunlight. A child's own exposure to pesticides is thought to be linked to childhood leukemia [8, 42]. In addition, persistent chemicals, including the organochlorine pesticides dichlorodiphenyldichloroethylene (DDE) and chlordane, have been linked to the risk of developing testicular cancer [65, 87].

Exposure to solar ultraviolet (UV) radiation from working on farms can cause sunburn, nevi (moles), freckling, and skin cancer, including malignant melanoma. Some of these cancers appear in childhood and adolescence, and the age of diagnosis of melanoma is becoming progressively younger, but the great majority emerges in adult life. A meta-analysis of 57 studies found a stronger correlation between melanoma and a history of sunburns during childhood compared to sunburns during adulthood. A meta-analysis of 46 epidemiologic studies showed a dose–response relationship between melanoma and the numbers of common or atypical nevi on the body; these nevi are caused by childhood sun exposure, and approximately 20–30 % of melanomas develop in nevi [25].

Conclusions on Child Labor and Pediatric Cancer

The short-term and long-term health effects of children's occupational exposures have not been well-studied. The adult literature on the health effects of occupational exposure raises serious concern about the health implications of occupational exposures to carcinogens during childhood and adolescence. Because child labor, especially in developing countries, is inextricably tied to pervasive issues of poverty and income inequality, governments everywhere need to consider this issue in a context of social justice and human rights.

An important action that governments around the world can take to protect children against occupational exposures to carcinogens is to enact and enforce legislation banning the most dangerous forms of child labor. Governmental support for efforts by the International Labour Organization is another important step to reducing child labor. In the United States, actions to ensure safe work practices among youth workers are essential as part of a greater framework to minimize toxic exposures among children and workers.

Studies evaluating the impact of this labor on the child's short- and long-term health effects can further support sound precautionary policies.

References

1. Taub JW, Ge Y. The prenatal origin of childhood acute lymphoblastic leukemia. Leuk Lymphoma. 2004;45:19–25.
2. Shu XO, Stewart P, Wen WQ, et al. Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. Cancer Epidemiol Biomarkers Prev. 1999;8:783–91.
3. Feychting M, Plato N, Nise G, et al. Paternal occupational exposures and childhood cancer. Environ Health Perspect. 2001;109:193–6.
4. Buffler PA, Kwan ML, Reynolds P, et al. Environmental and genetic risk factors for childhood leukemia: appraising the evidence. Cancer Invest. 2005;23:60–75.
5. Colt JS, Blair A. Parental occupational exposures and risk of childhood cancer. Environ Health Perspect. 1998;106:909–25.
6. Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. Environ Health Perspect. 2009;117:1505–13.
7. Infante-Rivard C, Krajinovic M, Labuda D, et al. Parental smoking, CYP1A1 genetic polymorphisms and childhood leukemia (Quebec, Canada). Cancer Causes Control. 2000;11:547–53.
8. Infante-Rivard C, Labuda D, Krajinovic M, et al. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology. 1999;10:481–7.
9. Brown RC. Review: windows of exposure to pesticides for increased risk of childhood leukemia. Toxicol Environ Chem. 2006;88:423–33.
10. McKinney PA, Fear NT, Stockton D. Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. Occup Environ Med. 2003;60:901–9.
11. Shu XO, Gao YT, Brinton LA, et al. A population-based case-control study of childhood leukemia in Shanghai. Cancer. 1988;62:635–44.
12. Buckley JD, Robison LL, Swotinsky R, et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer Res. 1989;49:4030–7.
13. Linet MS, Cartwright RA. The leukemias. In: Schottenfeld D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 1996. p. 841–92.
14. van Steensel-Moll HA, Valkenburg HA, van Zanen GE. Childhood leukemia and parental occupation. A register-based case-control study. Am J Epidemiol. 1985;121:216–24.
15. Schüz J, Kaletsch U, Meinert R, et al. Risk of childhood leukemia and parental self-reported occupational exposure to chemicals, dusts, and fumes: results from pooled analyses of German population-based case-control studies. Cancer Epidemiol Biomarkers Prev. 2000;9:835–8.
16. Sung TI, Wang JD, Chen PC. Increased risk of cancer in the offspring of female electronics workers. Reprod Toxicol. 2008;25:115–9.
17. Infante-Rivard C, Siemiatycki J, Lakhani R, et al. Maternal exposure to occupational solvents and childhood leukemia. Environ Health Perspect. 2005;113:787–92.

18. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, vol. 98 and 100. Lyon: IARC; 2010 and 2012.
19. Infante-Rivard C, Deadman JE. Maternal occupational exposure to extremely low magnetic fields during pregnancy and childhood leukemia. Epidemiology. 2003;14:437–41.
20. Feychting M, Floderus B, Ahlbom A. Parental occupational exposure to magnetic fields and childhood cancer (Sweden). Cancer Causes Control. 2000;11:151–6.
21. Sorahan T, Hamilton L, Gardiner K, et al. Maternal occupational exposure to electromagnetic fields before, during, and after pregnancy in relation to risks of childhood cancers: findings from the Oxford Survey of Childhood Cancers, 1953–1981 deaths. Am J Ind Med. 1999;35:348–57.
22. Bunch KJ, Muirhead CR, Draper GJ, et al. Cancer in the offspring of female radiation workers: a record linkage study. Br J Cancer. 2009;100:213–8.
23. Hug K, Grize L, Seidler A, et al. Parental occupational exposure to extremely low frequency magnetic fields and childhood cancer: a German case-control study. Am J Epidemiol. 2010;17:27–35.
24. Giles D, Hewitt D, Stewart A, et al. Malignant disease in childhood and diagnostic irradiation in utero. Lancet. 1956;271:447.
25. Wigle DT, Arbuckle TE, Walker M, et al. Environmental hazards: evidence for effects on child health. J Toxicol Environ Health B Crit Rev. 2007;10:3–39.
26. Meinert R, Kaletsch U, Kaatsch P, et al. Associations between childhood cancer and ionizing radiation: results of a population-based case-control study in Germany. Cancer Epidemiol Biomarkers Prev. 1999;8:793–9.
27. Lowengart RA, Peters JM, Ciconi C, et al. Childhood leukemia and parents' occupational and home exposures. J Natl Cancer Inst. 1987;79:39–46.
28. McKinney PA, Alexander FE, Cartwright RA, et al. Parental occupations of children with leukemia in west Cumbria, north Humberside, and Gateshead. Br Med J. 1991;302:681–7.
29. Magnani C, Pastore G, Luzzato L, et al. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case control study. Tumori. 1990;76:413–9.
30. Fabia J, Thuy TD. Occupation of father at time of birth of children dying of malignant diseases. Br J Prev Soc Med. 1974;28:98–100.
31. Olshan AF, van Wijngaarden E. Paternal occupation and childhood cancer. Adv Exp Med Biol. 2003;518:147–61.
32. Savitz DA, Chen J. Parental occupation and childhood cancer: review of epidemiologic studies. Environ Health Perspect. 1990; 88:325–37.
33. Gardner MJ, Snee MP, Hall AJ, et al. Results of case-control study of leukemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. Br Med J. 1990;300:423–9.
34. Ali R, Yu C, Wu M, et al. A case-control study of parental occupation, leukemia and brain tumors in an industrial city in Taiwan. J Occup Environ Med. 2004;46:985–92.
35. Pearce MS, Hammal DM, Dorak MT, et al. Paternal occupational exposure to electro-magnetic fields as a risk factor for cancer in children and young adults: a case-control study from the North of England. Pediatr Blood Cancer. 2007;49:280–6.
36. Flower KB, Hoppin JA, Lynch CF, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. Environ Health Perspect. 2004;112:631–5.
37. Cordier S, Mandereau L, Preston-Martin S, et al. Parental occupations and childhood brain tumors: results of an international case-control study. Cancer Causes Control. 2001;12:865–74.
38. McKean-Cowdin R, Preston-Martin S, Pogoda JM, et al. Parental occupation and childhood brain tumors: astroglial and primitive neuroectodermal tumors. J Occup Environ Med. 1998;40: 332–40.
39. Cordier S, Lefeuvre B, Filippini G, et al. Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). Cancer Causes Control. 1997;8:688–97.
40. van Wijngaarden E, Stewart PA, Olshan AF, et al. Parental occupational exposure to pesticides and childhood brain cancer. Am J Epidemiol. 2003;157:989–97.
41. Cordier S, Monfort C, Filippini G, et al. Parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors: the SEARCH International Childhood Brain Tumor Study. Am J Epidemiol. 2004;159:1109–16.
42. Zahm SH, Ward MH. Pesticides and childhood cancer. Environ Health Perspect. 1998;106 Suppl 3:893–908.
43. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. Environ Health Perspect. 1997;105:1068–77.
44. Olshan AF, De Roos AJ, Teschke K, et al. Neuroblastoma and parental occupation. Cancer Causes Control. 1999;10:539–49.
45. Kerr MA, Nasca PC, Mundt KA, et al. Parental occupational exposures and risk of neuroblastoma: a case-control study (United States). Cancer Causes Control. 2000;11:635–43.
46. De Roos AJ, Olshan AF, Teschke K, et al. Parental occupational exposures to chemicals and incidence of neuroblastoma in offspring. Am J Epidemiol. 2001;154:106–14.
47. MacCarthy A, Bunch KJ, Fear NT, et al. Paternal Occupation and neuroblastoma: a case control study based on cancer registry data for Great Britain 1962–1999. Br J Cancer. 2010;102:615–9.
48. de Nully BP, Hertz H, Olsen JH, Yssing M, Scheibel E, Jensen OM. Incidence of childhood cancer in Denmark 1943–1984. Int J Epidemiol. 1989;18(3):546–55.
49. Sharpe CR, Franco EL, de Camargo B, et al. Parental exposures to pesticides and risk of Wilms' tumor in Brazil. Am J Epidemiol. 1995;141:210–7.
50. Fear NT, Vincent TJ, King JC, et al. Wilms tumour and paternal occupation: an analysis of data from the National Registry of Childhood Tumours. Pediatr Blood Cancer. 2009;53:28–32.
51. Moore LE, Gold L, Stewart PA, et al. Parental occupational exposures and Ewing's sarcoma. Int J Cancer. 2005;114:472–8.
52. Valery PC, Williams G, Sleigh AC, et al. Parental occupation and Ewing's sarcoma: pooled and metaanalysis. Int J Cancer. 2005; 115:799–806.
53. Hum L, Kreiger N, Finkelstein MM. The relationship between parental occupation and bone cancer risk in offspring. Int J Epidemiol. 1998;27:766–71.
54. Holly EA, Aston DA, Ahn DK, et al. Ewing's bone sarcoma, paternal occupational exposure, and other factors. Am J Epidemiol. 1992; 135:122–9.
55. Winn DM, Li FP, Robison LL, et al. A case-control study of the etiology of Ewing's sarcoma. Cancer Epidemiol Biomarkers Prev. 1992;1:525–32.
56. Jemal A, Siegel R, Ward E, et al. Cancer statistics. CA Cancer J Clin. 2008;58:71.
57. McGlynn KA, Devesa SS, Sigurdson AJ, et al. Trends in the incidence of testicular germ cell tumors in the United States. Cancer. 2003;97:63.
58. Richiardi L, Akre O, Montgomery SM, et al. Fecundity and twinning rates as measures of fertility before diagnosis of germ-cell testicular cancer. J Natl Cancer Inst. 2004;96:145.
59. Raman JD, Nobert CF, Goldstein M. Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. J Urol. 2005;174:1819.
60. Walsh TJ, Croughan MS, Schembri M, et al. Increased risk of testicular germ cell cancer among infertile men. Arch Intern Med. 2009;169:351.
61. Zheng T, Holford TR, Ma Z, et al. Continuing increase in incidence of germ-cell testis cancer in young adults: experience from Connecticut, USA, 1935–1992. Int J Cancer. 1996;65:723.

62. Ekbom A, Richiardi L, Akre O, et al. Age at immigration and duration of stay in relation to risk for testicular cancer among Finnish immigrants in Sweden. J Natl Cancer Inst. 2003;95:1238.
63. Kardaun JW, Hayes RB, Pottern LM, et al. Testicular cancer in young men and parental occupational exposure. Am J Ind Med. 1991;20:219–27.
64. Hardell L, van Bavel B, Lindstrom G, et al. Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. Environ Health Perspect. 2003;111:930–4.
65. Swan SH, Main KM, Liu F, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect. 2005;113:1056–61.
66. Swan SH. Prenatal phthalate exposure and anogenital distance in male infants. Environ Health Perspect. 2006;114:A88–9.
67. Damgaard IN, Skakkebæk NE, Toppari J, et al. Persistent pesticides in human breast milk and cryptorchidism. Environ Health Perspect. 2006;114:1133–8.
68. Andersen HR, Schmidt IM, Grandjean P, et al. Impaired reproductive development in sons of women occupationally exposed to pesticides during pregnancy. Environ Health Perspect. 2008;116:566–72.
69. Main KM, Kiviranta H, Virtanen H, et al. Flame retardants in placenta and breast milk and cryptorchidism in newborn boys. Environ Health Perspect. 2007;115:1519–26.
70. Main KM, Skakkebaek NE, Virtanen HE, et al. Genital anomalies in boys and the environment. Best Pract Res Clin Endocrinol Metab. 2010;24:279–89.
71. Chen Z, Stewart PA, Davies S, et al. Parental occupational exposure to pesticides and childhood germ-cell tumors. Am J Epidemiol. 2005;162:858–67.
72. Perez-Saldivar ML, Ortega-Alvarez MC, Fajardo-Gutierrez A, et al. Father's occupational exposure to carcinogenic agents and childhood acute leukemia: a new method to assess exposure (a case-control study). BMC Cancer. 2008;8:1–11.
73. Landrigan PJ, Trasande L, Thorpe LE, et al. The National Children's Study: a 21-year prospective study of 100,000 American children. Pediatrics. 2006;118:2173–86.
74. Slimani N, Kaaks R, Ferrari P, et al. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. Public Health Nutr. 2002;5:1125–45.
75. Brown RC, Dwyer T, Kasten C, et al. Cohort profile: the International Childhood Cancer Cohort Consortium (I4C). Int J Epidemiol. 2007;36:724–30.
76. Loewenson R, Forastieri V, Matos E. Special exposure circumstances. In: Pearce N, Matos E, Vainio H, Boffetta P, Kogevinas M, editors. Occupational cancer in developing countries. Lyon: International Agency for Research on Cancer (WHO) Institute of Occupational Health, Finland International Labour Office. No 129; 1994. p. 97–108.
77. Accelerating action against child labour. Global Report under the follow-up to the ILO declaration on fundamental principles and rights at work 2010. www.ilo.org/declaration. Accessed 5 May 2010.
78. Loewenson R, Forastieri V, Matos E. Special exposure circumstances. In: Pearce N, Matos E, Vainio H, Boffetta P, Kogevinas M, editors. Occupational cancer in developing countries. Lyon: International Agency for Research on Cancer (WHO) Institute of Occupational Health, Finland International Labour Office. No 129; 1994. p. 103.
79. A detailed look at employment of youths aged 12 to 15. United States Department of Labor. http://www.dol.gov/dol/topic/youthlabor/childlaborstatistics.htm. Accessed 5 May 2011.
80. Trends in youth employment: data from the current population survey. United States: Department of Labor. http://www.dol.gov/dol/topic/youthlabor/childlaborstatistics.htm. Accessed 5 May 2011.
81. Developmental toxicity: special considerations based on age and developmental stage. In: Etzel, RA, editor. Pediatric environmental health. 2nd ed. Elk Grove Village: American Academy of Pediatrics; 2003. p. 9–23.
82. Landrigan PJ, Goldman LR. Protecting children from pesticides and other toxic chemicals. J Expo Sci Environ Epidemiol. 2011;21:119–20.
83. Loewenson R, Forastieri V, Matos E. Special exposure circumstances. In: Pearce N, Matos E, Vainio H, Boffetta P, Kogevinas M, editors. Occupational cancer in developing countries. Lyon: International Agency for Research on Cancer (WHO) Institute of Occupational Health, Finland International Labour Office. No 129; 1994. p. 106–7.
84. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, vol. 100C. Lyon: IARC; 2010 and 2012.
85. Ramazzini C. Asbestos is still with us: repeat call for a universal ban. Odontology. 2010;98:97–101.
86. Asbestos. In: Etzel RA, editor. Pediatric environmental health. 2nd ed. Elk Grove Village: American Academy of Pediatrics; 2003. p. 99–111.
87. McGlynn KA, Quraishi SM, Graubard BI, et al. Persistent organochlorine pesticides and risk of testicular germ cell tumors. J Natl Cancer Inst. 2008;100:663–71.

Strategies for Primary Prevention of Occupational Cancer

31

Per Gustavsson

Keywords
Occupational cancer • Primary prevention • Risk identification • Risk quantification • Risk elimination

Introduction and Historical Perspective

Primary prevention of cancer refers to the prevention of new cases of cancer, whereas secondary prevention is aimed at reducing the negative health effects of the disease by early detection or treatment. There are three basic steps in the process of cancer prevention: risk identification, risk quantification, and risk reduction. These are discussed in detail below, after an introduction presenting the burden of occupational cancer and a review of the process in the identification and prevention of some well-established occupational carcinogens.

Cancer is a major cause of death and a disease of large public health impact. Each year over 12 million cancers are diagnosed in the world, and 7.6 millions of deaths are due to cancer [11]. Cancer is a disease often causing substantial negative impact on health and well-being. Cancer is generally hard to cure even if there have been great improvements in cancer treatment. Primary prevention is of high priority to decrease the cancer burden worldwide [1].

Environmental factors play a large role in cancer development, the most notable example being tobacco smoking. Worldwide mortality from cancer at all sites has been estimated to be reduced by 21 % if tobacco smoking was eliminated, this proportion being substantially higher for cancer known to be induced by smoking, e.g., lung cancer showing a population attributable fraction of 70 % [5]. There have been several attempts to estimate the proportion of deaths or incident cancer cases that could be attributed to occupational exposures. The most widely cited figure is 4 % for US cancer deaths estimated by Doll and Peto [8]. This figure is probably an underestimation, and more recent estimations have arrived at higher proportions (see Chap. 20 in this book). Rushton et al. [40] estimated that 5.3 % of all cancer deaths in the UK were attributable to occupational exposures. This can be considered as a conservative estimate only taking established and probable carcinogens into account. A study from Finland, using a wider definition of occupational carcinogens, estimated that 8 % of cancer deaths in Finland were attributable to occupational exposures [35].

Although the proportion of all cancers attributed to occupational exposures is not large on a population level, the proportion preventable is much higher among those in the population actually exposed to occupational carcinogens, and the proportion is also much higher for cancer sites known to be induced by occupational carcinogens. Unlike lifestyle-associated cancers, occupational cancer is in principle fully avoidable through legislation leading to exposure-reducing measures [29].

The leading occupational carcinogen in the USA, the UK, and Finland has been asbestos. In the study from the UK, the following substances/exposures were identified as the most important occupational carcinogens, in declining order: shift work, exposure to mineral oils, solar radiation, silica, diesel engine exhaust, PAHs from coal tar, pitches, etc. [40]. The cancer site giving rise to the largest number of occupationally induced cases in the UK was cancer of the lung, followed by nonmelanoma skin cancer, breast cancer, and mesothelioma [40].

Much of the research on occupational cancer has been focused on men despite women since long have entered the labor market. An association between shift work that disrupts circadian rhythm and female breast cancer was identified

P. Gustavsson, MD, PhD
Unit of Occupational Medicine,
Institute of Environmental Medicine,
Karolinska Institutet, Stockholm 17176, Sweden
e-mail: per.gustavsson@ki.se

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_31, © Springer-Verlag London 2014

relatively recently and has been classified as group 2a by the IARC [22].

There are a number of obstacles on the road, from the identification of a cancer hazard through risk quantification to risk reduction/elimination. These steps will be discussed below, first looking into examples of how established occupational carcinogens were first recognized and possibly prevented.

Scrotal Cancer in Chimney Sweeps

The famous report on chimney sweeps' cancer by the British surgeon Percivall Pott came in 1776 and is often mentioned as the first scientific report of occupationally induced cancer. The report was based on a series of scrotal cancer in young chimney sweeps in Pott's practice, suffering from what the trade called "soot warts" on the scrotum. Pott describes the clinical features of local and invasive cancer of scrotal skin in detail and discusses surgical treatment and the failure in the treatment if surgery comes in too late. In the twentieth century, PAH in soot was identified as the underlying causative agent, first in experimental animals and later in epidemiological studies [18]. Not much seems to have happened to improve working conditions until the twentieth century; skin cancer was still reported in excess among chimney sweeps in England and Wales in the beginning of the twentieth century [21]. No cases of scrotal cancer were found in over 5,000 Swedish chimney sweeps active since 1918 [10], and there was no excess of skin cancer among Nordic chimney sweeps in a recent record linkage study (Pukkala et al. [36]). Improved working conditions and hygiene is probably underlying this improvement.

Soot is not the only occupational cause of scrotal cancer. Clinical observations of an association with skin exposure to mineral oil ("mule spinners' disease") were reported already in 1910 and have been established in later epidemiological studies. Polycyclic aromatic hydrocarbons in mineral oil have been identified as causative agent [17].

Skin cancer of the scrotum is a very rare disease in the general male population (incidence one in one million person per year) [46]. For such a rare disease, the probability of being detected by clinical clusters is much higher than for more common cancers and for cancers of multifactorial origin.

Breast Cancer in Nuns

There is one earlier example of occupationally related cancer, although not related to external chemical exposure. Already in 1713, Bernardino Ramazzini, the famous Italian physician and investigator of the diseases of workers, noted a remarkably high frequency of breast cancer among nuns at several Italian nunneries [33]. Ramazzini could not explain this phenomenon, which today is known to be caused by hormonal factors related to the absence of pregnancies and breastfeeding among nuns [14]. This disease is still today the leading cancer form among women [11], and the hormonal risk factors are the same as in Ramazzini's days. Ramazzini's observation of an occupational overrepresentation of cancer is unusual in that it concerns a common cancer. Only very strong associations between occupation and cancer can be identified by observational methods.

Bladder Cancer and Aromatic Amines

The first observation of an occupational origin of bladder cancer was made by the German surgeon Ludwig Rehn, who noted that a large proportion of cases of bladder cancer had worked in a nearby dye factory. He attributed the disease to exposure to aniline, although later research showed that it was caused by exposure to aromatic amines. His report did not lead to action to reduce exposures although he successively reported further cases [6]. It was not until about 1950 when an excess of bladder cancer was reported from the British dye industry [2], and aromatic amines (specifically beta-naphtylamine) were identified as the underlying agent, that exposure reduction and substitution with supposedly less harmful substances took place. There are several later reports of excesses of bladder cancer in the rubber industry, also using aromatic amines [28], and it is not known if the disease is fully prevented today.

Sinonasal Cancer and Wood Dust

The first scientific report of a cluster of 20 cases of sinonasal cancer in association with furniture making came in England in 1965 [31]. It was based on an unpublished report by the otolaryngologist Esme Hadfield:

> One striking small series must, however, be mentioned, and I am indebted to Miss Esme Hadfield of High Wycombe for drawing my attention to these patients. Out of a total of 20 patients from High Wycombe no less than 15 were directly associated with the making of wooden chairs, and if we subtract the three females (who were not wood workers) we have 15 out of 17 males. As is well known, chair-making has been High Wycombe's main industry for years, but this proportion of wood workers in a cancer series is higher than that of wood workers in the local male population as a whole (23-5 per cent.). I am uncertain to what extent these figures are statistically significant. If there is anything in them other than chance one might guess that some chemical constituent of wood dust related to the coal-tars might be implicated. Of the two males not wood workers one is a chimney sweep. It may or may not be relevant that in Wycombe wood waste is extensively burnt as house fuel. (Quoted from [45].)

A large number of subsequent epidemiological studies have confirmed an association between exposure to fine dust from hard wood and sinonasal cancer, especially adenocarcinoma [19, 29]. Probably, exposure levels have been reduced, but there are no epidemiological studies confirming a reduced risk.

Asbestos, Lung Cancer, and Mesothelioma

Asbestos is a fibrous mineral which has come into wide use during the twentieth century due to its insulation against heat, cold and noise, incombustibility, and high tensile strength. Asbestos causes asbestosis, a nonmalignant fibrotic progressive lung disease that may lead to death, as well as mesothelioma, lung cancer, and a number of other cancers. Suspicions that asbestos may cause lung disease (fibrosis) were raised already in the beginning of the twentieth century. The first case reports indicating an association with lung cancer were published in 1935, both from the USA and UK. Animal experimental data indicating that asbestos could produce tumors came in 1943 but was suppressed by the industry sponsoring the study [30]. The first epidemiological study was presented by Richard Doll in 1955. He reported an increased risk of lung cancer among 113 workers exposed to asbestos for at least 20 years 11 deaths from lung cancer vs. 0.8 expected were found, indicating a strong excess [7]. The study was sponsored by the asbestos industry which tried to stop publication, although the Journal decided to publish it anyway [30]. Numerous later publications have confirmed that asbestos causes lung cancer [23]. Asbestos was banned for insulation in Denmark in 1982 and has subsequently been banned in a large number of states including all European Union states (in 2005) up till today (June 2011) (http://ibasecretariat.org/chron_ban_list.php). However, asbestos is still produced in large parts of the world, mainly in Asia and in Eastern Europe, and there is still no worldwide ban of asbestos, although this is required by a large majority of researchers (Collegium Ramazzini [37]).

That asbestos causes mesothelioma was accepted much quicker than that it causes lung cancer. The first case reports came in the 1940s [16] and the first epidemiological study in 1960 [44]. There is a large subsequent scientific literature investigating the different potency of different asbestos fiber types, the relation with smoking, etc. The present controversy deals with the difference in carcinogenic potency between asbestos types, specifically to what extent chrysotile (a serpentine asbestos) is less carcinogenic than other asbestos types, specifically crocidolite. Not enough is known about dose-response, especially in the low-dose range.

Vinyl Chloride and Angiosarcoma of the Liver

Vinyl chloride (VC) is used in the manufacturing of the very widely used polyvinyl chloride plastic (PVC). The discovery and acceptance of the association between exposure to vinyl chloride and liver angiosarcoma followed a pattern very different than that for asbestos and cancer. In January 1974, a manufacturer of VC and PVC alarmed its employees and authorities about three cases of this very rare tumor among its employees [4]. Animal experiments were started and within short time confirmed that VC produced angiosarcomas as well as other tumors in rats [32]. Regulatory action was taken, and already in January 1975, a regulation requiring much lowered exposure levels in industry was enforced by OSHA, and authorities from other parts of the world followed soon [43]. Numerous case reports confirming the association followed, and the first epidemiological study was published in 1981 [20].

Benzene and Leukemia

The first report linking benzene to the development of leukemia was a single case reported as early as in 1928, reporting a man with lymphoblast leukemia who had been exposed to benzene for 5 years [15]. The report does not seem to have attracted much attention. From 1939 until the 1960s, several case series were reported linking exposure to benzene with aplastic anemia and also reported cases of leukemia. It seems as if the hematotoxic effect of benzene was recognized earlier than its leukomogenic effect [15]. When IARC Vol 7 was published in 1974, there were no animal data supporting that benzene caused cancer, and a leukomogenic effect was based on several systematic case reports with supportive evidence from a single epidemiological study [15]. When IARC Vol 29 was published in 1982, more data were available, and benzene was classified as a human carcinogen based on limited animal data and sufficient data from humans.

The ACGIH successively lowered the adopted exposure limit values for benzene from 100 ppm in the 1940s to 0.5 ppm in 1997 (see Fig. 31.1).

In 1978, the OSHA decided on a reduction of the permissible occupational exposure standard for benzene from 10 ppm to 1. By action from the industry, this lowering was

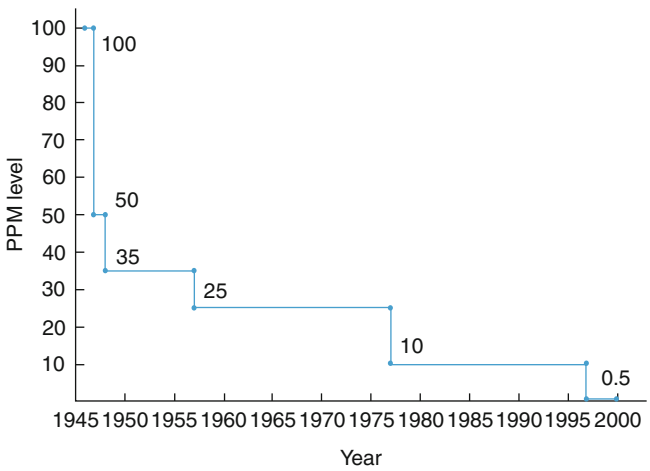


Fig. 31.1 Chronology of ACGIH-adopted exposure limits for benzene (Reproduced from Verma et al. [43] with permission from BMJ Publishing Group Ltd)

overruled and postponed until 1987. It has been estimated that between 30 and 490 leukemia cases have been induced by this delay [34].

Risk Identification

It is noteworthy that nearly all of today's established occupational cancer hazards (and all of those cited above) were first identified by local cancer clusters and not by toxicological or epidemiological methods. This seems to be true not only for the historical but also for the most recent examples [29, 43]. For acceptance of a cancer hazard and effective prevention, epidemiological, animal experimental, and other relevant data play a very important role. In addition, it is not known how many substances that have been discarded from industrial use due to positive findings in premarket tests.

Cancer development is a multistage process where clinical disease develops decades after first exposure. This multistage process involves many molecular events which may be monitored for early detection of a potential cancer hazard. There are markers of exposure, markers of early effects, as well as markers indicating an increased susceptibility. Clinical or epidemiological methods cannot be used for surveillance of newly introduced substances or processes in the work environment. Premarket screening by short-term methods is necessary for effective surveillance in introduction of new chemicals. Biomarkers also play a role in personal exposure assessment that can be used for epidemiological studies.

Systematic cancer risk identification is performed by a number of national and international organizations. The International Agency for Research on Cancer (IARC) is a WHO organization producing evaluations of carcinogenicity to humans from both environmental and occupational exposure and naturally occurring substances (see Chap. 20 of this book for the description of the IARC evaluation process). IARC has until today (June 2011) evaluated 942 substances or exposure circumstances for carcinogenicity, classifying 107 of them as carcinogenic to humans, 59 as probably carcinogenic, 257 as possibly carcinogenic, 58 as not classifiable, and 1 as probably not carcinogenic. Considering the very large number of chemical substances and exposure circumstances worldwide, this is a small fraction, and many substances are unevaluated. IARC evaluates carcinogenicity but does not evaluate dose-response which could be used for risk quantification.

There is a need for a systematic premarket screening for carcinogenicity. The REACH program (Registration, Evaluation, Authorization and Restriction of Chemicals) was adopted by the EU in 2006 and represents the first international systematic attempt for premarket toxicity testing. The REACH program specifies requirements for testing of toxicity and mutagenicity/carcinogenicity of substances used or imported into the EU. The responsibility for evaluation and testing is on the manufacturer/industry. The requirements differ due to the used/imported amounts: for substances used in less than 1,000 metric tons, REACH will not require data for classification of carcinogenicity, and the criteria vary for substances used or imported in higher amounts [39]. It remains to be evaluated to what extent REACH will improve the early detection of new chemical carcinogens.

Future identification of carcinogenic substances must be based on premarket screening – in case this does not work, clinical observations and epidemiological studies may still be necessary although not desirable as a primary tool for cancer risk identification. For effective epidemiology, there is a need for high-quality national registers of cancer incidence and mortality which can be used to identify cancer cases in occupational cohorts and as a source for case-control studies. Effective exposure assessment, preferably based on a lifetime history of occupations, as well as individual data on important confounders is necessary.

Risk Quantification

Quantification of cancer risk is a process which needs to combine data from epidemiology, toxicology, and occupational hygiene. Animal experimental data are rarely useful in risk quantification since the difference in sensitivity between species precludes valid risk quantification. Epidemiological data are required to identify not only a substance/exposure circumstance as carcinogenic but also dose-response relationships in exposed populations, as well as information on the prevalence of exposure and exposure levels in the population. Biomarkers of exposure or effect may be of value in this step. The process of assessing how large cancer excess a certain exposure will cause in the population has similarities to assessing population attributable fractions (PAFs) (see above), but is not identical. While the assessment of PAF aims at investigating how large part of currently diagnosed cancers that could be prevented by elimination of a certain exposure, the process of risk quantification deals with how large cancer burden current exposures will give rise to in the future. Exposure conditions in the Western world have improved over the last 40 years, and estimations of how large the proportion of future cancers that will be caused by occupational exposure usually come up with lower proportions than PAFs. It should be noted, though, that the large majority of occupationally induced cancers that occur today are caused by low-dose exposure to a large number of persons and that the high exposures encountered in certain rare occupations account for a small part [40]. Thus, elimination of high-exposed situations will reduce the population burden of occupationally induced cancers only to a small extent.

Systematic data on exposure prevalence and exposure levels in the population are scarce but developing. CAREX (Carcinogen Exposure) is a project aimed at assessing the prevalence of exposure to occupational carcinogens in the European Union. CAREX has given detailed information on the number of workers exposed to IARC carcinogen groups 1, 2A, and some 2B agents. About 33 million European workers, i.e., 23 % of all employed, were exposed to an occupational carcinogen in the period 1990–1993. The most prevalent exposures were solar radiation ($n=9.1$ million), crystalline silica (3.2 million), diesel engine exhaust (three million), radon (2.7 million), wood dust (2.6 million), and inorganic lead compounds (1.5 million) [26].

However, CAREX is essentially presenting the prevalence of exposure, not exposure levels needed to estimate cancer risks more precisely. Population-based job exposure matrices represent a further step in the process of assessing exposure levels in the population, and the FINJEM is the so far most extensive initiative in this direction. FINJEM defines the prevalence of exposure and exposure levels for around 75 substances/exposure factors. The estimates are specific for calendar time but not for gender [27]. The matrix has recently been extended to cover all Scandinavian countries [25].

Information on cancer risks in relation to occupational exposure and dose-response must be derived from epidemiological studies. A number of problems are involved in the process of applying epidemiological data to other settings than from which they were derived. Typically, cohort studies are often given a high weight in risk quantification since they may be more valid than case-control studies in some aspects. In a cohort study, a good exposure assessment may be possible based on industrial hygiene surveys, measurement programs, etc. On the other hand, cohort studies rarely have information on a lifetime history of occupations and rarely have access to full individual data on tobacco smoking habits (if any). In addition, there are problems in applying the exposure (dose-response) data obtained from cohort studies to other settings, since exposure information of similar and comparable quality rarely is available for the general population. Population-based case-control studies have the advantage of assessing exposures for a sample of the population in the same way as for the cases, and there is no problem to extend the findings, provided that the sample of controls is representative for the population. In addition there is often access to a lifetime smoking history and a lifetime history of occupations. The drawback is that exposure information often is derived from the individuals themselves, with a potential for s. c. recall bias which may tend to overestimate effects. In addition, detailed exposure data can rarely be included. Nesting of case-control studies within occupational cohorts is a useful way to overcome some of these methodological problems.

A special issue in cancer risk quantification is the question of the presence or absence of a threshold in the dose-response curve below which there is no cancer hazard. It is generally accepted that mutagenic substances are assumed to have no threshold effect, allowing linear extrapolation down to zeros exposure, whereas cancer developed by other modes of action may have a threshold. This has been discussed in association with carcinogens supposed to act via irritation on the cellular level, e.g., strong inorganic acid mist [24].

Women constitute a substantial part of the workforce today, although many epidemiological studies concern time periods when women were rare in high-exposed jobs and often were excluded. Differences in sensitivity to toxic substances and carcinogens between genders are attracting an increasing research interest, and more data on cancer risks and exposure to carcinogens among women are needed.

In some circumstances extrapolations are needed from high-exposed cohorts to the lower exposure levels present today. Asbestos is a good example, where information on dose-response has been derived from high-exposed cohorts, used to establish a widely cited dose-response of an increase in lung cancer risk by 1 % unit per fiber-year of exposure (an exposure of 1 f/ml for 1 year) [9]. Recent research based on low-exposed populations indicates that the often used estimate of 1 % increase in SMR per fiber-year leads to an underestimation of risk at low doses (Gustavsson et al. [12]).

The problem of evaluation of interaction of occupational exposures in carcinogenesis is a special topic that is addressed in an ongoing multicenter study of lung cancer, SYNERGY (www.synergy.iarc.fr).

Risk Reduction/Elimination

In Western countries, exposure levels for most workplace chemicals have successively decreased. Symanski and coworkers analyzed time trends in exposure levels for a large set of substances using nearly 700 data sets, mainly but not entirely representing USA and Europe. They found an average annual decline in exposure levels typically ranging from 4 to 14 % over a 30-year period [41, 42]. An annual decline of 10 % equals to a reduction of 95 % over a 30-year period, which represents a considerable reduction in exposure. This general trend is a product of several complex processes, and the contribution of single components of the process may be hard to discern. There are at least three components that interchange in driving this process: (a) a formal regulatory action by national legislative authorities; (b) a local workplace action by companies, trade unions, or the occupational health service; and (c) a less well-defined process of general improvements in working conditions related to economic development.

Preventive Strategies on the Regulatory Level

Formal regulatory action is taken by the national authorities with legislative power, often in form of threshold limit values (TLV). The first occupational exposure limits were proposed by individual researchers already in the nineteenth century. The first official list of exposure limits was probably published in the USSR in 1939 [11, p 13]. In 1946, the American Conference of Governmental Industrial Hygienists (ACGIH) issued its first list, which since then has been revised annually and has become very influential for similar list worldwide. It has no legal status; such a list is issued in the USA by the Occupational Safety and Health Administration (OSHA) since 1969. The process of setting official TLVs is typically slower, results in a higher TLV, and covers fewer substances than the list published by the ACGIH [13]. Today many national authorities issue national lists of TLVs. The Scientific Committee on Occupational Exposure Limits (SCOEL) was set up in 1995 to advise the European Commission on occupational exposure limits for workplace chemicals in the EU. Draft recommendations undergo a stakeholder consultation to allow health-based scientific comments and further data.

The concept of TLVs may superficially seem simple but has turned out to be very complex. The ACGIH list stated in 1953 that a TLV is "the maximum average concentration of contaminants to which workers may be exposed for an 8-h working day (day after day) without injury to health." There are number of problems inherent in this definition. First, what is "injury to heath"? Some health effect, e.g., mild mucosal irritation or psychomotor changes like prolonged reaction time, may not cause chronic damage and may in some instances be considered as less relevant to define a NOAEL (no observed adverse effect level). Secondly, what is a maximum average concentration? Much research in occupational hygiene has revealed that there is a substantial variation in exposure levels, both between and within workers (day to day) among workers doing the same job task [38]. Due to this variation, increasing the number of measurements will lead to a larger number of samples showing exposure over a certain level. Another problem is to achieve comparable measurements between the present environments and the epidemiological studies underlying the dose-response data used for the risk quantification.

A legislative TLV is a product considering not only health hazards but also economic and industrial aspects [13]. For carcinogens, the legislative process may lead to a ban, a TLV with specific regulations, or an ordinary TLV. An ordinary TLV is sometimes applied for carcinogens that are not mutagenic and for which the carcinogenic effect is not the critical effect (e.g., strong acid mist). For mutagenic carcinogens, a ban may be theoretically the only way of preventing future cancer cases. A ban may be problematic if the causative agent in a certain environment is not identified, e.g., what causes lung cancer in house painters.

Prevention at the Workplace

A legislative TLV is not automatically complied with at all workplaces, and the actual exposure for a worker is a product of a series of other factors. A strong local occupational health organization may result in exposures that are well below the TLV. In other situations, TLVs may be exceeded, and a long process of argumentation regarding interpretation from the industry against the local work environment authority takes place. Local prevention may include programs of monitoring exposure levels, as well as biomonitoring of exposure or early health effects. Biomarkers may also be used in identification of susceptible groups. The use of personal protective devices may be enforced more or less strictly by the employer.

Conclusion

Occupational exposure accounts for a substantial number of cancers occurring today, and these cancers are in principle all avoidable. Risk identification is a first step to risk reduction, and it is noteworthy that nearly all of today's well-established occupational carcinogens were first identified by such a crude method as local case clusters. It is not acceptable that new future carcinogens should be identified first when cases occur, while a large number of persons already have been exposed and future cases will appear, even if the risk is eliminated instantaneously, due to the long biological latency from first exposure to cancer development.

The process from identification of risk until elimination/reduction has in several instances been embarrassingly slow. The worst example so far is probably asbestos, for which carcinogenic properties were identified already in the 1950s, which is not yet being banned worldwide. On the other hand, a quick action was taken when vinyl chloride was found to cause liver angiosarcoma, and the TLV was revised within 1 year from the identification of the cluster. It seems as if tumors which both are rare in the general population and are caused only by occupational exposure have led to faster legislative action (e.g., angiosarcoma, mesothelioma) than more common tumors of multifactorial origin (e.g., lung cancer, leukemia).

A systematic assessment of occupational exposures in the UK showed that there is still a substantial number of workers exposed to occupational carcinogens (Cherrie et al. [3]). New substances are continuously introduced, and effective methods for early identification of new cancer hazards are necessary. The following infrastructural factors will all contribute to such a development:

- Access to high-quality national cancer registers and good exposure data are crucial for effective epidemiology.
- Large, well-designed epidemiological studies are needed, especially to study health effects in the low-dose range.
- Methods must be improved for studies of the interaction of occupational and other environmental- or lifestyle-associated exposures.
- Premarket screening needs to be developed systematically, and the effectiveness of the REACH program should be evaluated.

References

1. Adami HO, Day NE, Trichopoulos D, Willett WC. Primary and secondary prevention in the reduction of cancer morbidity and mortality. Eur J Cancer. 2001;37 Suppl 8:S118–27.
2. Case RAM, Hosker ME, MC Donald DB, et al. Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. Br J Ind Med. 1954;11:75–104.
3. Cherrie JW, Van Tongeren M, Semple S. Exposure to occupational carcinogens in great britain. Ann Occup Hyg. 2007;51(8):653–64.
4. Creech Jr JL, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med. 1974;16(3):150–1.
5. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M. Comparative risk assessment collaborating group (cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366(9499):1784–93.
6. Dietrich H, Dietrich B. Ludwig Rehn (1849–1930) – pioneering findings on the aetiology of bladder tumours. World J Urol. 2001;19(2):151–3.
7. Doll R. Mortality from lung cancer in asbestos workers. Br J Ind Med. 1955;12(2):81–6.
8. Doll R, Peto J. The causes of cancer, 1981. J Natl Cancer Inst. 1981;66(6):1191–308.
9. Doll R, Peto J. Asbestos. In: Effects on health of exposure to asbestos. Health and Safety Commission. London: Her Majesty's Stationery Office; 1985.
10. Evanoff BA, Gustavsson P, Hogstedt C. Mortality and incidence of cancer in a cohort of Swedish chimney sweeps: an extended follow up study. Br J Ind Med. 1993;50(5):450–9.
11. GLOBOCAN 2008. Website www.globocan.iarc.fr. Accessed 15 Aug 2011.
12. Gustavsson P, Nyberg F, Pershagen G, Schéele P, Jakobsson R, Plato N. Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. Am J Epidemiol. 2002;155(11):1016–22.
13. Hansson SO. Setting the limit. Occupational health standards and the limits of science. New York: Oxford University Press; 1998.
14. Henderson BE, Pike MC, Bernstein L, Ross RK. Breast cancer. In: Schottenfeld D, Fraumeni J, editors. Cancer epidemiology and prevention. 2nd ed. Oxford: Oxford University Press; 1996. p. 1022–39.
15. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Some anti-thyroid and related substances, nitrofurans and industrial chemicals, vol. 7. Lyon: International Agency for Research on Cancer; 1974.
16. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Asbestos, vol. 14. Lyon: International Agency for Research on Cancer; 1977.
17. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Polynuclear aromatic compounds, Part 2: carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes, vol. 33. Lyon: International Agency for Research on Cancer; 1984.
18. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Polynuclear aromatic compounds, Part 4: bitumens, Coal-tars and derived products, shale-oils and soots, vol. 35. Lyon: International Agency for Research on Cancer; 1985.
19. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Wood dust and formaldehyde, vol. 62. Lyon: International Agency for Research on Cancer; 1995.
20. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide), vol. 97. Lyon: International Agency for Research on Cancer; 2008.
21. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures, vol. 92. Lyon: International Agency for Research on Cancer; 2010.
22. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Painting, firefighting, and shiftwork, vol. 98. Lyon: International Agency for Research on Cancer; 2010.
23. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: arsenic, metals, fibres, and dusts, vol. 100C. Lyon: International Agency for Research on Cancer; 2012.
24. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: chemical agents and related occupations, vol. 100F. Lyon: International Agency for Research on Cancer; 2012.
25. Kauppinen T, Heikkilä P, Plato N, Woldbaek T, Lenvik K, Hansen J, Kristjansson V, Pukkala E. Construction of job-exposure matrices for the Nordic Occupational Cancer Study (NOCCA). Acta Oncol. 2009;48(5):791–800.
26. Kauppinen T, Toikkanen J, Pedersen D, Young R, Ahrens W, Boffetta P, Hansen J, Kromhout H, Maqueda Blasco J, Mirabelli D, de la Orden-Rivera V, Pannett B, Plato N, Savela A, Vincent R, Kogevinas M. Occupational exposure to carcinogens in the European Union. Occup Environ Med. 2000;57(1):10–8.
27. Kauppinen T, Toikkanen J, Pukkala E. From cross-tabulations to multipurpose exposure information systems: a new job-exposure matrix. Am J Ind Med. 1998;33(4):409–17.
28. Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. Occup Environ Med. 1998;55(1):1–12.
29. Landrigan PJ. The prevention of occupational cancer. CA Cancer J Clin. 1996;46(2):67–9.
30. Lilienfeld DE. The silence: the asbestos industry and early occupational cancer research – a case study. Am J Public Health. 1991;81(6):791–800.
31. MacBeth R. Malignant disease of the paranasal sinuses. J Laryngol Otol. 1965;79:592–612.
32. Maltoni C, Lefemine G. Carcinogenicity bioassays of vinyl chloride: current results. Ann N Y Acad Sci. 1975;246:195–218.
33. Mustacchi P. Ramazzini and Rigoni-Stern on parity and breast cancer. Clinical impression and statistical corroboration. Arch Intern Med. 1961;108:639–42.

34. Nicholson WJ, Landrigan PJ. Quantitative assessment of lives lost due to delay in the regulation of occupational exposure to benzene. Environ Health Perspect. 1989;82:185–8.
35. Nurminen M, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. Scand J Work Environ Health. 2001;27(3):161–213.
36. Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, Weiderpass E, Kjaerheim K. Occupation and cancer - follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48(5):646–790.
37. Ramazzini C. Asbestos is still with us: repeat call for a universal ban. J Occup Environ Med. 2010;52(5):469–72.
38. Rappaport SM, Kupper LL. Quantitative exposure assessment. El Cerrito: Rappaport; 2008.
39. Rudén C, Hansson SO. Registration, Evaluation, and Authorization of Chemicals (REACH) is but the first step-how far will it take us? Six further steps to improve the European chemicals legislation. Environ Health Perspect. 2010;118(1):6–10.
40. Rushton L, Bagga S, Bevan R, Brown TP, Cherrie JW, Holmes P, Fortunato L, Slack R, Van Tongeren M, Young C, Hutchings SJ. Occupation and cancer in Britain. Br J Cancer. 2010;102(9): 1428–37.
41. Symanski E, Kupper LL, Hertz-Picciotto I, Rappaport SM. Comprehensive evaluation of long-term trends in occupational exposure: Part 2. Predictive models for declining exposures. Occup Environ Med. 1998;55(5):310–6.
42. Symanski E, Kupper LL, Rappaport SM. Comprehensive evaluation of long-term trends in occupational exposure: Part 1. Description of the database. Occup Environ Med. 1998;55(5):300–9.
43. Verma DK, Purdham JT, Roels HA. Translating evidence about occupational conditions into strategies for prevention. Occup Environ Med. 2002;59(3):205–13.
44. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med. 1960;17:260–71.
45. Whiteside OJH, Corbridge RJ, Capper JWR. Esme Hadfield (1921–92) and the Wycombe woodworkers. J Med Biogr. 2010;18:24–6.
46. Wright JL, Morgan TM, Lin DW. Primary scrotal cancer: disease characteristics and increasing incidence. Urology. 2008;72(5):1139–43. Epub 2008 Sep 16.

Screening for Occupational Cancer

32

Douglas B. Trout, Paul A. Schulte, and Simone L. Tramma

Keywords
Medical screening • Medical surveillance • Lung cancer screening • Bladder cancer screening • Skin cancer screening • Biomonitoring

Background and Definitions

Many known and potential human carcinogens are related to workplace exposures; the practice of occupational health is founded upon the key concept that virtually all such exposures can be prevented [1–3]. Primary prevention is the optimal prevention strategy for occupational cancer control through activities intended to eliminate harmful exposure(s) in the workplace [4].

Given the above, secondary prevention provided by medical screening remains an important component of sound occupational health practice in many instances. Such instances may include provision of medical screening for (1) workers with occupational exposures experienced before introduction of more recently enacted (and more protective) occupational exposure limits; (2) workers in workplaces where efforts are being made, but remain incomplete, in controlling exposures to acceptable levels; and (3) workers in occupations or industries known to be associated with cancer but with unknown specific causative exposure (e.g., the rubber manufacturing industry). Screening is among the tools available to complement exposure control for prevention of occupational cancer. The fact that most cancers caused by occupational exposures are pathologically and clinically indistinguishable from cancers not caused by these exposures [5] supports the role of screening for occupational cancer in workplaces. Health professionals with the ability to recognize the role that exposures may be playing in the development of cancer are crucial to this process [2]. Early detection of cancer via screening is a component of a complete strategy for cancer control [6]. One of the aims of secondary prevention is to reduce morbidity and mortality through detection of illness at an early stage when treatment may succeed in altering progression of disease.

Appropriate implementation of screening activities requires an understanding of the principles of screening and of the related activities of hazard and medical surveillance.

The terms *surveillance* and *screening* have sometimes been used interchangeably (and sometimes inconsistently) in the past—it is important to understand distinctions between these activities [7–9]. Gochfeld provides useful distinctions for the medical terms and defines *medical surveillance* as an activity that targets health events or a change in a biologic function of an exposed person or persons, with recurrent longitudinal examinations and data analysis over time. *Medical screening* is a complementary activity designed to detect early signs of work-related illness by administering tests to apparently healthy persons in a repeated cross-sectional approach [7]. Medical screening for occupational cancer therefore involves the application of physical examination or medical tests to detect medical effects of exposure to cancer-causing agents [4, 10]. Screening activities have a clinical focus—the screened person may be directly evaluated and

D.B. Trout, MD, MHS (✉)
Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, 4676 Columbia Parkway, R-12, Cincinnati, OH 45226, USA
e-mail: dyt1@cdc.gov

P.A. Schulte, PhD
Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

S.L. Tramma, MD, MS
Surveillance Branch, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, WV, USA

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_32, © Springer-Verlag London 2014

treated in response to a screening test. Medical screening data, ideally collected in a standardized manner, aggregated, and evaluated over time, can also be evaluated as a part of a surveillance program and play an important role in primary prevention. However, screening and surveillance activities without follow-up do not prevent occupational disease [11].

Biomarkers and Biomonitoring

A topic directly related to both screening and surveillance is biomonitoring, the measurement of workplace agents or metabolites in biological specimens. Biomonitoring may allow for assessment of exposure via all routes of exposure and absorption [12]. Biomarkers are objective measures of normal physiologic processes, pathologic processes, or pharmacologic responses to a therapeutic intervention [13]. Biomarkers can be used in screening and surveillance to assess exposure, effects of exposure (including preclinical, early, or clinically apparent disease), and susceptibility to illness [14–17]. Biomonitoring for carcinogens can involve testing for changes in deoxyribonucleic acid (DNA) or chromosomes, presence of markers of exposure in cells or body fluids, or detections of mutagens in biologic samples [4] and has long held potential as a form of medical screening [10]. As with any medical test, health professionals should understand what question the test is intended to answer and whether the biomarker is validated (validity is the best approximation of the truth of a test or the degree to which the results correspond to the endpoint or phenomenon being measured) so that the results can be accurately interpreted and informative [17]. Validation of biomarkers for use in screening for carcinogenicity remains an important issue both for occupational and environmental carcinogens [18, 19]. Frameworks for the use of biomarkers as clinical screening tools, particularly when other sources of medical data are not readily available, have been published [17]; however, the utility of biomarkers remains primarily in the area of research, as established and emerging biomarkers are used in clinical, etiologic, and hypothesis-generating studies [19].

A broad range of biomarkers have been used to assess exposures to potential carcinogens. Assays to detect DNA damage and DNA adducts have been used in a number of epidemiologic studies and have been among the most informative biomarkers of exposure to genotoxic agents [20, 21]. Other biomarkers of exposure used in research studies include 1-hydroxypyrene, oxidative damage to DNA, and adducts of N-nitroso compounds [18, 22]. Although these biomarkers remain important research tools [18], poor specificity and positive predictive value (PPV) (among other issues) currently preclude their routine use as workplace screening tools for cancer. Ongoing research to augment available data concerning biomarkers of exposure with data related to biomarkers of effect will greatly enhance risk assessment efforts [20]. Research into biomarkers of genetic susceptibility is an emerging field; the evolving science is prompting important considerations related to ethical and social concerns [23, 24].

Initiation of Screening for Occupational Cancer

The initiation of workplace screening for occupational cancer involves consideration of a number of factors.

Nature of the Health Outcome: Burden of Disease

Important diseases are candidates for screening [10]. Cancers, including occupational cancers, clearly represent illnesses posing substantial burden across the world. The global burden of cancer is increasing, with more than 7.6 million cancer deaths in 2008 [25]. Twelve million cancer deaths have been predicted for 2030, making primary and secondary prevention of great importance [6, 26]. In the United States, more than 1.5 million people were expected to be diagnosed with cancer in 2010; more than 550,000 people in the United States were expected to die from cancer in that year [27]. Estimates of the burden of occupational cancer have been published, recently summarized in 2008 [28, 29], and well described in other parts of this text. Estimates of the percentages of occupational cancer among the total are widely considered underestimates due to several factors; nevertheless, it is clear that successful prevention activities could have major impact [2, 28].

Impact on the Health Outcome

An overarching consideration related to the initiation of screening relates to expected benefit to workers from the screening, and specifically, that there is a preclinical state of the health condition of concern that can be identified prior to the presence of symptoms [30]. Adequate evidence of reduction in mortality has been a gold standard measure of efficacy when applying evidence-based methods to assess the value of screening tests. For cancer in the general population, recommendations for screening are often made on the basis of such considerations [31–33]; however, it has been pointed out that evaluations that assess improved survival as a measure of the value of screening activities are subject to known biases [34].

Experts have proposed different levels of evidence, including expert opinion [35], to support screening or other types of preventive health examinations, and screening may

be recommended for subgroups on a case-by-case basis taking into account more qualitative aspects of importance to those groups [31]. For example, preventive health examinations or testing can play an important role in occupational safety and health even in the absence of direct evidence of benefit to the screened individuals [10, 12, 16].

Availability of Tests to Detect the Health Outcome

Tests considered for screening must be able to detect cancer early in the illness, during the detectable preclinical phase [34]. The goal of screening is to increase the time between detection of cancer and the usual onset of symptoms (lead time). Ideally, this increased lead time would allow for intervention (e.g., treatment) to modify the development of illness. In addition to being practical and feasible [36], several defined characteristics of the screening tests are important when considering the initiation of a screening program. Sensitivity, specificity, and PPV (the proportion of persons with the health outcome among all persons who test positive) are important characteristics. PPV varies with the burden of the illness in the group being screened. Therefore, a screening test judged as having inadequate PPV for a cancer outcome in the general population may have adequate PPV in a group of workers at risk related to occupational exposure if that exposure leads to increased illness in the tested workers.

Assessment of Medical Benefits and Concerns

In addition to the above, other benefits of screening include improved access to counseling for workers, exposure reduction or other modifications of the workplace, and contributions to medical surveillance efforts in the relevant workplace [10]. The benefits of a screening program should be considered against potential concerns. Concerns include direct complications from the screening test itself, complications from follow-up testing performed because of a positive screening test, and the potential emotional impact on a person receiving a false-positive test. Concerns also include monetary costs to the individual workers or to the employer. For employers, resources devoted to poorly planned screening programs may have been put to better use for other methods of prevention such as exposure control. Analyses of costs may be done in a qualitative or quantitative (in cost-benefit or cost-effectiveness analyses) manner. Another consideration is potential impact on the employment status of a worker who has been found to have an abnormal screening test (whether true or false positive) [4, 10]. Genetic biomonitoring that assesses potential predisposition to cancer has been raised as an ethical concern and a potential risk to workers [10], and such concerns have contributed to current recommendations for caution in the use of genetic screening [23]. In spite of rapid technologic advances in the ability to use genetic biomarkers in workplace screening programs, the program administrator must still consider the test characteristics (i.e., usefulness for screening) [37].

Component of a Sound Occupational Health Practice

Sound occupational health practice around the world includes elements of screening for many occupational exposures. Screening for occupational cancer is a component of a comprehensive approach for prevention among groups of workers exposed to occupational carcinogens [38, 39]. This comprehensive approach to prevention may need to be balanced with clinical approaches to prevention in which complete consensus is commonly not achieved relative to recommended screening tests for cancer [31]. In the United States, elements of screening are included in many standards and recommendations related to agents known or suspected to cause cancer [40, 41].

Occupational Cancer and Latency

The factors noted above should be considered with knowledge of temporal relationships between exposure to occupational carcinogens and detection of cancer. Most cancer-related health effects among workers exposed to occupational carcinogens are not observed until 10–45 years after exposure. This observed latency presents a challenge to effective screening for occupational cancers in the workplace [4]; workplace-based screening programs should consider screening not only of currently exposed workers but also of workers previously exposed. Ideally, screening programs should be organized in employer-independent manner (e.g., based on exposure registries).

Components of a Medical Screening Program

The following factors are important components to consider in all types of workplace medical screening programs [8, 10, 12]:

1. Purpose and objective
2. Target population
3. Testing modalities and frequency of testing
4. Data maintenance and interpretation
5. Communication
6. Intervention
7. Program evaluation

A medical screening program should have a clearly defined purpose or objective. The target population should be clearly defined and may include that subset of workers with the highest potential for exposure. Testing modalities must be available to accomplish the defined objective. Testing modalities may include such tools as physical examinations or medical testing. These types of evaluations should be used within the target population to gain data concerning a specific organ system(s) or health effect(s). A plan for initiation of testing (e.g., periodically and/or post-incident) should be formulated at the start of the program. The frequency of the screening test will depend in part on some or all of the following: test characteristics, the incidence of disease in the exposed group, information related to latency of the disease of concern and the length of the preclinical detection period, and the level and frequency of exposure [10].

Screening activities should be undertaken with a plan in place that ensures confidentiality of the medical data and of the interpretation of results. Privacy concerns related to collection of screening data have become more prominent with recent advances in and discussion of genetic screening [23].

Several issues related to data interpretation should be considered. For example, screening test results may not be simply positive or negative. For data that may be interpreted as borderline, the level of abnormal test results that triggers some follow-up or intervention should be defined. Follow-up may include diagnostic evaluation and treatment (including medical removal if appropriate). In addition, for most tests, availability of baseline (ideally, before exposure) medical tests is important so that those test results can be compared with results from testing at a later date. Furthermore, those persons conducting medical screening should understand the concepts of *sentinel events* [42] and should watch carefully for unusual clinical findings which may be important indicators of failure of prevention in the workplace. The detection of a malignancy that may be related to an occupational exposure may be considered a sentinel health event. When screening data are aggregated and analyzed over time and used for surveillance, such analysis may alert practitioners to elevated rates of an illness that warrants follow-up investigation. For example, the data may signal when an illness such as a malignancy occurs in excess or in a "cluster" in time and space. Finally, expertise in epidemiology is useful when analyzing and interpreting medical screening data, cancer rates, and potential cancer clusters and when conducting surveillance [12, 43].

An effective medical screening program requires several levels of communication with individuals being screened and with other relevant groups. If the screening is based in a workplace, communications with workers and management should include the objectives of the screening program and limitations of the data as well actual communication of the results. Screening test results should be understandable, and workers being screened should receive them promptly, as effective and timely communication is key to avoid creating false anxiety or false assurance. An explanation of the level of uncertainty associated with test results should be routinely included in communications about screening test results. With the individual workers' consent, results of medical tests may be shared with those workers' personal physicians. Communication of summary information should only be done in accordance with privacy and confidentiality protections. Communication of screening test results with professionals coordinating other aspects of the workplace hazard and medical surveillance provides for an effective, complete occupational health program. As discussed above, the availability of effective clinical follow-up is an important consideration in a screening program. For workplace-based screening programs, consideration should be given to whether analysis of screening program data may result in a need for workplace intervention. A final phase of a medical screening program is assessment of the program effectiveness over time. Quality assurance and control should be considered for all workplace screening programs.

Considerations Related to Screening: Updates on Specific Cancers

On the basis of the rationale and principles reviewed above, screening activities are currently components of sound occupational health practice for a number of exposure scenarios and in relationship to several types of cancer. Current information related to screening for several types of occupational cancer is described below.

Lung Cancer

Lung cancer is the leading cause of cancer death worldwide [25] and an important cancer in working populations [1, 3]. Until recently, lung cancer was not among the cancers for which screening among asymptomatic individuals in the general population had been recommended. Although lung cancer contributes to substantial morbidity and mortality, previous studies of lung cancer screening have not yielded evidence of the benefit seen by programs of screening for other cancers such as breast, cervical, and colorectal [31]. For example, studies have not shown reduction in lung cancer mortality after screening with chest X-ray (CXR) or sputum cytology [5, 35]. Some authorities interpreted available data as being insufficient to provide for a recommendation for or against lung cancer screening in the general population [34, 44]. However, more recent developments in the use of low-dose computed tomography (CT) have raised the question of whether CT techniques will lead to improvements in occupational lung cancer screening [45].

Cohort studies using low-dose CT (LDCT) scanning have demonstrated that lung cancer can be diagnosed at a significantly earlier stage with CT screening than in current clinical practice [44], and improved sensitivity has been observed when CT scanning has been used in comparison to CXR [46]. However, no CT studies had been able to demonstrate the mortality benefit of CT-based screening programs until the National Lung Screening Trial (NLST) released its preliminary findings in late 2010 indicating a 20.3 % reduction in deaths from lung cancer among current or former heavy smokers who were screened with low-dose helical CT versus those screened by CXR [47].

The NLST is a national randomized controlled trial launched by the US National Cancer Institute in 2002 to determine whether annual screening with low-dose helical CT would lead to earlier detection and reduced mortality from lung cancer relative to screening with CXR. In this trial 53,454 participants at high risk for lung cancer—current and former heavy smokers of at least 30 pack-years between 55 and 74 years of age—were randomly assigned to receive low-dose helical CT or CXR screenings once a year for 3 years and were then followed for 3.5 additional years with no further screening. During the screening phase, 24.2 % of the low-dose helical CT tests and 6.9 % of the CXR tests were classified as positive. However, 96.4 % of the "positive" low-dose helical CT tests and 94.5 % of the "positive" CXR tests turned out to be false positives upon a diagnostic evaluation, meaning that the positive finding did not prove to be lung cancer. Lung cancer was confirmed in 3.6 % of the positive screenings in the low-dose helical CT group and in 5.5 % of the positive screenings in the CXR group. The rate of at least one complication after a diagnostic evaluation for a positive screening test was less than 2 % for either type of screening [48].

In the wake of NLST, several professional societies have released guidelines for LDCT lung cancer screening. The National Comprehensive Cancer Network (NCCN), a consortium of 21 US cancer treatment centers, released their lung cancer screening guidelines in October 2011 [49]. The NCCN recommended screening with LDCT for people aged 55 and greater with smoking histories of 30 or greater pack-years who still smoked or quit smoking less than 15 years ago (NLST criteria). In addition to those who would have met NLST inclusion criteria, NCCN also recommended LDCT screening for people aged 50 and greater with smoking histories of 20 or greater pack-years and one additional risk factor other than second-hand smoke. A variety of additional risk factors are described, including chronic obstructive pulmonary disease, pulmonary fibrosis, and various occupational exposures (asbestos, arsenic, chromium, silica, nickel, cadmium, beryllium, and diesel fumes). Although the NCCN recommendation includes occupational exposure to lung carcinogens, it provides no guidance as to how much exposure is needed before LDCT screening for lung cancer should be considered. In April 2012, the American Lung Association released a guidance statement [50] to patients and physicians indicating that LDCT screening should be recommended only for people who meet NLST criteria because of the questions that remain about optimal methods and effectiveness in other populations. Soon after, in May 2012, the American College of Chest Physicians and the American Society of Clinical Oncology, with collaboration from the American Cancer Society, released their clinical practice guidelines [51], based on a systematic review of the evidence regarding the benefits and harms of lung cancer screening with LDCT. They recommend that only people who specifically meet NLST criteria should undergo LDCT screening and *not* to screen individuals who (1) have accumulated fewer than 30 pack-years of smoking, (2) are either younger than 55 years or older than 74 years, (3) who quit smoking more than 15 years ago, or (4) with severe comorbidities that would preclude potentially curative treatment, limit life expectancy, or both.

In July 2012, screening guidelines were issued by the American Association for Thoracic Surgery. These guidelines recommend annual lung cancer screening with LDCT for (1) smokers and former smokers with a 30 pack-year history of smoking, (2) persons with a 20 pack-year history of smoking and additional comorbidity that produces a cumulative risk of developing lung cancer of 5 % or greater over the following 5 years, and (3) long-term lung cancer survivors, aged 55–79 years. The American Association for Thoracic Surgery guidelines differ from the others since they recommend that screening begin at age 50 years and end at age 79, instead of 74, arguing that there is little evidence to show that lung cancer risk drops after that age. They also differ in recommending the screening to patients who have survived lung cancer [52]. The US Preventive Services Task Force currently recommends annual screening for lung cancer with LDCT in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery [53].

A number of basic principles related to screening remain applicable as these data are considered. First, the data derived from the NLST were obtained from a very specific population group—individuals aged 55–74 at high risk for developing lung cancer due to present or past heavy smoking. This study group is not necessarily comparable to a specific population of workers. As the data from other current studies become available, it will be important to evaluate how the data from studies of cigarette smokers may apply to occupationally exposed groups. As noted above, the predictive value of CT as a screening test will be directly affected by the incidence of lung cancer in the groups being screened.

Second, screening with CT scans is not risk-free. Radiation exposure from repeated CT scans is cumulative and can lead to illness, including cancer. While a "low-dose" method was used in the NLST, this is relative to a full diagnostic helical CT scan (average radiation effective dose of 7 millisieverts [mSv]) [54]. The radiation dose for this "low-dose" method (1.5 mSv in the NLST) is about 15 times higher than a CXR (average effective dose 0.1 mSv) [54]. The radiation risks of CT scanning have been reviewed and must be considered in these types of screening programs [55].

Third, the greater sensitivity of CT as a screening test may potentially generate a high rate of false-positive results, and the overdiagnosis of clinically nonrelevant lesions is another important issue. Potential for unnecessary testing with extra radiation, invasive diagnostic and surgical procedures, and complications, along with anxiety and expense, needs to be considered [35]. Currently available data do not allow for quantitative assessment of morbidity or mortality related to follow-up of all findings from screening protocols using low-dose CT. Other researchers have published protocols that are being developed and used to minimize unnecessary follow-up testing [56, 57].

The value of incorporating other clinical data readily available from standard clinical care into lung cancer screening has been and continues to be evaluated in current research [58–60]. Additional criteria or tests may be developed to refine the "at-risk" groups to be entered into screening programs, allowing for increased specificity and PPV of subsequent screening tests [61]. As the clinical and public health significance of current screening trials are debated and reviewed [61–63], individuals at elevated risk of lung cancer on the basis of occupational exposure(s) may wish to consider screening tests only after consultation with their healthcare provider. A decision would require an informed discussion between clinicians and patients [31]; such a discussion should include clear communication concerning the potential benefits and harms of screening with LDCT. For example, the risk of the NLST cohort developing lung cancer was approximately 0.6 % per year; 320 patients needed to be screened with three yearly chest LDCT scans to find one case of lung cancer, and only 3.6 % of all lung nodules 4 mm or larger were actually lung cancer. In a group at lower risk, the number that needed to be screened to find one case of cancer would be higher, and the percentage of lung nodules that truly were lung cancer would be lower.

Bladder Cancer

It has been estimated that more than 380,000 new cases and 150,000 deaths from bladder cancer occurred worldwide in 2008 [25]. Occupational exposures (along with smoking) are a major risk factor for bladder cancer in Western countries; a number of occupational agents are known bladder carcinogens [25, 64]. Issues related to screening for occupationally related bladder cancer have been an important topic for many years [65] and remain an area of active work. Urine cytology has been the primary test employed for bladder cancer screening among workers exposed to agents raising the risk for bladder cancer [64]. Cytology with other tests such as urinalysis and cell-based tests has been used in well-described screening and surveillance programs as part of research studies [66, 67]. Individually, urinalysis for hematuria may have adequate sensitivity (particularly with repeated testing) but specificity is low. Urine cytology has been shown to have low sensitivity, even among those with high-grade cancers [68]. Clinical evaluation by cystoscopy, an invasive test, is commonly used as the diagnostic tests for bladder cancer among the screened population. The unique clinical characteristics of transitional cell bladder cancer and inadequate sensitivity and specificity of current screening tests, along with inability to demonstrate reduced mortality among the screened groups, all contribute to the current determination that the effectiveness of screening for occupational bladder cancer has not been determined [69, 70].

Use of one or more "prescreening" tests to identify an appropriate target population (thereby increasing the PPV of subsequent screening tests) is being evaluated in the hope of improving bladder cancer screening and minimizing excess morbidity related to screening and subsequent clinical follow-up [69]. There are a variety of noninvasive tests (along with assessment of risk factors such as smoking history and/or occupational exposure to bladder carcinogens) that may be used to identify high-risk populations within which to perform subsequent screening—examples include genetic and cell-based tests [69, 71–73]. A recent review of screening of adults for bladder cancer by the US Preventive Services Task Force concluded that additional research is needed to determine whether screening for bladder cancer improves clinical outcomes [74].

Skin Cancer

Skin cancers are the most common cancers [75] with both nonmelanoma skin cancers (more common but not commonly associated with mortality) and melanoma (less common and accounting for most mortality from skin cancers) representing significant health problems worldwide [76–78]. Environmental and occupational exposures are known to be associated with several types of skin cancer, with exposure to ultraviolet radiation an important environmental [79] and occupational [80] risk factor. The fact that visual examination is available, along with clinical observations that early detection may lead to improved clinical outcomes [81], has led to coordinated examination programs for skin cancer in

many countries [78]. Examination of the skin is an established prevention activity for clinicians [80, 82]; however, reviews of examination programs in the general population have shown limited evidence that they lead to earlier detection of cancers and lack of evidence of improved health outcomes [83].

Some data suggest that targeted examination for both nonmelanoma and melanoma skin cancers can improve clinical outcomes [76, 84]. Although these activities did not involve identification of occupational risk factors, improvements in our knowledge concerning occupational risk factors for skin cancer may lead to similar targeted activities related to occupational risk in the future [77]. Studies examining the relationship of exposure to ultraviolet radiation to skin cancers are ongoing [79]; these studies should incorporate elements that will allow health-care professionals to improve both primary and secondary prevention activities to prevent skin cancers in the future [85].

Other Cancers

Although exposures to a number of agents (including ionizing radiation, benzene, and cytotoxic drugs) are associated with acute leukemia, clinical screening tests to detect the health outcome (leukemia) or cytogenetic abnormalities associated with leukemia are not routinely used for workers exposed to these agents [86]. Development of screening methods for hematologic cancers is an active area of research. Fluorescent in situ hybridization techniques have been used to demonstrate that detection of chromosomal damage in cells from peripheral blood may be a useful screening tool in the future for workers at risk for acute myeloid leukemia [87]. Similar cytogenetic techniques have been used to evaluate chromosomal damage among benzene-exposed workers [88] and to provide evidence supporting the carcinogenicity of formaldehyde [89]. Potential future clinical application of these techniques in screening programs will be informed by continued research in these areas.

Pleural mesothelioma, primarily associated with occupational exposure to asbestos, is a cancer for which there has been a high level of interest in early detection due to the associated generally poor prognosis and high mortality. Radiologic tests (CXR, CT) have not been shown to be useful screening tests for mesothelioma in the past. Serum biomarkers have also been considered, sometimes in conjunction with radiologic tests, as screening tools. A recent study concluded that one such serum biomarker, soluble mesothelin-related protein, is not likely to be an effective screening test for mesothelioma [90]. To date, the use of screening tools for persons at risk of mesothelioma remains investigational, and future work may help increase their clinical applicability [91, 92].

Screening has been shown to reduce cancer mortality for breast, colorectal, and cervical cancers [93–95], common cancers not considered among the main sites of occupational cancer in the past [96]. Regarding breast cancer, there is increasing evidence from human and animal studies that shift work involving circadian disruption may be an important risk factor [97]; occupational exposures have been suggested as being associated with colorectal cancer [98]. Just as the work relatedness of these cancers is continually being investigated as new data become available, guidelines for appropriate screening protocols for these cancers are updated based on the most current scientific evidence [99].

Considerations Related to Screening: Integration with Other Program Elements

From a workplace perspective, screening for occupational cancer should be occurring as a component of a complete occupational health program [10]. From an individual's perspective, screening for occupational cancer should be occurring as component of complete clinical care for the individual [41]. Among the factors to consider here is that a worker may be exposed to multiple agents and that such agents may be associated with both malignant and nonmalignant illness. Approaches to integration of screening for health effects related to exposure to multiple agents in the workplace are described in the literature [100]. When agents are known or suspected to be associated with both malignant and nonmalignant illness, issues related to latency will need to be considered as the screening program develops over time. For example, the unprecedented occupational exposures that occurred related to the attack on the World Trade Center (WTC) in New York City are being partly addressed by a screening, surveillance, and medical treatment program [101]. Issues concerning cancer endpoints related to potential occupational exposure during the WTC attack and subsequent work may become of increasing importance in the future [102]. Emerging occupational exposures also present a challenge in the consideration of medical screening and prevention of occupational cancer as a component of a complete occupational health program. For example, health concerns and issues related to medical screening have been raised relative to the increasing development and use of nanomaterials [103, 104]. The principles underlying the rationale for screening and how screening for endpoints including occupational cancer fit into a program of prevention should be carefully considered for those workers potentially exposed to agents for which evidence of toxicity is emerging [105–107].

Acknowledgments The authors thank Eileen Storey, Lynne Pinkerton, and Ellen Galloway for assistance in creating this chapter.

References

1. Boffetta P. Epidemiology of environmental and occupational cancer. Oncogene. 2004;23:6392–403.
2. Landrigan PJ. The prevention of occupational cancer. CA Cancer J Clin. 1996;46:67–9.
3. Siemiatycki J, Richardson L, Straif K, et al. Listing occupational carcinogens. Environ Health Perspect. 2004;112(15):1447–59.
4. Cone JE, Rosenberg J. Medical surveillance and biomonitoring for occupational cancer endpoints. Occup Med. 1990;5(3):563–81.
5. Ward E. Cancer. In: Levy BS, Wegman DH, Baron SL, Sokas RK, editors. Occupational and environmental health: recognizing and preventing disease and injury. 6th ed. Oxford: University Press; 2011. p. 366–97.
6. Bode AM, Dong Z. Cancer prevention research – then and now. Nat Rev Cancer. 2009;9(7):508–16.
7. Gochfeld M. Medical surveillance and screening in the workplace: complementary preventive strategies. Environ Res. 1992;59:67–80.
8. Silverstein MA. Medical screening, surveillance, and the prevention of occupational disease. J Occup Med. 1990;32(10):1032–6.
9. Baker E, Matte T. Occupational health surveillance. In: Rosenstock L, Cullen MR, Brodkin CA, Redlich CA, editors. Textbook of clinical occupational and environmental medicine. 2nd ed. Philadelphia: Elsevier Saunders Company; 2005. p. 76–82.
10. Halperin WE, Ratcliffe J, Frazier TM, Wilson L, Becker SP, Schulte PA. Medical screening in the workplace: proposed principles. J Occup Med. 1986;28(8):547–52.
11. Millar JD. Screening and monitoring: tools for prevention. J Occup Med. 1986;28(8):544–6.
12. Matte TD, Fine L, Meinhardt TJ, Baker EL. Guidelines for medical screening in the workplace. Occup Med. 1990;5(3):439–56.
13. Atkinson Jr AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.
14. Schulte PA. Opportunities for the development and use of biomarkers. Toxicol Lett. 1995;77:25–9.
15. National Research Council Committee on Biological Markers. Biological markers in environmental health research. Environ Health Perspect. 1987;74:3–9.
16. Schulte PA. Problems in notification and screening of workers at high-risk of disease. J Occup Environ Med. 1986;28(10):951–7.
17. Schulte PA. The use of biomarkers in surveillance, medical screening, and intervention. Mutat Res Fundam Mol Mech Mutagen. 2005;592(1–2):155–63.
18. Gallo V, Khan A, Gonzales C, et al. Validation of biomarkers for the study of environmental carcinogens: a review. Biomarkers. 2008;13(5):505–34.
19. Vineis P, Perera F. Molecular epidemiology and biomarkers in etiologic cancer research: the new in light of the old. Cancer Epidemiol Biomarkers Prev. 2007;16(10):1954–65.
20. Swenberg JA, Fryar-Tita E, Jeong YC. Biomarkers in toxicology and risk assessment: informing critical dose-response relationships. Chem Res Toxicol. 2008;21(1):253–65.
21. Gyorffy E, Anna L, Kovács K, Rudnai P, Schoket B. Correlation between biomarkers of human exposure to genotoxins with focus on carcinogen-DNA adducts. Mutagenesis. 2008;23(1):1–18.
22. Valverde M, Rojas E. Environmental and occupational biomonitoring using the comet assay. Mutat Res Rev Mutat Res. 2009;681:93–109.
23. Christiani D, Mehta A, Yu CL. Genetic susceptibility to occupational exposures. Occup Environ Med. 2008;65:430–6.
24. Rueff J, Teixeirab JP, Santosa LS, Gaspara JF. Genetic effects and biotoxicity monitoring of occupational styrene exposure. Clin Chim Acta. 2009;399(1–2):8–23.
25. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
26. National Toxicology Program. Report on carcinogens. 12th ed. Research Triangle Park: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program; 2011.
27. American Cancer Society Cancer Facts & Figures. 2010. http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024113.pdf. Accessed 6 Jun 2011.
28. Straif K. The burden of occupational cancer. Occup Environ Med. 2008;65(12):787–8.
29. Rushton L, Hutchings S, Brown T. The burden of cancer at work: estimation as the first step to prevention. Occup Environ Med. 2008;65:789–800.
30. Viera AJ. Predisease: when does it make sense? Epidemiol Rev. 2011;33:122–34.
31. Smith RA, Cokkinides V, Brooks D, et al. Cancer screening in the United States, 2011: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin. 2011;61(1):8–30.
32. Cancer prevention and control. http://www.cdc.gov/cancer/dcpc/prevention/screening.htm. Accessed 6 Jun 2011.
33. Recommendations for adults – cancer. http://www.uspreventiveservicestaskforce.org/adultrec.htm#cancer. Accessed 6 Jun 2011.
34. Smith RA, Mettlin CJ. Cancer detection. In: Lenhard Jr RE, Osteen RT, Gansler T, editors. Clinical oncology. Atlanta: American Cancer Society; 2001. p. 75–122.
35. Levin B, Prorok PC. Principles of screening. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. Oxford: University Press; 2006. p. 1310–7.
36. Smith RA, Mettlin CJ, Davis KJ, Eyre H. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin. 2000;50:34–49.
37. Schulte PA. Some implications of genetic biomarkers in occupational epidemiology and practice. Scand J Work Environ Health. 2004;30(1):71–9.
38. Samuels SW. Medical surveillance-biological, social, and ethical parameters. J Occup Environ Med. 1986;28(8):572–7.
39. Samuels SW. The Selikoff agenda and the human genome project: ethics and social issues. In: Samuels SW, Upton AC, editors. Genes, cancer, and ethics in the work environment. Beverly Farms: OEM Press; 1998. p. 3–9.
40. Screening and surveillance: a guide to OSHA standards. http://www.osha.gov/Publications/osha3162.pdf. Accessed 23 Jun 2011.
41. Herbert R, Szeinuk J. Integrating clinical care with prevention of occupational illness and injury. In: Rosenstock L, Cullen MR, Brodkin CA, Redlich CA, editors. Textbook of clinical occupational and environmental medicine. 2nd ed. Philadelphia: Elsevier Saunders Company; 2005. p. 1263–74.
42. Rutstein D, Mullan RJ, Frazier TM, et al. Sentinel health events (occupational): a basis for physician recognition and public health surveillance. Am J Public Health. 1983;73:1054–62.
43. Schulte PA, Ehrenberg RL, Singal M. Investigation of occupational cancer clusters: theory and practice. Am J Public Health. 1987;77(1):52–6.
44. Humphrey LL, Teutsch S, Johnson M. Lung cancer screening with sputum cytologic examination, chest radiography, and computed tomography: an update for the US Preventive Services Task Force. Ann Intern Med. 2004;140(9):740–53.
45. McCunney RJ. Should we screen for occupational lung cancer with low-dose computed tomography? J Occup Environ Med. 2006;48:1328–33.
46. Clin B, Morlais F, Guittet L, et al. Performance of chest radiograph and CT scan for lung cancer screening in asbestos-exposed workers. Occup Environ Med. 2009;66(8):529–34.
47. Statement concerning the national lung screening trial. http://www.cancer.gov/images/DSMB-NLST.pdf. Accessed July 2011.

48. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. New Engl J Med. 2011;365(5):395–409.
49. Wood DE, Eapen GA, Ettinger DS, et al. Lung cancer screening. J Natl Compr Canc Netw. 2012;10:240–65.
50. American Lung Association. Providing guidance on lung cancer screening to patients and physicians. 2012. Available at http://www.lung.org/finding-cures/research-news/new-screening-guidelines/lung-cancer-screening.pdf. Accessed 7 Jun 2013.
51. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012;307(22):2418–2429.
52. Jacobson FL, Austin JH, Field JK, et al. Development of The American Association for Thoracic Surgery guidelines for low-dose computed tomography scans to screen for lung cancer in North America: recommendations of The American Association for Thoracic Surgery Task Force for lung cancer screening and surveillance. J Thorac Cardiovasc Surg. 2012;144(1):25–32.
53. U.S. Preventive Services Task Force (USPSTF). Screening for lung cancer recommendation statement 2013. Available at http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanfinalrs.htm. Accessed 9 April 2014.
54. Mettler F, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology. 2008;248(1):254–63.
55. Brenner D. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology. 2004;231(2):440–5.
56. Markowitz SB, Miller A, Miller J, et al. Ability of low-dose helical CT to distinguish between benign and malignant noncalcified lung nodules. Chest. 2007;131:1028–34.
57. Baldwin DR, Duffy SW, Wald NJ, et al. UK lung screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. Thorax. 2011;66:308–13.
58. Tammemagi MC, Lam SC, McWilliams AM, et al. Incremental value of pulmonary function and sputum DNA image cytometry in lung cancer risk prediction. Cancer Prev Res. 2011;4(4):552–61.
59. Tammemagi MC, Pinsky PF, Caporaso NE, et al. Lung cancer risk prediction: prostate, lung, colorectal and ovarian cancer screening trial models and validation. J Natl Cancer Inst. 2011;103:1–11.
60. Vehmas T. Factors influencing the prevalence of pulmonary nodules in lung cancer screening trials: re-evaluation of a CT study. Ups J Med Sci. 2008;113(3):279–86.
61. Mazzone PJ. Lung cancer screening: an update, discussion, and look ahead. Curr Oncol Rep. 2010;12(4):226–34.
62. Pegna AL, Picozzi G. Lung cancer screening update. Curr Opin Pulm Med. 2009;15(4):327–33.
63. Twombly R. Lung cancer screening debate continues despite international CT study results. J Natl Cancer Inst. 2007;99(3):190–5.
64. Ruder AM, Carreon T, Ward EM, Schulte PA, Halperin W. Bladder cancer. In: Rosenstock L, Cullen MR, Brodkin CA, Redlich CA, editors. Textbook of clinical occupational and environmental medicine. 2nd ed. Philadelphia: Elsevier Saunders Company; 2005. p. 757–66.
65. Schulte PA. Screening for bladder cancer in high-risk groups – delineation of the problem. J Occup Environ Med. 1990;32(9):789–92.
66. Marsh GM, Leviton LC, Talbott EO, et al. Drake chemical workers health registry study – notification and medical surveillance of a group of workers at high-risk of developing bladder cancer. Am J Ind Med. 1991;19(3):291–301.
67. Chen HI, Liou SH, Loh CH, et al. Bladder cancer screening and monitoring of 4,4′-methylenebis(2-chloroaniline) exposure among workers in Taiwan. Urology. 2005;66(2):305–10.
68. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. Urology. 2003;61(1):109–18.
69. Fradet Y. Screening for bladder cancer: the best opportunity to reduce mortality. Can Urol Assoc J. 2009;3(6 Suppl 4):S180–3.
70. Katz MH, Steinberg GD. Editorial comment – bladder cancer screening in a high risk asymptomatic population using a point of care urine based protein tumor marker. J Urol. 2009;182(1):58.
71. Carreon T, Ruder AM, Schulte PA, et al. NAT2 slow acetylation and bladder cancer in workers exposed to benzidine. Int J Cancer. 2006;118(1):161–8.
72. Wang YH, Yeh SD, Shen KH, et al. A significantly joint effect between arsenic and occupational exposures and risk genotypes/diplotypes of CYP2E1, GSTO1 and GSTO2 on risk of urothelial carcinoma. Toxicol Appl Pharmacol. 2009;241(1):111–8.
73. Lotan Y, Elias K, Svatek RS, et al. Bladder cancer screening in a high risk asymptomatic population using a point of care urine based protein tumor marker. J Urol. 2009;182(1):52–7.
74. Chou R, Dana T. Screening adults for bladder cancer: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2010;153(7):461–8.
75. Skin cancer facts. http://www.cancer.org/Cancer/CancerCauses/SunandUVExposure/skin-cancer-facts. Accessed 13 Jun 2011.
76. Silva JH, de Sa' BC, de A'vila ALR, et al. Atypical mole syndrome and dysplastic nevi: identification of populations at risk for developing melanoma – review article. Clinics. 2011;66(3):493–9.
77. Kasparian NA, McLoone JK, Meiser B. Skin cancer-related prevention and screening behaviors: a review of the literature. J Behav Med. 2009;32(5):406–28.
78. Osborne JE. Skin cancer screening and surveillance. Br J Dermatol. 2002;146(5):745–54.
79. Lin JS, Eder M, Weinmann S. Behavioral counseling to prevent skin cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;154(3):190–201.
80. Cohen DE, Bassiri S, Forrester BG, Nethercott J. Skin cancers. In: Rosenstock L, Cullen MR, Brodkin CA, Redlich CA, editors. Textbook of clinical occupational and environmental medicine. 2nd ed. Philadelphia: Elsevier Saunders Company; 2005. p. 811–24.
81. Goldberg MS, Doucette JT, Lim HW, et al. Risk factors for presumptive melanoma in skin cancer screening: American Academy of Dermatology National Melanoma/Skin Cancer Screening Program experience 2001–2005. J Am Acad Dermatol. 2007;57(1):60–6.
82. Markovic SN, Erickson LA, Rao RD, et al. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. Mayo Clin Proc. 2007;82(3):364–80.
83. Wolff T, Tai E, Miller T. Screening for skin cancer: an update of the evidence for the U. S. Preventive Services Task Force. Ann Intern Med. 2009;150(3):194–8.
84. Swetter SM, Waddell BL, Vazquez MD, Khosravi VS. Increased effectiveness of targeted skin cancer screening in the Veterans Affairs population of Northern California. Prev Med. 2003;36(2):164–71.
85. Schmitt J, Seidler A, Diegpen TL, Bauer A. Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis. Br J Dermatol. 2011;164(2):291–307.
86. Kipen HM, Wartenberg D. Lymphohematopoietic malignancies. In: Rosenstock L, Cullen MR, Brodkin CA, Redlich CA, editors. Textbook of clinical occupational and environmental medicine. 2nd ed. Philadelphia: Elsevier Saunders Company; 2005. p. 744–56.
87. McDevitt MA, Condon M, Stamberg J, Karpa JE, McDiarmid M. Fluorescent in situ hybridization (FISH) in bone marrow and peripheral blood of leukemia patients: implications for occupational surveillance. Mutat Res Genet Toxicol Environ Mutagen. 2007;629(1):24–31.

88. Zhang LP, Lan Q, Guo W, et al. Chromosome-Wide Aneuploidy Study (CWAS) in workers exposed to an established leukemogen, benzene. Carcinogenesis. 2011;32(4):605–12.
89. Zhang LP, Tang X, Rothman N, et al. Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells. Cancer Epidemiol Biomarkers Prev. 2010;19(1):80–8.
90. Park EK, Sandrini A, Yates DH, et al. Soluble mesothelin-related protein in an asbestos-exposed population – the dust diseases board cohort study. Am J Respir Crit Care Med. 2008;178(8):832–7.
91. van Meerbeeck JP, Hillerdal G. Screening for mesothelioma – more harm than good? Am J Respir Crit Care Med. 2008;178(8):781–2.
92. Pass HI, Carobone M. Current status of screening for malignant pleural mesothelioma. Thorac Cardiovasc Surg. 2009;21:97–104.
93. U.S. Preventive Services Task Force. Screening for cervical cancer topic page. www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm. Accessed 6 May 2013.
94. U.S. Preventive Services Task Force. Screening for colorectal cancer topic page. www.uspreventiveservicestaskforce.org/uspstf/uspscolo.htm. Accessed 6 May 2013.
95. U.S. Preventive Services Task Force. Screening for breast cancer topic page. www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm. Accessed 6 May 2013.
96. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. Am J Ind Med. 2005;48:419–31.
97. Stevens RG, Hansen J, Costa G, et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. Occup Environ Med. 2011;68:154–62.
98. Clin B, Morlais F, Launoy G, et al. Cancer incidence within a cohort occupationally exposed to asbestos: a study of dose response relationships. Occup Environ Med. 2011;68:832–6.
99. Smith RA, Brooks D, Cokkinides V, et al. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. CA Cancer J Clin. 2013;63(2):87–105.
100. Breysse PN, Weaver V, Cadorette M, et al. Development of a medical examination program for former workers at a Department of Energy National Laboratory. Am J Ind Med. 2002;42(5):443–54.
101. Moline JM, Herbert R, Levin S, et al. WTC medical monitoring and treatment program: comprehensive health care response in aftermath of disaster. Mt Sinai J Med. 2008;75(2):67–75.
102. Moline JM, Herbert R, Crowley L, et al. Multiple myeloma in World Trade Center responders: a case series. J Occup Environ Med. 2009;51(8):896–902.
103. Trout DB, Schulte PA. Medical surveillance, exposure registries, and epidemiologic research for workers exposed to nanomaterials. Toxicology. 2010;269(2–3):128–35.
104. Nasterlack M, Zober A, Oberlinner C. Considerations on occupational medical surveillance in employees handling nanoparticles. Int Arch Occup Environ Health. 2008;81(6):721–6.
105. Fischman M, Storey E, McCunney RJ, Kosnett M. National Institute for Occupational Safety and Health nanomaterials and worker health conference – medical surveillance session summary report. J Occup Environ Med. 2011;53(6 Suppl):S35–7.
106. Schulte PA, Trout DB. Nanomaterials and worker health: medical surveillance, exposure registries, and epidemiologic research. J Occup Environ Med. 2011;53(6 Suppl):S3–7.
107. Nasterlack M. Role of medical surveillance in risk management. J Occup Environ Med. 2011;53(6 Suppl):S18–21.

Role of Registers in Occupational Cancer Control

33

Tom K. Grimsrud and Elisabete Weiderpass

Keywords
Cancer incidence • Cancer registries • Cancer mortality • Cause-of-death register • Exposure • Occupational disease

Introduction

Three hundred years ago, Ramazzini described the clustered occurrence of breast cancer in Italian nunneries and ascribed it to life in celibacy [1]. His finding pointed at central risk factors for this hormone-related disease (see Chap. 22) [2]. Ramazzini profited from a contemporary stark contrast between the lives in two occupational groups: housewives (usually mothers) and nuns. The latter avoided the risk of death connected with pregnancy and labor, leaving them with a greater chance of contracting any common cancer after the age of 50.

Ramazzini's observation was confirmed 260 years later, when Fraumeni reported a 40–60 % higher probability for nuns of dying from breast cancer before the age of 75 compared to other US women [3]. Even in non-Catholic Nordic societies, women with higher education – often seen to postpone their first childbirth – show an incidence of breast cancer 20–30 % above average [4]. The use of medical registers was instrumental for these recent identifications and quantifications of the risk.

Register-based studies of morbidity and mortality connected with occupation started around 1840 in the UK when William Farr identified hazardous work from British death records [5]. Present-day Nordic traditions, which include the assignment of unique personal identification numbers for all citizens in continuously updated population registers, as well as nationwide compulsory cancer registration, have recently been utilized in a long-term follow-up for incident cancers of 15 million people according to occupational group [4]. Information on this project (Nordic Occupational Cancer Study, NOCCA) is freely accessible on the Internet (http://astra.cancer.fi/NOCCA/), and it inspired the writing of this chapter.

In general, some sort of systematic observation and registration is, of course, fundamental for all medical research, and we will restrict the following discussion to the introduction and use of already established registers in occupational cancer control.

What Is a Register?

In a broad sense, a register may present any systematic file or list of individuals, events, or data, often kept as documentation for statistical or fiscal purposes. For health-care services, the use of registers may help assure quality or assist in planning. A registry is the place or work unit where such data are aggregated. Some kind of register data is almost indispensable for the enumeration of a study population, and they may provide the denominator for any estimate of absolute risk or disease rate.

Throughout the last decades, it has been considered essential in epidemiology to define the study group, both for inter-

T.K. Grimsrud, MD, PhD (✉)
Department of Research, Cancer Registry of Norway,
PB 5313 Majorstuen, Oslo N-0304, Norway
e-mail: tom.k.grimsrud@kreftregisteret.no

E. Weiderpass, MD, MSc, PhD
Department of Medical Epidemiology and Biostatistics,
Karolinska Institutet, Stockholm, Sweden

Department of Community Medicine, Faculty of Health Sciences,
University of Tromsø, The Arctic University of Norway,
Tromsø, Norway

Department of Genetic Epidemiology,
Folkhälsan Research Center, Helsinki, Finland

Department of Research, Cancer Registry of Norway,
Oslo, Norway

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_33, © Springer-Verlag London 2014

pretation of the results and for assessment of validity and generalizability [6]. For follow-up studies, death registers are essential in defining end of observation and thereby time at risk.

The two other pillars that modern etiologic epidemiology rests on – the outcome (disease- or cause-specific death) and the exposure of interest – may be acquired in a number of ways. For outcome measures, data from a register are often preferred, as disease registers and cause-of-death registers may both provide independent data on outcome and appropriate age- and gender-specific background rates for comparison. When quality is satisfactory, in terms of completeness, reliability, and linkage possibilities, the register may add valuable data to any study group or reference group.

Historically, however, the detrimental effect of strong carcinogens has often been discovered as a clustering of cancers, rather than by means of register data. Clusters may occur in time, or geographically, or among workers of the same kind, or they may be identified by medical personnel as a "clustering" of similar exposures in a uniform group of patients.

Weak or moderately strong risk factors are less likely to be recognized by cluster observations, and for rare diseases, the use of medical records from a register, hospital, or physicians' files may be indispensable. The benefit of a cross-sectional study can be limited, and even repeated surveys over decades can be subject to selection and uncertainty, especially if they rely on recollection and reporting by participants. Data from registries therefore have become more and more important in studies of low-prevalent chronic diseases that develop over decades, which are typical characteristics of many cancer forms.

Still, it should be underscored that numerous and valuable studies indeed have been conducted in the absence of register data. Large cohorts and careful follow-up for disease or death may very well approach the quality of a good register-based study. Also, diagnostic data from hospitals may contain important details that remain unreported in many registers.

While acknowledging important achievements based on other sources, we would like to continue our discussion with a rather narrow definition of a register. In the following paragraphs, a register designates a set of data on disease, death, or demographic characteristics collected with the ambition to cover completely the population of a state or a nation in an updated and continuous way. For an optimal use, the data should carry identifiers for linkage with information from other sources.

Occupational Cancer Control

The identification of hazards in certain occupations was easier in times when high exposures were common and most people remained in the same occupation throughout their lives. Legislation for the protection of workers' health came in the early 1800s in some countries, and insurance and compensation rules appeared toward the end of that century. These measures were motivated by the ethical and social aspects of a worker losing his life and the family losing its breadwinner as a result of conscientious and devoted labor. The identification of cancer causes has been important for the question of responsibility, and primary prevention must rely on such knowledge.

Through more than two centuries, occupational studies have contributed significantly, not only to better industrial hygiene but to the knowledge of cancer etiology in general. In fact, cancer clusters observed in occupational groups provided the most important leads for recognition of human carcinogens well into the second half of the twentieth century [7].

The stages in occupational cancer control can be illustrated by the early history of nickel-related cancer. The first awareness of an elevated risk of respiratory cancer in nickel refinery workers was prompted by a cluster in the 1920s [8]. A decade later, observed and expected cancer mortality was evaluated in an unpublished report to the company, based on national mortality statistics (Bradford Hill, 1939 – cited in Ref. [9]). By 1949, lung cancer and sino-nasal cancer were considered industrial diseases giving rise to compensation in nickel workers [10]. Another decade passed before the first complete epidemiologic study was published in a medical journal, in the form of a proportional cancer mortality study, based on information from death records [10].

The emergence of modern epidemiology after World War II [6] led to great advances in the characterization of already recognized occupational cancer risks, as well as better opportunities for identification of new ones. Access to large sets of data from health (or disease) registers and additional details on exposure and background conditions from other sources have been indispensable for much of this progress. The information has been used to develop occupational exposure limits and as an incentive to reduce exposures in workplaces.

The term register-based epidemiology seems to be coined by Nordic epidemiologists, although the tradition with systematic collection of data for epidemiologic research is, of course, universal. We will discuss the use of registers and its relation to occupational cancer control in the form of surveillance, etiologic research, prevention, and compensation.

Surveillance and Research

Internationally, there is no uniform system for surveillance of occupational cancer hazards, although most countries in Europe have legislation that requires employers to keep records of workers who are exposed to carcinogens [11]. In Finland, a national register was established in 1979 [12], while Sweden, Denmark, and Norway instruct all employers to keep such registers within their undertaking [13–15]. Employers do not always comply with these rules, and the data may suffer from incompleteness and lack of important details.

Judged by the frequencies of notifications and compensation claims, the occurrence of occupational cancers seems to be underreported worldwide [16–22]. A number of reasons may exist for this incomplete reporting – from a general lack of knowledge of disease etiology to uncertainty in individual cases whether the evidence is sufficient to consider the cancer as occupationally caused. A better recording of relevant exposure could potentially improve the basis for epidemiologic studies and for the evaluation of compensation claims. Interestingly, the underreporting of occupational cancers illustrates the universal challenge associated with completeness and good record keeping in a registry. Good registers need clear definitions for classification of disease, and they profit from networking between institutions, as well as alertness and dedication among the employees.

In Norway, notification to the Cancer Registry of some specific cancer types (lung cancer, mesothelioma, sino-nasal cancer) prompts the addressing of routine individual information in order to increase the patient's awareness of compensation rules [23].

The acquisition of reliable data on occupational exposure represents a great challenge in the evaluation of occupational cancer, both for research purposes and for individuals claiming compensation. Expert assessment of workplace exposure, or self-reported exposure information, preferably supported by measurements and detailed local knowledge, has the potential to provide reasonably good data about chemical exposures [24]. Still, exposure assessment is often found to be a weak part of occupational cancer studies.

Personnel Lists, Family Registers, and Pension Funds

In the absence of registers of carcinogenic exposure, personnel lists from industries or workshops may identify groups with a higher-than-average probability of such exposure. An industry-specific approach has been essential for the identification of many carcinogens and for the advances in the understanding of occupational cancer disease. For population- or hospital-based studies, the assessment of occupational influence on disease risk often relies on work history obtained by interview or questionnaire. Although job-specific exposure estimates may be developed subsequently by experts in industrial hygiene, a problem may remain with the low number of workers from each industry and a corresponding heterogeneity in the exposure groups. Duration of work is often used as a proxy metric for the degree of exposure, and it may be one of the parameters that can be estimated with least misclassification.

Progress in studies of genes, polymorphisms, and hereditary susceptibility to cancer has led to increased interest in data on family relationships. In some countries, family members can be identified through register data, and such data may potentially add to the value of studies of effects from occupational exposure.

When personnel lists or disease and death registers are unavailable nationally, pension funds or company benefits records have proved useful for the identification of death or disease. The usefulness of pension funds is dependent on their historical completeness, and the value may be severely threatened if company files have been subject to routine removal of deceased individuals, retired workers, and of people claiming compensation.

Cancer and Cause-of-Death Registration

Cancer registration, in terms of continuous notification of new diagnoses of cancer (incident cancers) at the state or national level, has taken place in a number of countries since the 1940s and 1950s. The aims have been to improve the etiologic understanding and to provide long-term surveillance of distribution and trends in order to facilitate the organization of cancer care and prevention [25]. Registration of deaths typically has a substantially longer history, with provision of data for demographic statistics, disease surveillance, and research.

For highly lethal cancers such as lung cancer, cause-of-death registers may offer almost equally good opportunities for surveillance and research as do cancer registers. Incidence registers are considered superior for the study of less lethal cancers and for studies that address details in histology, diagnoses, and therapy. Alternatively, hospital-based cancer registries or discharge lists can contribute directly to a study, although some uncertainty may remain as to the representativity and the outline of the underlying study group.

Some cancer registries do not include as incident cancers those that are notified from death certificates only. For highly lethal cancer forms, this practice can lead to a situation where the mortality rates equal or exceed the incidence rates, as seen for lung cancer and pancreatic cancer in Swedish men in the NORDCAN database [26, 27]. This phenomenon calls for attentiveness when trends or incidence rates are compared within nations or across borders [28].

It should be pointed out that material contributions to the occupational cancer literature have, in fact, come from studies that were *not* based on national cancer incidence data or cause-of-death registers. Hospital discharge data, or hospital-based cancer registries, may contribute high-quality information, both for case identification and for selection of appropriate reference groups. For case-control studies, controls may also be sampled from the general population. Combined hospital- and population-based studies in Canada have contributed importantly on cancer risk in relation to numerous occupational exposures [29, 30]. Large follow-up

studies of exposed population samples in China have been successfully performed, and they may surpass register-based studies in size and quality [31]. In the UK, the occupational cancer burden was recently estimated from the occupational cancer literature and a number of national data sources [32].

Protection of Personal Data

Since around 1980, public and political attention has been directed toward a reinforcement of the individual right to decide participation in processing of personal or sensitive data (autonomy). Epidemiologists have commented that this trend has hampered the feasibility to conduct national censuses [33] and that it has become an obstacle for epidemiologic research [34].

It is easy to accept that informed consent is required before an individual is included in a trial of a new therapy or an intervention study. Slightly less obvious is the claim that informed consent is necessary for an observational study conducted with discretion and care, especially when it is performed under the license of an ethical board. In retrospect, it may be argued that epidemiologists should have put more effort in the education of the public about the common interest shared by most people in knowledge derived from epidemiologic studies [35]. The benefit of avoiding a potential selection bias due to differential participation in a cohort study has not been fought for with the same zeal as that seen from one-sided advocates for protection of sensitive data.

Despite the large amount of important information that has been derived from register-based studies, the establishment of new registers has met resistance. Skepticism may be expressed toward any research or register activity that potentially can be taken as offensive or intrusive. These attitudes may restrict society's ability to address issues of major relevance for the quality of health care, for protection of public health, and for workers' safety and health in an efficient and appropriate way [36].

The system is clearly counterproductive when employers are required to register all workers who are exposed to carcinogens, meanwhile the ethical board works hard to secure workers' right to withdraw from, and thereby weaken, studies designed to investigate effects on their health. Such a threat against good conduct of a study is in conflict with the interest that most people share in being properly informed about cancer hazards at the workplace.

Strengths and Limitations of Register-Based Studies

Occupational cancer studies are mostly observational in design. Intervention studies (prevention or treatment) may, under certain circumstances, be acceptable for randomization and thus approximate an experimental situation. Else, the observational design forces epidemiologists to address potential biases that may distort the associations and lead to alternative and potentially false explanations to the findings. Register-based research has a number of strengths that may improve the control of these biases.

The value of a register-based study will, however, vary with the characteristics and qualities of the register. Typically, these are questions of validity, completeness, and timeliness [37, 38].

Selection Bias

Studies based on register linkage and a complete enumeration of citizens, workers, or cancer cases have the potential to address or avoid problems with response rate, or self-selection, which can be influenced by socioeconomic status, disease outcome, or exposure-related factors. Studies performed on complete data from registers with good coverage are valuable in any discussion of generalizability.

A bias induced by a funding company may be difficult to recognize, although the possibility of such effects always should be kept in mind, stressful as it is for employers and owners to be charged with responsibility for occupational health hazards. There may also be economic interests driving this bias. Industrial cooperation can be useful or even *necessary* in occupational cancer studies, but the biases and pitfalls can be detrimental. The simple act of claiming compensation for a work-related disease may – intentionally or unintentionally – lead to removal of the individual data in question from a personnel file later to be used for a follow-up study.

The risk of introducing errors can increase when requirements for protection of personal data are strengthened, because quality control of de-identified or anonymous data often becomes more challenging. Data from complete and independent registers may help to assess validity of the data.

Information Bias

When cohort enumeration, exposure information, and disease or mortality data are recorded in this order or alternatively if they come from independent historical sources, many potential problems associated with retrospective collection of information may be avoided. An information bias, such as recall bias or attribution, can potentially be strong and difficult to measure.

Issues involving occupational cancer often attract much attention in the media, and claims of compensation, or pressure from interest groups, may create a situation where it is difficult to obtain unbiased information by interview or

questionnaire. Important issues may end up as out of reach for common retrospective research methods. Any scientific clarification may then ultimately rely on the availability of historically registered data for the outline of a study group, for exposure data, and for outcome.

Challenges

Through the last 50 years, industrial hygiene has reduced the risk of cancer in many industries and trades. New or remaining unrecognized hazards cannot be expected to compare in severity with those revealed in studies from the twentieth century. The identification of low-risk exposures requires larger and more detailed data to obtain necessary statistical strength. Data from registers may provide a rapid, economic, and secure access to complete data sets with more cases than that seen in most epidemiologic studies.

Still, as always the scientific benefit depends on data quality. National registers may be superior in quantity and completeness, but the level of details in the classification of diagnoses, exposure, and background factors may be inferior compared to data collected for a specific study. Access to exposure measurements, good procedures for exposure assessment, and collection of biological samples for biomarkers therefore remain universal challenges.

The socioeconomic homogeneity, typical of an occupational cohort, supplied with outcome data from a register may create a sound platform for internal comparisons of cancer risk. External reference groups, however, can have other lifestyle characteristics than the study group; and differences in smoking habits, alcohol consumption, diet, or leisure time activities may confound the risks otherwise ascribed to occupation. Sometimes data on lifestyle characteristics are available at an aggregated level [39], but for large registers of cancer- or cause-specific mortality, details on potentially relevant confounders are often limited or absent.

Nordic Experience and Cooperation

The Nordic tradition with numerous population-based registers has paved the way for large studies that can be based on more than 25 million present-day inhabitants, or subsamples thereof, inclusive of millions who have died during the last decades. The rather uniform structure of these country's national health-care systems and the good population coverage of the registers add to the comparability. Cancer registries were established in all five Nordic countries between 1942 and 1958, and the national population registers are continuously updated, and they are based on unique personal identification numbers (PIDs) given to each citizen.

PIDs and Linkage

Unique PIDs were introduced in the Nordic countries between 1947 and 1968, that is, somewhat later than the start of cancer registration. The PIDs are based on date of birth and gender and are organized by governmental institutions. The system is widely used for public services; for taxation, banking, and health care; and in passports; and they are mostly perceived as beneficial by the public. For research, it is highly useful that PIDs facilitate computerized linkage to governmental statistical data and data on cancer incidence and mortality. The PIDs also allow for linkage between rosters of workers and disease registers, as well as a number of other registers with data that may influence cancer risk.

The transition from manual linkage – based on name, residence, and date and place of birth – to electronic linkage by PIDs constituted a great improvement in study quality, shown by a decrease in the frequency of linkage failures in Finland [40].

Another advantage of the PIDs rarely focused on is the improved possibility of preserving anonymity. PIDs are less recognizable and need not follow the data provided for the researcher, for laboratories, or data handlers, since linkage can be performed in a completely mechanical and computerized way, and the PID easily may be substituted by a code or artificial number. The cost is the negative effect this may have on the opportunity for quality control, which has already been commented on.

As mentioned above, the enthusiasm for better protection of personal data has made it more difficult to conduct observational epidemiologic studies even in the Nordic countries [35]. Admittedly, though, we have seen improvements in the information from research institutions to the public, and ethical deliberations are now included in the planning of every new study. In the long run, a system based on mutual trust may be better than one based on sheer obedience.

Registers Providing Background Data

National statistical offices may provide individual data on length and type of education; family relationships; occupation, industry, and trade registered in national censuses; current and historical data on employments and employers; and information on type and size of income. The quality, the historical span, and the completeness of these data may vary, and an ethical approval has to be obtained, which can be easier when data can be de-identified or made anonymous before delivery to the researcher. Data on residence and vital status are continuously updated and are more readily available when they are not linked to sensitive information.

Cause-of-death registers have the longest traditions for research on occupational cancer and often provide data to

studies of severe chronic disease. However, death records are usually not subject to the same quality control as may be the routine in a cancer registry. Nordic cancer registries are acknowledged to be of high quality, offering good population coverage and completeness of data [27, 41–45].

Except for highly lethal cancers (lung and pancreas, see above), and some historical changes in registration practice, comparisons of incident cancer data between the Nordic countries are largely valid, and they have been facilitated through an open-access and interactive website in the NORDCAN database [26].

Nordic Studies on Occupational Cancer

For some forms of cancer, the mean time between exposure and diagnosis may span several decades. The Nordic model offers a good opportunity to repeat and extend follow-up studies with additional entrants, updated employment histories, and more background data.

Extended follow-ups and new study designs may give a more complete picture of the cancer burden, along with more precise risk estimates and a better understanding of the causal pattern. Several lines of studies in Nordic countries have provided important information on health effects from specific exposures, such as copper smelters exposed to arsenic [46–50], nickel refinery workers [51–57], aluminum smelters [58–60], and silicon carbide smelter workers [61, 62]. A review of Nordic occupational cancer studies was conducted by Kjærheim in 1999 [63].

Occupational data from national censuses offer virtually complete cross-sectional pictures of the working population. Nordic linkage studies based on occupation at census and subsequent cancer incidence have been performed since the 1980s [64–66]. The Nordic scientists followed the track of colleagues in large countries like the USA, UK, Canada, and Australia, examples of which were briefly listed by Blair [67].

A cooperative study between four of the Nordic countries in 1999 was based on occupation recorded for the 1970 census and subsequent incident cancers [68]. An even larger study of the same kind was published 10 years later, based on occupational data from several censuses between 1960 and 1990 for 15 million people, some of whom were subsequently diagnosed with 2.8 million cancer cases until about 2005 [4]. For the latter project (NOCCA), national matrices with estimates of occupational carcinogenic exposure have also been developed [69], with contribution by experts from each country. The latter effort was inspired by the 10 years older Finnish occupational exposure matrix [70]. For some of the countries, the Nordic exposure matrix and the linked census and cancer data allow for more detailed studies.

Present and Future Challenges

The study of genes, intracellular regulation, and carcinogenic process has improved our understanding of pathways and causes of cancer. Still, one should remember that the epidemiologic frames are essential for assessing the relevance of biomolecular observations. The long time it takes for some cancers to appear in man implies that animal experiments, identification of biomarkers, and mechanistic studies will become increasingly important for an early evaluation of new and suspected carcinogens.

A future challenge is to combine traditional studies with these new sources of information and to find the best use of biobanks and pathology specimens. For the conduct of such studies, researchers need to convince the public that the benefit of better knowledge probably will outweigh the potential threat against protection of personal data.

Conclusion

Independent registers of cancer incidence, cause-specific mortality, occupation and industry, education, and other demographic data constitute useful tools for surveillance and research on occupational cancer and for the study of effects of carcinogenic exposure in general. Regulations established for personal data protection have been seen to hamper the use of health registers and the building of new ones, and the growing demand of better knowledge may motivate a change in the balance between personal data autonomy and research needs. The best of the existing data sources must be incorporated in studies with additional exposure measurements and biomolecular analyses.

References

1. Ramazzini B. De morbis artificum [diseases of workers]. 2nd ed. Padova: Archi-Lycæo; 1703. p. 156. [In Latin] http://archive.org/stream/bernramazzinide00porzgoog#page/n160/mode/1up. Accessed 17 Nov 2012.
2. Labrèche F, Goldberg MS, Weiderpass E. Chapter 27. Breast cancer. In: Anttila S, Boffetta P, Straif K, editors. Occupational cancer. Springer.
3. Fraumeni Jr JF, Lloyd JW, Smith EM, Wagoner JK. Cancer mortality among nuns: role of marital status in etiology of neoplastic disease in women. J Natl Cancer Inst. 1969;42(3):455–68.
4. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48(5):646–790.
5. Whitehead M. William Farr's legacy to the study of inequalities in health. Bull World Health Organ. 2000;78(1):86–7.
6. Rothman KJ, Greenland S, Lash TL, editors. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 1–851.
7. Doll R. Part III: 7th Walter Hubert lecture. Pott and the prospects for prevention. Br J Cancer. 1975;32(2):263–72.
8. Doll R. Nickel exposure: a human health hazard. IARC Sci Publ. 1984;53:3–21.

9. Morgan JG. Some observations on the incidence of respiratory cancer in nickel workers. Br J Ind Med. 1958;15(4):224–34.
10. Doll R. Cancer of the lung and nose in nickel workers. Br J Ind Med. 1958;15(4):217–23.
11. European Union Carcinogens Directive (2004/37/EC). https://osha.europa.eu/en/legislation/directives/exposure-to-chemical-agents-and-chemical-safety/osh-directives/directive-2004-37-ec-indicative-occupational-exposure-limit-values. Accessed 17 Nov 2012.
12. Kauppinen T, Saalo A, Pukkala E, Virtanen S, Karjalainen A, Vuorela R. Evaluation of a national register on occupational exposure to carcinogens: effectiveness in the prevention of occupational cancer, and cancer risks among the exposed workers. Ann Occup Hyg. 2007;51(5):463–70.
13. Danish Working Environment Authority. Executive order on measures to protect workers from the risks related to exposure to carcinogenic substances and materials at work. Copenhagen: Danish Working Environment Authority; 2005. https://arbejdstilsynet.dk/en/engelsk/regulations/executive-orders/908-kraeftrisiko-stoffer-og-materialer.aspx. Accessed 17 Nov 2012.
14. Arbetsmiljöverket [Work Environment Authority]. Chemical hazards in the working environment (provisions and general recommendations). Stockholm: Arbetsmiljöverket; 2011. http://www.av.se/dokument/inenglish/legislations/eng1119.pdf. Accessed 16 Nov 2012.
15. Arbeidstilsynet [Norwegian Labour Inspection]. Kjemikalier [chemicals]. Oslo: Arbeidstilsynet; 2012. [In Norwegian] http://www.arbeidstilsynet.no/fakta.html?tid=206422#Arbeidstakerregister. Accessed 16 Nov 2012.
16. Safe work Australia. Occupational disease indicators. http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/724/Occupational-Disease-Indicators-report-2012.pdf. Accessed 16 Nov 2012.
17. Cancer care Ontario. Occupational cancer is the leading cause of work-related fatalities in Ontario. Ontario Cancer Facts, Special Issue. 2012. https://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=129578; https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=129585. Accessed 17 Nov 2012.
18. Teschke K, Barroetavena MC. Occupational cancer in Canada: what do we know? CMAJ. 1992;147(10):1501–7.
19. Scarselli A, Scano P, Marinaccio A, Iavicoli S. Occupational cancer in Italy: evaluating the extent of compensated cases in the period 1994–2006. Am J Ind Med. 2009;52(11):859–67.
20. Gisquet E, Chamming's S, Pairon JC, Gilg Soit Ilg A, Imbernon E, Goldberg M. The determinants of under-reporting occupational diseases. The case of mesothelioma. Rev Epidemiol Sante Publique. 2011;59(6):393–400.
21. Hansen J, Rasmussen TR, Omland Ø, Olsen JH, Danish National Board of Industrial Injuries. Registration of selected cases of occupational cancer (1994–2002) with the Danish National Board of Industrial Injuries. Ugeskr Laeger. 2007;169(18):1674–8.
22. Wergeland E, Bjerkedal T, Andersen A, Mowé G. Use of occupational disease benefits. Tidsskr Nor Laegeforen. 1997;117(2):211–6 [in Norwegian].
23. Cancer in Norway 2010. Oslo: Cancer Registry of Norway; 2012. p. 92. http://www.kreftregisteret.no/no/Generelt/Nyheter/Cancer-in-Norway-2010/. Accessed 10 Oct 2012.
24. Teschke K, Olshan AF, Daniels JL, et al. Occupational exposure assessment in case-control studies: opportunities for improvement. Occup Environ Med. 2002;59(9):575–93.
25. Wagner G. History of cancer registration. In: Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG, editors. Cancer registration: principles and methods. IARC Scientific Publication No. 95. Lyon: International Agency for Research on Cancer; 1991. p. 3–6.
26. Engholm G, Ferlay J, Christensen N, et al. NORDCAN – a Nordic tool for cancer information, planning, quality control and research. Acta Oncol. 2010;49(5):725–36.
27. Lund EM, Clemmesen IH, Storm HH. Survey of Nordic cancer registries. In: ANCR, editor. Survey of Nordic cancer registries. Copenhagen: Danish Cancer Society; 2000. p. 7–18. http://www.ancr.nu/survey.asp. Accessed 17 Nov 2012.
28. Luo J, Adami HO, Reilly M, Ekbom A, Nordenvall C, Ye W. Interpreting trends of pancreatic cancer incidence and mortality: a nation-wide study in Sweden (1960–2003). Cancer Causes Control. 2008;19(1):89–96.
29. Siemiatycki J, Gérin M, Richardson L, Hubert J, Kemper H. Preliminary report of an exposure-based, case-control monitoring system for discovering occupational carcinogens. Teratog Carcinog Mutagen. 1982;2(2):169–77.
30. Vida S, Pintos J, Parent ME, Lavoué J, Siemiatycki J. Occupational exposure to silica and lung cancer: pooled analysis of two case-control studies in Montreal, Canada. Cancer Epidemiol Biomark Prev. 2010;19(6):1602–11.
31. Hayes RB, Yin SN, Dosemeci M, et al. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine–National Cancer Institute Benzene Study Group. J Natl Cancer Inst. 1997;89(14):1065–71.
32. Rushton L, Hutchings SJ, Fortunato L, et al. Occupational cancer burden in Great Britain. Br J Cancer. 2012;107 Suppl 1:S3–7.
33. Redfern P. Which countries will follow the Scandinavian lead in taking a register-based census of population? J Off Stat. 1986;2(4):415–24.
34. Peto J. Cancer epidemiology in the last century and the next decade. Nature. 2001;411(6835):390–5.
35. Lynge E. Implication for epidemiology of disease registers. Public Health Rev. 1993–1994;21(3–4):263–70.
36. Hansson MG. Need for a wider view of autonomy in epidemiological research. BMJ. 2010;340:c2335.
37. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. Eur J Cancer. 2009;45(5):747–55.
38. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. Eur J Cancer. 2009;45(5):756–64.
39. Haldorsen T, Andersen A, Boffetta P. Smoking-adjusted incidence of lung cancer by occupation among Norwegian men. Cancer Causes Control. 2004;15(2):139–47.
40. Pukkala E. Use of record linkage in small-area studies. In: Elliott P, Cuzick J, English D, Stern R, editors. Geographical & environmental epidemiology: methods for small-area studies. Oxford: Oxford University Press; 1992. p. 125–31.
41. Sigurdardottir LG, Jonasson JG, Stefansdottir S, et al. Data quality at the Icelandic Cancer Registry: comparability, validity, timeliness and completeness. Acta Oncol. 2012;51(7):880–9.
42. Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health. 2011;39(7 Suppl):42–5.
43. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27–33.
44. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218–31.
45. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. Acta Oncol. 1994;33(4):365–9.
46. Pershagen G, Elinder CG, Bolander AM. Mortality in a region surrounding an arsenic emitting plant. Environ Health Perspect. 1977;19:133–7.
47. Axelson O, Dahlgren E, Jansson CD, Rehnlund SO. Arsenic exposure and mortality: a case-referent study from a Swedish copper smelter. Br J Ind Med. 1978;35(1):8–15.
48. Wall S. Survival and mortality pattern among Swedish smelter workers. Int J Epidemiol. 1980;9(1):73–87.

49. Pershagen G. Lung cancer mortality among men living near an arsenic-emitting smelter. Am J Epidemiol. 1985;122(4):684–94.
50. Sandström A, Wall S. Cancer incidence among male salaried employees at a smeltery in Northern Sweden. Acta Oncol. 1993;32(1):9–14.
51. Pedersen E, Høgetveit AC, Andersen A. Cancer of respiratory organs among workers at a nickel refinery in Norway. Int J Cancer. 1973;12(1):32–41.
52. Magnus K, Andersen A, Høgetveit AC. Cancer of respiratory organs among workers at a nickel refinery in Norway. Int J Cancer. 1982;30(6):681–5.
53. Andersen A, Berge SR, Engeland A, Norseth T. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occup Environ Med. 1996;53:708–13.
54. Grimsrud TK, Berge SR, Martinsen JI, Andersen A. Lung cancer incidence among Norwegian nickel-refinery workers 1953–2000. J Environ Monit. 2003;5:190–7.
55. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? Epidemiology. 2005;16:146–54.
56. Karjalainen S, Kerttula R, Pukkala E. Cancer risk among workers at a copper/nickel smelter and nickel refinery in Finland. Int Arch Occup Environ Health. 1992;63(8):547–51.
57. Anttila A, Pukkala E, Aitio A, Rantanen T, Karjalainen S. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. Int Arch Occup Environ Health. 1998;71(4):245–50.
58. Andersen A, Dahlberg BE, Magnus K, Wannag A. Risk of cancer in the Norwegian aluminium industry. Int J Cancer. 1982;29(3):295–8.
59. Rønneberg A, Andersen A. Mortality and cancer morbidity in workers from an aluminium smelter with prebaked carbon anodes–Part II: cancer morbidity. Occup Environ Med. 1995;52(4):250–4.
60. Romundstad P, Andersen A, Haldorsen T. Cancer incidence among workers in six Norwegian aluminum plants. Scand J Work Environ Health. 2000;26(6):461–9.
61. Romundstad P, Andersen A, Haldorsen T. Cancer incidence among workers in the Norwegian silicon carbide industry. Am J Epidemiol. 2001;153(10):978–86.
62. Bugge MD, Kjærheim K, Føreland S, Eduard W, Kjuus H. Lung cancer incidence among Norwegian silicon carbide industry workers: associations with particulate exposure factors. Occup Environ Med. 2012;69(8):527–33.
63. Kjaerheim K. Occupational cancer research in the Nordic countries. Environ Health Perspect. 1999;107 Suppl 2:233–8.
64. Wiklund K, Einhorn J, Wennström G, Rapaport E. A Swedish cancer-environment register available for research. Scand J Work Environ Health. 1981;7(1):64–7.
65. Andersen A, Bjelke E, Langmark F. Cancer in waiters. Br J Cancer. 1989;60(1):112–5.
66. Lynge E. Occupational mortality and cancer analysis. Public Health Rev. 1990–1991;18(2):99–116.
67. Blair A. Occupation and cancer in the Nordic countries. Acta Oncol. 2009;48(5):644–5.
68. Andersen A, Barlow L, Engeland A, Kjaerheim K, Lynge E, Pukkala E. Work-related cancer in the Nordic countries. Scand J Work Environ Health. 1999;25 Suppl 2:1–116.
69. Kauppinen T, Heikkilä P, Plato N, et al. Construction of job-exposure matrices for the Nordic Occupational Cancer Study (NOCCA). Acta Oncol. 2009;48(5):791–800.
70. Kauppinen T, Toikkanen J, Pukkala E. From cross-tabulations to multipurpose exposure information systems: a new job-exposure matrix. Am J Ind Med. 1998;33(4):409–17.

Appendix: Questionnaire on Exposure to Asbestos

Personal Data

Name_____
Street address_____
Postal code and city/town_____ __
Area code and home telephone number_____
Occupation (current or most recent)_____
Employer (current or most recent)_____
Year of retirement (for pensioners) _____

Information on Sector of Employment

Record the work time (from year to year) for sectors and tasks in which you have primarily worked (e.g., years 1945–1946, 1963–1968, 1975–).

Building industry	Years
1. Installing new pipes _____	_____
2. Disassembling old pipelines _____	_____
3. Pipe insulation work _____	_____
4. Other insulating works _____	_____
5. Electrical installations works _____	_____
6. Other construction work in new buildings ____	_____
7. Other construction work in renovations _____	_____

Shipbuilding industry	Years
8. Equipment work (after launching) _____	_____
9. Works in renovated ships_____	_____
10. Asbestos spraying and insulation works_____	_____
11. Other works in the shipbuilding industry_____	_____

Asbestos product industry and mines	Years
12. Work in the manufacturing of asbestos products_____	_____
13. Work in asbestos mines_____	_____
14. Other work in the asbestos product industry_____	_____

Power plants	Years
15. Insulating and dismantling boilers_____	_____

Lining of industrial ovens (glass, cement, metal industry, foundries)	Years
16. Insulating and dismantling ovens_____	_____
_____	_____

Car repair shops	Years
17. Brake and clutch work_____	_____
18. Other work in car repair shop_____	_____
19. Other work-related matters_____	_____

List the sectors other than those listed above that you have primarily been employed in. Mention your occupation during these work periods.

Occupation	Years
e.g., farmer	1955–1965
_____	_____
_____	_____
_____	_____
_____	_____

Information on Occupation

Record the work time (from year to year) for occupations in which you have primarily worked (e.g., years 1968–1970, 1972–1974).

Construction industry occupations	Years
1. Insulation sheet metal worker_____	_____
2. Insulator_____	_____
3. Cleaner_____	_____
4. Tin worker, sheet metal worker_____	_____

	Years
5. Driller_____	_____
6. Pipe fitter_____	_____
7. Pipe insulator_____	_____
8. Construction worker_____	_____

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0, © Springer-Verlag London 2014

	Years
9. Female construction worker____	_____
10. (Construction site) cleaner_____	_____
11. Renovation worker (janitor) _____	_____
12. General worker, unskilled man_____	_____
13. Electricity installer, electrician _____	_____
14. Filler applier _____	_____
15. Other occupations in the building industry _____	_____
Please specify: _____ _____	_____

Shipbuilding industry occupations	Years
16. Insulator_____	_____
17. Maintenance technician_____	_____
18. Ship cleaner_____	_____
19. Plater_____	_____
20. Firefighter_____	_____
21. Pipe fitter_____	_____
22. Interior decoration fitter_____	_____
23. Electricity installer, electrician _____	_____
24. Other shipbuilding occupations _____	_____
With work taking place in a ship in the outfitting stage _____	_____
Please specify: _____	_____

Asbestos product industry occupations	Years
25. Asbestos sewer_____	_____
26. Asbestos miller_____	_____
27. Asbestos sawyer_____	_____
28. Asbestos pipe maker_____	_____
29. Insulation mass mixer_____	_____
30. Quarry employee_____	_____
31. Beater worker _____	_____
32. Maintenance technician_____	_____
33. Machine operator, machine user____	_____
34. Quarry employee_____	_____
35. Cleaner (production) _____	_____
36. Bagger_____	_____
37. Other asbestos industry occupations ___	_____
Please specify: _____	_____

Power plant occupations	Years
38. Industry_____	_____
39. Oven operator_____	_____
40. Melter_____	_____

Asbestos Exposure

Have you been involved in the following tasks with a possibility of exposure to asbestos-containing products? Answer by ticking the box next to the applicable option.
If your answer is "yes," please enter the years when you were employed in such work (e.g., 1956–1966, 1968–1982)

	No	Don't know	Yes	Years
1. Dismantling asbestos-containing materials				_____
2. Carrying out asbestos spray application tasks (fire protection, heat and acoustic insulation)				_____
3. Carrying out pipe insulation tasks using insulation mass				_____
4. Fitting boiler, oven, hot water boiler, machinery and electric equipment, heat and fire insulation				_____
5. Fitting asbestos cement plates, asphalt felt on roofs				_____
6. Fitting wall panels, interior wall panels, interior lining panels,				_____
acoustic panels, and fire protection panels				_____
(examples of commercial products can be listed here)				_____
7. Dismantling vinyl flooring or mass flooring				_____

Index

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0, © Springer-Verlag London 2014

F

R

S