Sisko Anttila
Paolo Boffetta
Editors

Occupational Cancers

Second Edition

Springer

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Foreword

A Cartography of Occupational Cancer Prevention

The radical strategy for combating cancer is to identify—and when possible—eliminate, or remedy the underlying causes of human cancer. 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, edited by S. Anttila and P. Boffetta, has reached its second edition, reflecting its practical success and usefulness in describing 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 more than 100,000 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 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, for example, China and Russia, and India is the largest importer. Brazil also has mines. The World Health Organization and the International Labour Organization have 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 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 tumor, in humans. Soon, it was revealed that VCM workers in many countries had developed this type of tumor [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]. The role of so-called molecular epidemiology in the study of cancer etiology and prevention is on the rise.

At the close of the twentieth century, many predicted that we were entering a period of "precision" prevention, as a consequence of the sequencing of the human genome [9]. Linking genomics knowledge into prevention gave hope to inaugurate a new era with unforeseen possibilities for cancer screening and for detection of early warning signs.

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 nonionizing radiation [10, 11].

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, 12]. Today's wide interest in developing engineered nanomaterial-based products has also been cautioned by the previous lessons learnt from asbestos fibers [13, 14].

In the face of the new findings of our present as a moment when all is in flux, when molecularization of biomedicine is giving us new tools to discover the molecular secrets of the cancer process, we need to confess that the actual progress in "precision" prevention of occupational cancer has remained meagre. Regardless of this pessimism, 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 understanding the mechanisms of cancer causation 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, 15]. I am wary of epochal claims, and it is necessary to recognize that the primary prevention still remains the most effective way of preventing occupational cancer. Occupational cancer continues to be of high priority in prevention, with a significant focus on diminishing the avoidable burden of cancers worldwide.

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Preface

When we edited the first edition of this book on occupational cancer, we were motivated first of all by the fact that a great proportion of occupational cancers are not recognized even in postindustrial 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 nonexposed, 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 lifestyle 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.

These considerations are still valid today. However, our understanding of occupational causes of cancer and the underlying mechanisms has greatly evolved since the publication of the previous edition of the book and justified our decision to update it.

Our primary aim remains 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. In this respect, we added to this second edition one chapter focused on the experience of the practicing occupational physician. To our knowledge, this remains the only 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 cancer in question with various occupations and with exposure to specific carcinogens and touch other environmental and lifestyle 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. The success of the first edition of the book with the public confirms the usefulness of our initiative.

There is an 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.

As in the first edition, we asked the authors not to address jurisdiction or compensation policies, 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 is a disputable question. 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 the individual chapters remains with the 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 the second edition of this book will continue to serve well and maintain 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.

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We express our deepest gratitude to all authors, the authors who updated chapters with new research data and who wrote new chapters on topics not covered in the first edition. This book rests on the enormous amount of expertise and intellect the authors have put into writing the chapters. The second edition is based largely on the first edition, the origin and contents of which were greatly influenced by our valued colleagues, above others, Dr. Kurt Straif. Finally, we thank our publisher and the Springer editors, Joanna Bolesworth and Prakash Jagannathan, who made possible this book to materialize.

Contents

Historical Overview of Occupational Cancer Research

1

Jack Siemiatycki

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 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

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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 8 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 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

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

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 also 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 has 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]; and lung cancer among asbestos miners and asbestos fibers [63]). 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]; and bladder cancer and benzidine [105]). For some associations, the evidence is suggestive (e.g., breast cancer and shift work [106]; and 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, may address a set of related agents, or 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 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

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

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 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.

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 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

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 five 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 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

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

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 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

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

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 nonoccupational 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 [126, 127].

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 that 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, 128]. In the early 1960s, reports appeared linking asbestos exposure to a hitherto unrecognized tumor of the pleura and peritoneum called mesothelioma [129]. 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 [130–136]. 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 [137].

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 [138, 139]. 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 [140]. 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 [141]. 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 [142–144]. A number of cohort studies have been carried out since then in Europe and the USA in various industries [145–149]. 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 [150].

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 [151].

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 [152]. 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 [153–155], 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 [154, 155]. 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 [156–158].

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 [159, 160]. 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, 161]. However, subsequent studies have failed to demonstrate such an effect, and it is likely that the early reports were distorted by confounding or chance [162]. 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 [162], 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 [163, 164], 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 [165–167].

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 [168].

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 [169]. 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 [169–171]. Notable examples include studies on formaldehyde [75, 172], asphalt workers [173], acrylonitrile [174, 175], and nickel compounds [176]. 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 [177]. 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 [178].

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 [179].

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. A majority of previous occupational cancer studies were conducted among male workers; however, given women's rising participation in the workforce, researchers start to investigate more into female occupational risk factors of cancer.

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 has 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 [180].

(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.

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Genetics, Epigenetics, and Environmental Interactions

2

Scott M. Langevin and Karl T. Kelsey

Genetics and Heritability

The field of genetics is generally considered to have originated with Charles Darwin's landmark book *On the Origin of the Species* (1854) [1] that presented his novel theory of evolution. This was followed shortly thereafter by Gregor Johann Mendel's 1866 publication of his work [2], in which he established the notion of heritability through his eminent observations of pea plants, noting 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—in part on the basis of the X-ray crystallography work by their colleague Rosalind Franklin [3, 4]—described the double-helical structure of deoxyribonucleic acid (DNA) [5], 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 [6], would allow rapid, accurate and affordable characterization of genetic variation. The advent of PCR would provide a crucial foundation for modern genetics 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 offspring in its basic most form: DNA. DNA is composed of two simple polymers, each consisting of a strand of nitrogenous bases connected to a sugar-phosphate backbone, known as a nucleotide. These strands are complementary to one another, forming a double-helical structure [5]. There are four possible nucleotides in DNA: adenine (A), thymine (T), guanine (G), and cytosine (C). Adenine and guanine are each double ring bases called purines that respectively pair with their single base—or pyrimidine—counterparts, thymine and cytosine [7]. Genetic code is read like a book, only instead of left to right, 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 (anti-parallel) on each molecule, so that the 5′ end of one strand is aligned with the 3′ end of the other.

DNA is housed within the nucleus of each cell. To allow it to fit into these tight confines—the diameter of a typical eukaryotic nucleus is only about 10 μm—the DNA is condensed by winding around histone proteins and organized into 23 distinct structures in humans called chromosomes [7]. Germline is a term used to describe gametes (i.e., sperm or ova) or gamete producing cells called germ cells. Gametes are generated by germ cells through a process called meiosis and are haploid—meaning that they only carry half of the genetic information of the individual, or one copy of each chromosome. In contrast, human germ cells and healthy somatic cells—which refers to all other non-gamete cells that make up the organism—are replicated via mitosis and are diploid. 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 chromosomal configuration. This is often the case with cancer cells. 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. Under normal circumstances, human somatic karyotypes—or chromosomal arrangements—consist of two copies of each autosomal chromosome. In addition, somatic cells in healthy

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women each contain two X chromosomes, whereas somatic cells in healthy men contain one X and one Y chromosome.

Each chromosome is made up a collection of genes, which are expressed as traits, such as the presence or absence of facial freckles. There are presently 19,077 known protein-coding genes in the human genome [8], along with another 7,143 nonprotein coding RNA genes and 13,057 pseudogenes (Fig. 2.1). For each of these genes, there are two copies—or alleles—with one on each respective parental chromosome in somatic cells. The collective genetic information of an organism is referred to as the genome. The first human genome was mapped in 2003 as a result of the Human Genome Project [9]. An individual with two of the same alleles for a given gene (i.e., gene copies containing identical genetic information) is referred to as homozygous for that gene, whereas someone with two different alleles for a gene is said to be heterozygous. The combination of alleles for a given gene is referred to as the genotype, whereas the physical manifestation of a trait is called the phenotype. A dominant allele is one for which the phenotype 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 exhibit the encoded trait. Using facial freckles as an example: the presence of freckles is a dominant trait, so a person with at least one allele coding for freckles will have facial freckles. Conversely, a recessive allele is one that requires both copies of the same allele for the trait 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 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

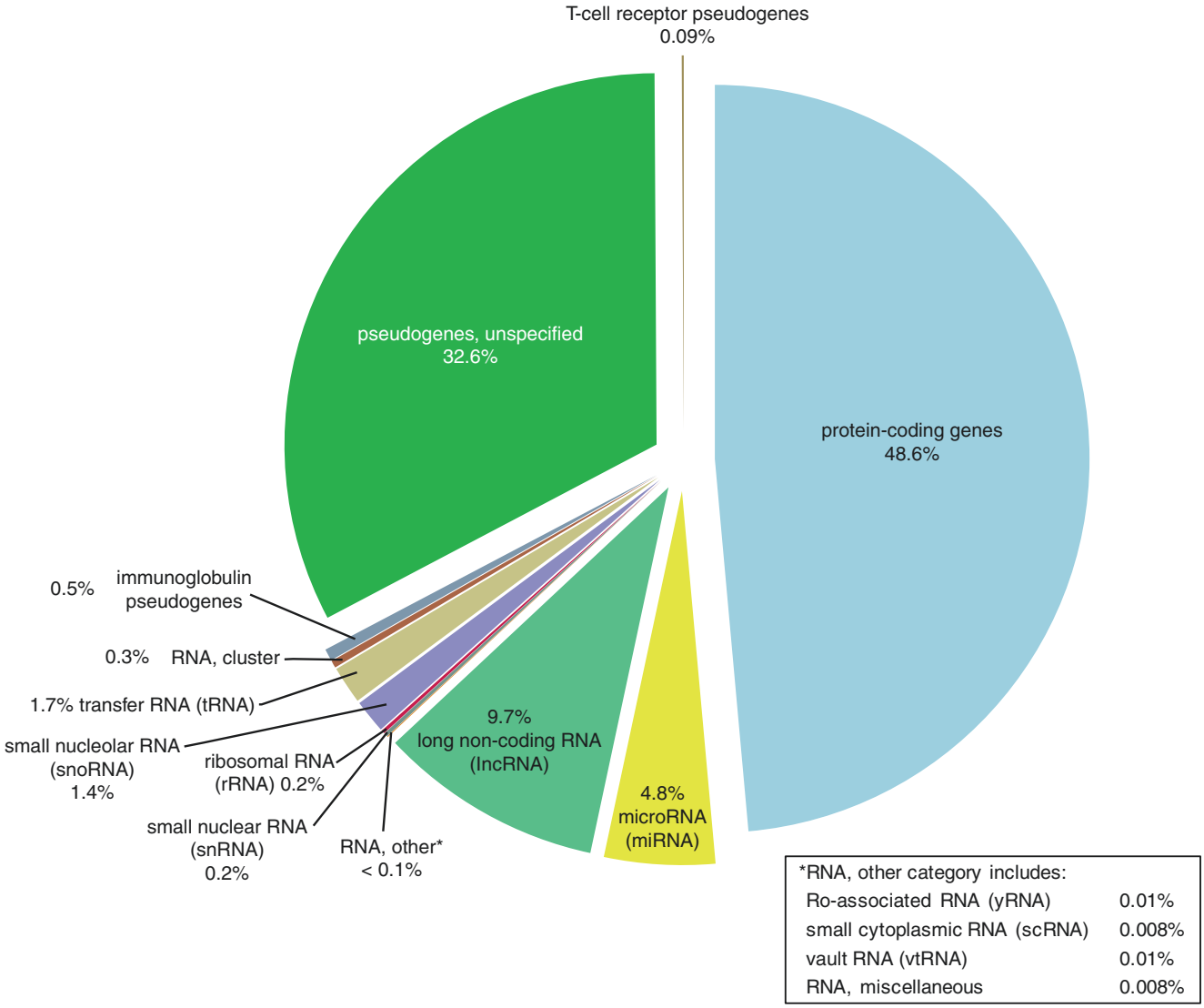

Fig. 2.1 Relative proportions of protein-coding genes, pseudogenes, and non-coding RNA in the human genome

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 [7]. Incomplete dominance occurs when neither one allele is dominant over the other, resulting in an intermediate phenotype. This is exemplified by familial hypercholesterolemia, in which someone 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 normal number of LDL receptors, and a homozygote with both normal alleles has a full complement of LDL receptors [10].

Now that we have introduced the concepts of chromosomes, genotype and phenotype, 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 and now contains much fewer active genes than the X chromosome, with limited homology between sex chromosomes [11]. To avoid a gender-imbalance of protein expression due to copy number differences in sex chromosomes, a dosage compensation process called X-chromosome inactivation occurs in women. During X-chromosome inactivation, there is random silencing of the genes on one of the two X chromosomes during embryogenesis, resulting in a mosaic pattern of X-linked gene expression, where about half of the cells express paternal X-linked genes and half express maternal X-linked genes [11]. It should be noted, however, that this is an imperfect process, with an estimated 12–20% X-linked genes escaping the X-inactivation process in human females [12]. X-chromosome inactivation is not, however, the only mechanism resulting in mono-allelic gene expression; genomic imprinting gives rise to parent-of-origin mono-allelic expression of less than 1% of autosomal protein-coding genes [13]. Imprinting plays a crucial role in early development, with the parent-of-origin suppression varying by imprinted gene, but also plays an important role beyond neonatal development. Accordingly, loss of imprinting has been associated with several developmental disorders arising early in life, as well as obesity, neurological and psychiatric disorders, and cancer risk in adults [14].

At the molecular level, expression of a protein-coding gene is a multistep process that begins with transcription of the gene into a complementary single-stranded ribonucleic acid called messenger RNA (mRNA), followed by translation to protein (Fig. 2.2). Induction of transcription is activated by the binding of transcription factors—proteins that signal the start of transcription—to the regulatory sequence of the promoter region, which is located upstream (5′) of the transcription start site. This signals the uncoupling of the complementary DNA strands and copying—or transcription—of the DNA into mRNA in a process catalyzed by RNA polymerase. Recall from earlier that in complementary strands of DNA, adenine (A) pairs with thymine (T)

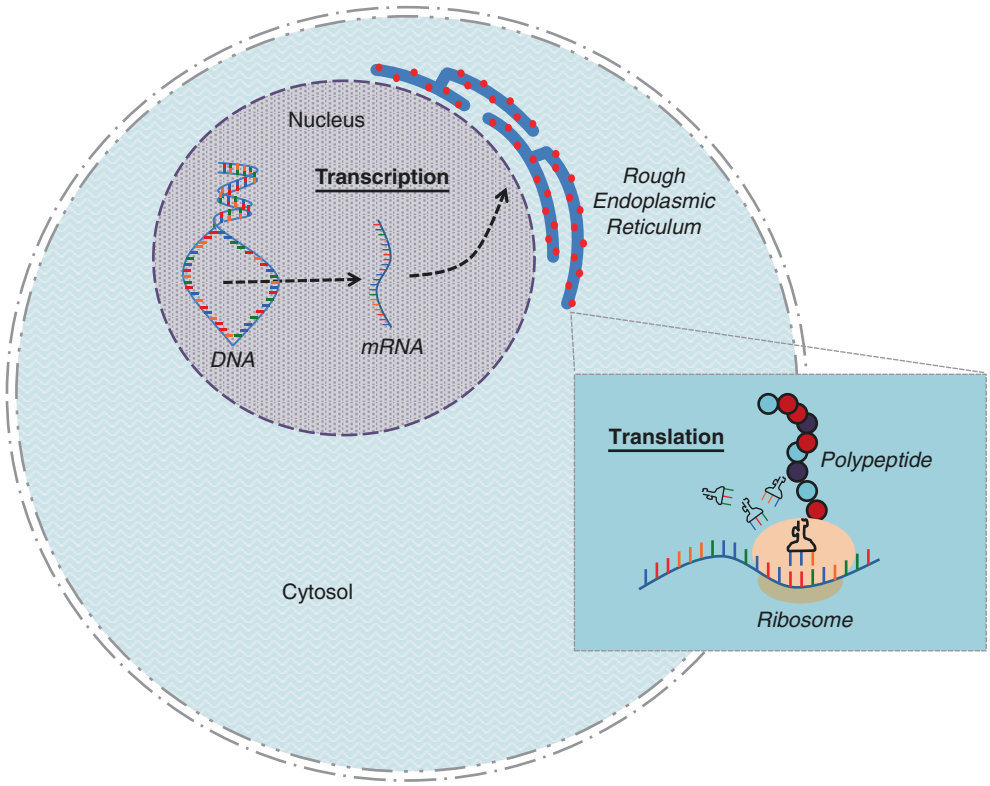

Fig. 2.2 A simplified schematic representation of gene expression. Transcription of DNA to mRNA occurs in the nucleus following binding of transcription factors to the promoter region of the gene. The mRNA is transported across the nuclear membrane to a ribosome in the cytosol where it is then translated into a single chain of amino acids called a polypeptide that is determined by the codons in the mRNA sequence and which will eventually undergo a folding process to form the final protein

and guanine (G) pairs with cytosine (C). The complementary mRNA is similar, except that RNA contains uracil (U), which is the pyrimidine analog of thymine, in lieu of thymine. So, for example, mRNA for the DNA sequence TAACTTG would be transcribed as AUUGAAC.

Genes from eukaryotic organisms—a term that encompasses organisms consisting of complex, nucleus-containing cells, including animals, plants, and fungi—are arranged into several subcomponents. These include a non-coding 5′ untranslated region (5′ UTR) that contains the promoter region; an open reading frame, which describes the region has the *potential* to be translated into protein; and another non-coding region at the terminal end of the gene called the 3′ untranslated region (3′ UTR). The open reading frame is comprised of exons, which are the segments that are subsequently translated into protein, and introns, which are untranslated segments that are ultimately spliced out of the mature mRNA 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. The mature mRNA then migrates from the nucleus to a ribosome in the cytosol. Each consecutive three-base combination along the mature mRNA sequence is called a codon. Each codon encodes either an amino acid or a stop codon during translation. Codons are recognized by transfer RNA (tRNA) molecules, which have a folded three-loop structure, including an anticodon loop that recognizes a specific codon sequence and carries an amino acid corresponding to it. Amino acids constitute the basic building blocks of proteins. The first codon in the sequence that signals the start of translation is aptly termed the start codon and always encodes the amino acid methionine in eukaryotes. As the mRNA is passed through the ribosome, the amino acid corresponding to each consecutive codon is sequentially added to form a linear amino acid chain—called a polypeptide—that will ultimately form the encoded protein. This continues until a stop codon is reached in the sequence, signaling the end of translation. The resultant polypeptide then undergoes a folding process to gain 3-dimensional structure to constitute the encoded protein. There are 20 different amino acids that appear in the genetic code, of which 10 are synthesized in humans, while the other 10 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*—mentioned at the start of this chapter—describes his 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 are more likely to 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% difference that makes us genetically diverse. Although it may at first seem like it, this is not an insignificant fraction if one considers that the human genome consists of nearly 3.2 billion bases [15]. Mutations that arise in the germline can be passed along to offspring and potentially propagated throughout the population, while mutations that occur in somatic cells—referred to as somatic mutations—cannot. Some genes, due to evolutionary pressures, are highly conserved, meaning that they are the same in nearly all people, or even across species or phyla. 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 [16], 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 [17]. A mutant allele present in at least 1% in the general population is generally 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 typically 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, polymorphisms also have different frequencies in different populations as a result of the migration patterns 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 substitution of a single base; and frameshift mutations, where one or more bases are inserted into or deleted from the coding sequence, which can potentially throw off the downstream amino acid sequence of the protein [7]. 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

[18]. A SNP 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 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 premature insertion of a stop codon, called a nonsense mutation, causes truncation of the protein, which can result in loss of function [7]. Although synonymous SNPs do not alter the protein structure itself, this does not mean that they cannot have a relevant effect on gene expression, as they can still potentially alter binding sites of regulatory elements that can impact expression and alternative splicing of the gene.

Phenotype Versus *Genotype*

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 trait associated with a gene is expressed [7], or otherwise put, it is the concordance between genotype and phenotype. With respect to cancer, genetic variants can be described as high-penetrance, moderate-penetrance, or low-penetrance risk alleles based on the level of risk that they confer to the carrier in terms of cancer development.

High-penetrance cancer alleles are those that impart a high risk for cancer development during the lifetime of the allele carrier; they have been referred to as "cancer genes" as a direct result of this high penetrance. Fortunately, these alleles are relatively rare, typically with a minor allele frequency that is less than 0.1% [19]. Although the individual risk of developing cancer to anyone carrying the high-penetrance allele is substantial, 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 [20]. There are several well-known examples of high-penetrance alleles associated with cancer development. Once such case is that of germline *BRCA1*/*BRCA2* mutations and the strong 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 [21]. The *BRCA2* mutation bears a slightly lower respective risk of 45% and 11% risk for developing breast or ovarian cancer, over the same timeframe [21]. 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 [22]. Note that although the risk of cancer is very high, not everyone with the mutation will develop cancer. 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 relatively early age of onset [23]. FAP is due to a germline mutation in the *APC* gene, characterized by early development of hundreds of adenomatous polyps in the colon [23]. It occurs at a frequency of approximately 1 in 8000 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 1000 to 1 in 3000 people [24] as a result of germline mismatch repair gene mutations (*MLH1*, *MSH2, MSH6, PMS1* or *PMS2*) [23]. In addition to its strong 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 [23]. Other examples of high-penetrance cancer risk alleles include constitutional *CDKN2A* mutation and melanoma [25]; familial *Rb* mutation and retinoblastoma [26]; Fanconi anemia (a rare recessive disorder) and myeloid and squamous cancers [27]; and constitutional *p53* mutation and Li–Fraumeni syndrome (a dominant disorder associated with drastically increased risk of various cancers with early age of onset) [28]. 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- and low-penetrance genes are often collectively referred to as susceptibility genes. 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 [19]. These mutations tend to be population-specific, often due to underlying founder effects [19]. There are several moderate-penetrance risk alleles associated with breast cancer, including constitutive mutations in *ATM*, *CHEK2*, *BRIP1*, or *PALB2* [19]. *APC* I1307K - in which lysine is substituted for isoleucine at codon 1307 - is another such allele, associated with a moderate increase in risk for colorectal cancer and is present in approximately 6% of Ashkenazi Jews [19]. Although carriers of the *APC* I1307K allele do not develop FAP, the mutation is still associated with a risk that is 1.5 to 2-times that of wild-type individuals [23]. Low-penetrance alleles tend to be relatively common, often

with a minor allele frequency greater than or equal to 10% [19]. Compared to high- and moderate-penetrance alleles, these confer a much lower individual risk for disease. However, while 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 have lower overall impact on population risk. Numerous low-penetrance alleles exist, including common polymorphisms found in genes coding for enzymes relating to 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 and their associated risks may combine or interact to exert a substantially elevated individual risk of disease.

Epigenetics

Heritable genetics are not the sole determinant of phenotypic diversity. The term *epigenetics* refers to stable and mitotically heritable changes (i.e., transferred from parent to daughter cells during mitotic division) that either alter or have the potential to alter gene expression without changing the underlying DNA sequence [29]. Epigenetics is generally considered to encompass three broad categories: (1) DNA methylation, (2) covalent histone modifications, and (3) noncoding RNA—each of which will be addressed in detail below.

DNA Methylation

DNA methylation is a normal physiological process in which a methyl ($–CH_3$) group is covalently attached to the carbon atom residing at the fifth position of a cytosine pyrimidine ring, forming 5-methylcytosine (5-meC) in a reaction catalyzed by DNA methyltransferase (DNMT) [30, 31]. DNA methylation primarily occurs at cytosine in the context of CpG dinucleotides, which are two-base sequences where cytosine is upstream and adjacent to guanine in a DNA strand.

CpG islands (CGI) are CpG-dense regions that are disproportionately (although not exclusively) situated in the promoter regions of genes. CGI methylation of the promoter region—often referred to as promoter methylation—is generally associated with transcriptional repression (Fig. 2.3), 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 [32]. Under non-pathologic conditions, promoter-associated CGIs are typically unmethylated in cells [33], however exceptions exist, such as during the normal genomic processes of X-inactivation and imprinting [34] or tissue differentiation [35–39]. It is important to note, however, that promoter methylation is not the only way in which DNA methylation can affect the genome. Methylation of CpG islands situated in inter- and intragenic enhancer regions can also impact the timing or spatial patterns of gene expression [40]. There is mounting evidence that methylation of CpG islands located in the gene body can lead to *increased* transcriptional activation [41–43]. Regional methylation can also impact the expression of non-coding RNA [40], the sequences of which are commonly situated in intronic or intergenic regions.

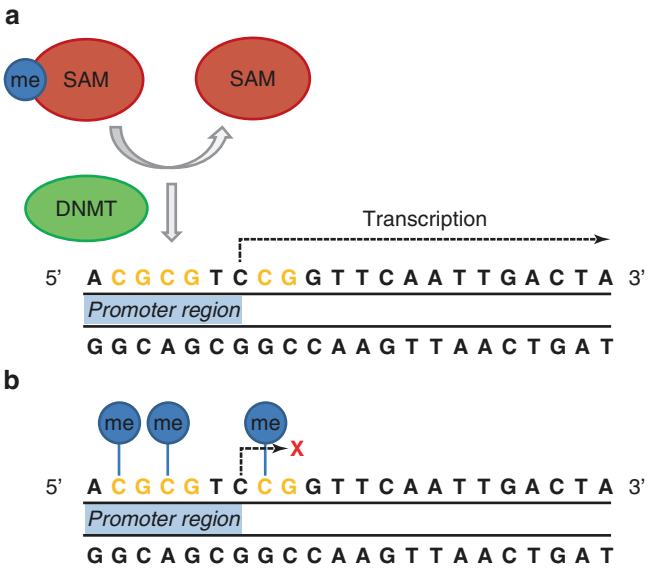

Fig. 2.3 Transcriptional silencing by DNA promoter methylation. (**a**) Cytosines in the CpG dinucleotides of the promoter CpG island of the gene are unmethylated, allowing for active transcription of the gene. (**b**) Methyl groups (me) donated by *S*-adenosyl methionine (SAM) are covalently attached to the 5-carbon on the pyrimidine rings of the cytosines in CpG dinucleotides in the CpG island in the promoter region in a reaction catalyzed by a DNA methyltransferase enzyme (DNMT), which results in transcriptional repression

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 often methylated under normal conditions [44]. Methylation of individual CpGs located outside of CGIs, particularly those located in DNA sequence repeat and pericentromeric regions, helps to maintain genomic stability [45, 46], and also plays a role in embryonic development and tissue differentiation [47]. With respect to sequence repeats, DNA methylation, in concert with chromatin conformational changes, helps maintain stability via repression of transposable elements (TE) [48], which are repetitive genomic

sequences that have a singular ability to relocate (or at least the potential) to another chromosomal location in the genome [49]. Active transcription and reinsertion of TE 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 [49]. Non-long terminal repeat (LTR) retrotransposable elements comprise the majority of TEs, and 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 [50].

Histone Modifications

DNA methylation is not the sole epigenetic mechanism capable of altering gene expression but rather is part of coordinated structural change manifested at the chromatin level through covalent histone modifications. Modification of histone proteins can result in the alteration of overall chromatin structure, directly affecting gene transcription, DNA repair, DNA replication, and chromosomal organization [31, 34]. Histones are protein octamers—meaning that they are composed of eight protein subunits—that contain 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 [31]. This is a recurring unit of eukaryotic DNA that makes up the chromosomes through condensation of the DNA so that the entire genome can fit into the nucleus. Most chromatin exists as tightly compacted nucleosomes—termed heterochromatin—that is transcriptionally incompetent and represented by the dark staining portion of the nucleus on light microscopy. In contrast, euchromatin is the term used to describe more loosely compacted nucleosomes that form an open chromatin structure that can be readily transcribed; this appears as the lightly staining portion of the nucleus on light microscopy [31].

Histone modifications involve the covalent attachment of various functional groups to varying amino acid residues, including lysine, arginine, and serine, on the N-terminal tail of different histone subunits. 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 [31, 34, 51].

Histone acetylation is generally associated with transcriptional activation (Fig. 2.4). It involves the attachment

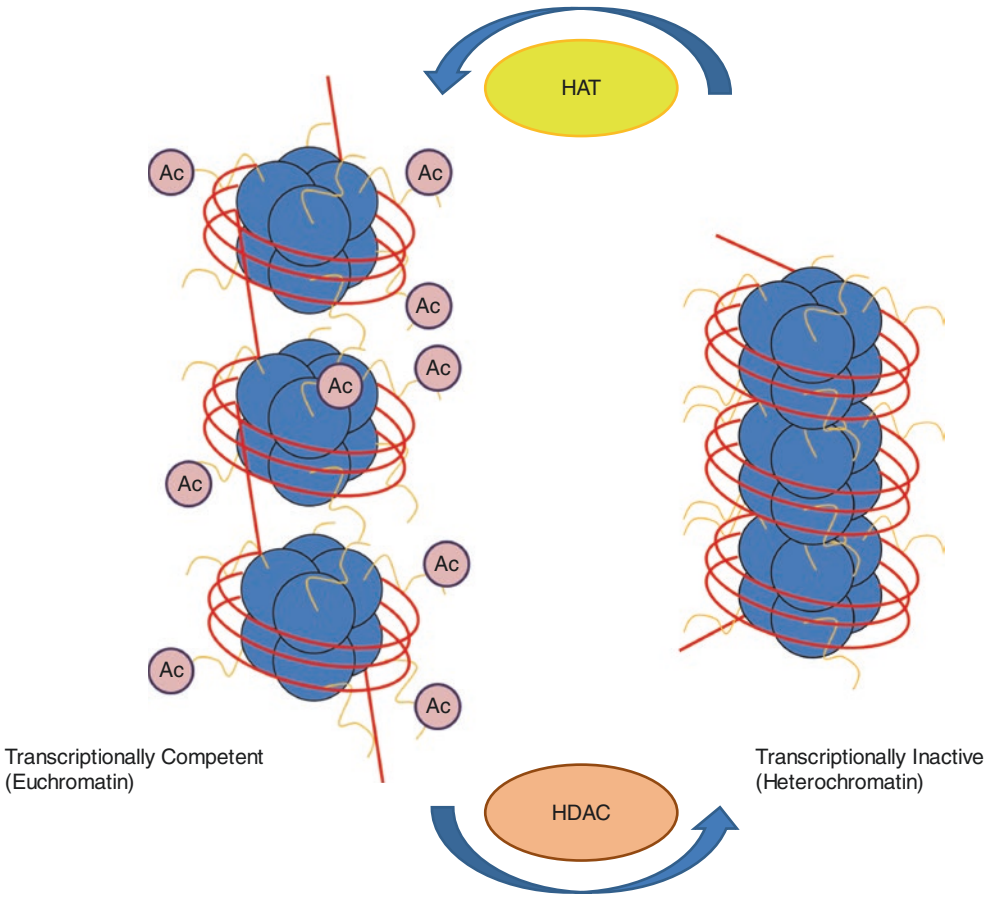

Fig. 2.4 Histone acetylation and transcriptional activation. Lysine residues on the N-terminal tails of histone proteins are acetylated in a reaction catalyzed by histone acetyl transferase enzymes (HAT), allowing the chromatin to exist in an open, transcriptionally active euchromatic state (depicted on the left side of the figure). Removal of the acetyl groups (Ac) is catalyzed by histone deacetylases enzymes (HDAC), resulting in condensation of the nucleosome (heterochromatin) and transcriptional inactivation (right side)

of acetyl groups to lysine residues in the N-terminal tail of histone proteins in a process catalyzed by histone acetyl transferases (HAT). This changes the charge of the residue from positive to neutral, resulting in a conformational shift to more loosely compacted chromatin that is accessible to the transcriptional machinery [52]. Conversely, histone deacetylases (HDAC) form complexes with methyl-CpG-binding-proteins (MBD) and methylated cytosines in the promoter, allowing them to remove acetyl groups from the N-terminal tails of the histones, leading to condensation of the nucleosome resulting in transcriptional inactivation [31, 34].

The effects of other types of histone modifications are much more complex and 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: a class of enzymes called histone methyltransferases catalyze histone methylation, while histone demethylases are responsible for removal of methylation [31, 53]. Histone methylation 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 that lead to transcriptional silencing (i.e., heterochromatin). Conversely, trimethylation of lysine at position 4, 36, or 79 on H3 (H3-K4 or H3-K79) is associated with looser compaction (i.e., euchromatin) and active transcription [53–55].

Non-coding RNA

Non-coding RNA (ncRNA) are a heterogeneous group RNA that are capable of being transcribed but not translated (i.e., they do not encode proteins), including long non-coding RNA (lncRNA), microRNA (miRNA), piwi-interacting RNA (piRNA) [56], small interferring RNA (siRNA) [57], small nuclear RNA (snRNA) [58], small nucleolar RNA (snoRNA) [59], transfer RNA (tRNA) [60], ribosomal RNA (rRNA) [60], and yRNA [61]. Several ncRNA, such as miRNA, piRNA, siRNA, are involved in post-transcriptional regulation of gene expression [62]; of these, miRNA have thus far been the most studied and are described in more detail in the ensueing section.

microRNA

MicroRNA (miRNA) are small, evolutionarily conserved, ncRNA molecules involved in post-transcriptional regulation of gene expression in essentially all eukaryotic organisms. Their mature transcripts are tiny in size, ranging from 18 to 25 nucleotides in length [63–67]. miRNA were first described in 1993 in the nematode *C. elegans* [68] with the identification of Lin-4, a small ncRNA that was observed to repress expression of Lin-14 protein. Presently, there are 2,588 mature human miRNA sequences cataloged in the miRNA registry (miRBase) [69]. miRNA are involved in control of crucial cellular functions, including proliferation, apoptosis, development, differentiation, and metabolism [64]. In fact, it is estimated that up to 60% of human genes are regulated by miRNA [70]. Part of the vital 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 [65, 67]. They are tightly controlled and have been observed to show tissue-specific expression patterns during embryogenesis [63], though all tissues at any given stage of development express at least some miRNA [71].

miRNA expression is regulated by transcription factors and transcribed by RNA polymerase II (pol II), akin to transcription of protein-coding genes, although the precise mechanisms of transcriptional control of miRNA are still not entirely understood. While most miRNA reside within intergenic (sequences containing few or no genes) non-coding regions [72], they can also be situated in introns or exons of coding genes [72]. Many miRNA are embedded close to other miRNA in the genome, giving rise to miRNA clusters [72]. Single and clustered miRNA 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 [71, 73].

Following transcription, miRNA undergo a multistep post-transcriptional maturation process, which is depicted in Fig. 2.5. The primary transcript, called pri-miRNA, is typically 3–4 kb in length with a 5′ 7-methylguanosine (m^7G) cap and poly-adenylated (poly-A) tail, similar to mRNA [74]. A stable hairpin structure of at least 30 base pairs is necessary to serve as the initiation signal for the processing steps [75]. The pri-miRNA 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-miRNA (pre-miRNA) [63–67]. 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 [75]. Pri-miRNA often contain several pre-miRNA, known as clusters.

Pre-miRNA are 65–100 nucleotides long with a hairpin structure containing a double-stranded RNA stem [75]. Exportin- 5 (Exp5) recognizes the 3′ overhang, which is characteristic of pre-miRNA, and a portion of the RNA duplex structure [76, 77] 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) that

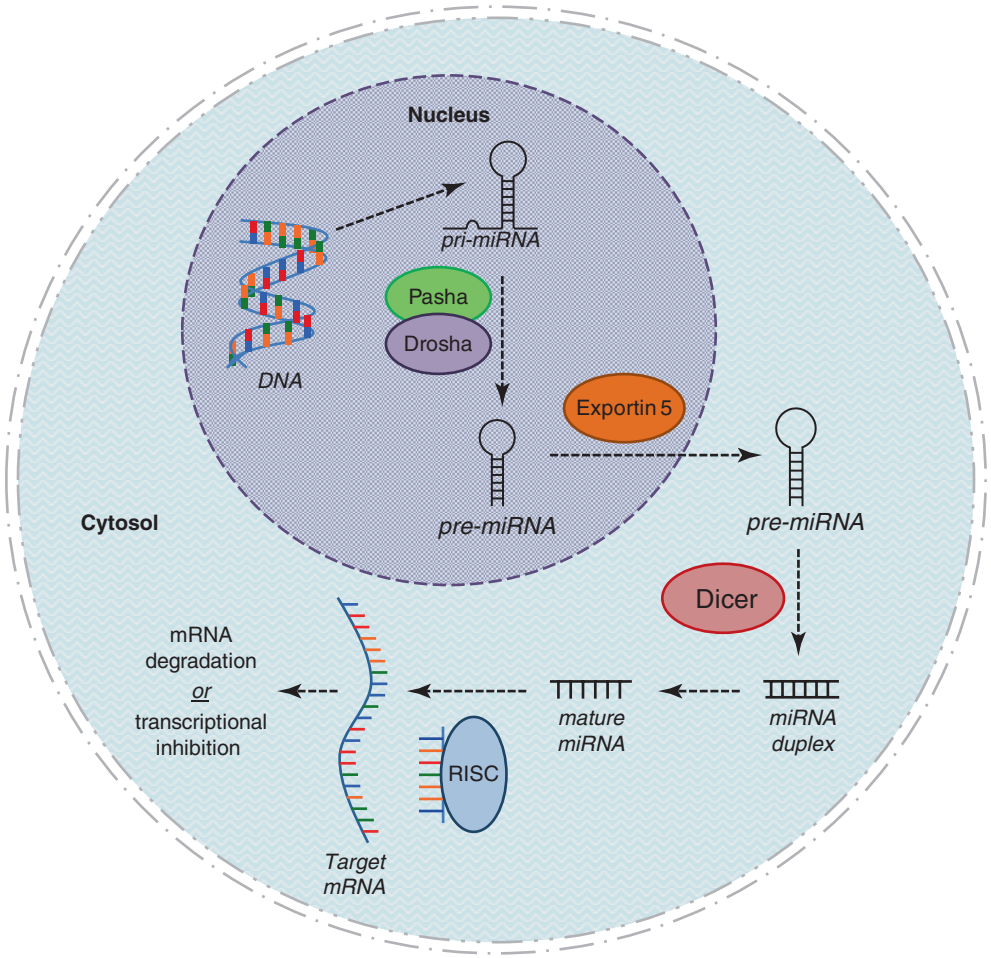

Fig. 2.5 MicroRNA processing and post-transcriptional regulation of gene expression. (**a**) MicroRNA (miRNA) is transcribed from DNA, giving rise to a primary miRNA transcript (pri-miRNA) containing a hairpin loop structure. (**b**) Pri-miRNA is cleaved in the nucleus by the Drosha/Pasha enzyme complex (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 base pair miRNA duplex (2 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 mature miRNA guides RISC to the target mRNA through base-pairing interactions at the 3′UTR of the target, resulting in degradation or translational inhibition

consists of another RNase III—called Dicer—along with Argonaut 2 and TAR RNA-binding proteins (TRBP) [63–67, 75]. Dicer recognizes the stem of the hairpin structure as double-stranded RNA and cleaves it on the loop side, leaving an 18–25 base pair miRNA duplex [63–67, 71]. 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 [78, 79] in a process facilitated by Dicer [71].

The mature miRNA forms a complex in conjunction with an Argonaut (Ago) protein called the RNA-induced silencing complex (RISC) [63–67, 71], which it guides specifically to target mRNA through base-pairing interactions generally at the 3′ UTR of the target. Nucleotides 2–7 of the miRNA, called the seed region, bind the target mRNA through perfect or near-perfect base pairing [18]. The remainder of the miRNA binds the target mRNA with varying degrees of complementarity [18]. If the entire miRNA is a perfect or near-perfect complement, cleavage and degradation of the mRNA is induced through decapping of the 5′ m^7G cap or de-adenylation of the poly(A) tail [63–67]. If it is a partial complement, RISC inhibits translation [63–67] through competitive m^7G cap binding by the Ago protein with the translational initiating factor eIF4E [15], 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) [71]. P-bodies contain decapping proteins and exoribonuclease, and therefore are capable of degrading the mRNA. However, there are some indications that miRNA translational silencing may be reversible, allowing mRNA to leave P-bodies and migrate to ribosomes for translation [80].

Long Non-coding RNA

In contrast to many of the ncRNA species, which are smaller in size (<200 bases), long non-coding RNA (lncRNA), as their name implies, are larger (>200 bases), typically reaching ~1–2 exons in length [81], and can have secondary and tertiary folding structure. Although new lncRNA are continuously being discovered and the functional significance of the vast majority is presently unclear, it is already apparent that they are diverse in function, playing roles in key pre- and post-transcriptional processes, including chromatin organization and modeling [82], alternative splicing [83], monoallelic gene silencing [84], protein scaffolding [85], telomere elongation [86], mRNA degradation [85], and transcriptional enhancement [85], to name a few.

Bringing Together the Concepts of Genetics, Epigenetics, and Phenotype

Genetic and epigenetic influence on phenotypic variability, in conjunction with differing lifetime exposures to environmental insults, forms the basis for interpersonal susceptibility to disease. Diversity in traits that play a role in protecting us from disease can result in differential risk levels between individuals with similar exposures. Variability in certain genes, or the expression of those genes, can impact, for example, the way that environmental toxicants and their metabolites are processed and excreted or cellular response to DNA damage [70] The remainder of this chapter will focus, in detail, on genetic susceptibility and interaction with environmental exposures.

Gene–Environment Interactions

Functional variation in a gene (or genes) with a key role in response to and metabolism of exogenous chemical exposures—termed xenobiotics—by itself may not be sufficient to alter disease susceptibility. The xenobiotic exposure may also be necessary in order for the physiological response (or lack thereof) to have an impact. In other words, an effect modification of environmental or occupational exposures by genotype can take place, which is known as a gene–environment interaction (Fig. 2.6). While we are in near constant contact with low-levels of carcinogens due to both man-made and naturally occurring exposures, there are 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

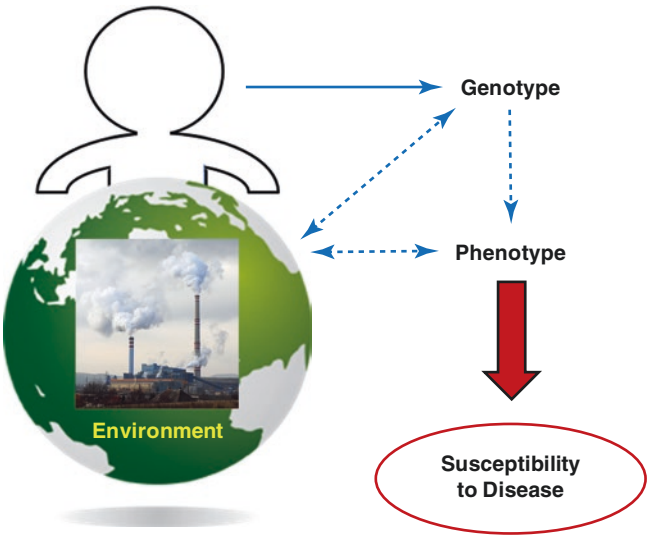

Fig. 2.6 This cartoon illustrates the interaction between genotype, phenotype and the environment, and the resultant effect on disease susceptibility. Each person has a unique collection of genes, collectively referred to as the genome. These genes may be expressed as phenotypes (traits) in varying degrees, dependent upon both host and environmental factors. Phenotypic expression - for example of a xenobiotic metabolizing enzyme or DNA repair gene - can interact with an environmental or occupational exposure to modify an individual's susceptibility to disease. (Source for the factory image: [161])

applications. Exposure to the metal usually stems from inhalation of beryllium dust, which is generated during a variety of industrial processes. Inhalation triggers a type IV antigen-specific immune response that can give rise to a granulomatous pathological process in the lung of those exposed, resulting in decreased breathing function. However, CBD only develops in an estimated 2–16% of those exposed [87]. The reason why some people develop CBD following beryllium exposure but others do not can be largely explained by a polymorphism in the *HLA-DPB1* gene (∗E69). The *HLA-DPB1*∗E69 allele has been associated with increased sensitivity to beryllium and thus with development of CBD among those exposed [88–92]. Otherwise put, CBD cannot occur without both a chronic beryllium exposure *and* the *HLA-DPB1*∗E69 allele. Thus, risk of CBD development is dependent upon an interaction between genetics (*HLA-DPB1*∗E69) and the environment (chronic beryllium exposure).

Xenobiotic Metabolism and Excretion

As previously discussed, we are constantly exposed to xenobiotics stemming from environmental and occupational exposures, as well as our own personal behaviors. Many of these exposures can confer cancer risk via DNA damage, 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 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. These notions will be discussed in further detail in the subsequent chapter 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 as a two-step process: activation followed by conjugation [93]. The activation step—or phase I—entails enzymatically catalyzed oxidation, reduction, hydroxylation, or other such reactions creating intermediaries for conjugation of the xenobiotic molecule. During conjugation—or phase II—a small polar molecule is covalently attached to the reactive metabolite generated in phase I, thus biotransforming it into a nonreactive molecule and allowing for eventual excretion. Since metabolites generated by phase I are often more reactive, and therefore potentially carcinogenic, 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 [93].

Several classes of xenobiotics are able to stimulate expression of xenobiotic metabolizing enzymes [93, 94]. 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 (XRE) - also sometimes called dioxin response elements - in the 5′ promoter region of their target xenobiotic metabolizing genes [94], 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*. Accordingly, 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, accounting for 70–80% [95]. 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 [96]. 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 [97]. Several commonly studied polymorphic—or genetically variable—CYPs are presented below, although this is merely intended to serve as an introduction and not meant to be an exhaustive list.

CYP1A1 is a polymorphic (i.e. highly variable) gene that is expressed hepatically and extrahepatically and encodes an enzyme involved in detoxification of a broad range of carcinogens, including but not limited to polycyclic aromatic hydrocarbons (PAH), *N*-nitrosamines, aromatic amines, 1,3-butadiene, and ethylene oxide [97, 98], 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 inconclusive results. To date, 12 variant *CYP1A1* alleles have been identified [99].

CYP1B1 is a another polymorphic cytochrome enzyme that is also expressed in hepatic and extrahepatic tissue. It is involved in metabolism of estrogen steroids but also plays a crucial role metabolism of polycyclic aromatic hydrocarbons (some of which it has very high affinity for), heterocyclic amines, arylamines, and nitroarenes [100]. More than 26 polymorphisms in the *CYP1B1* gene have been identified, 19 of which are non-synonymous [100]. As such, this enzyme has also been widely studied in relation to cancer and has been associated with several cancer types.

Yet another polymorphic and widely studied cytochrome enzyme is *CYP2E1*. This cytochrome, the only one identified in the CYP2E family, is hepatically expressed [100]. Several of the polymorphisms have been associated with altered levels of enzyme activity [101, 102], 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 [103], many of which are known to be carcinogenic. It is also the inducible cytochrome metabolizer of ethanol, known as the microsomal ethanol oxidizing system [104], 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 metabolism of other substrates stemming from environmental or occupational exposures. *CYP3A4* and *CYP2D6* are both hepatically expressed cytochromes and are considered to be two of the most important cytochrome enzymes for drug metabolism. However, they also have substrates that include organophosphate pesticides [105] and the tobacco smoke-derived procarcinogen 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK) [106]. 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 NAD(P)H:quinine oxireductase (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 PAHs found in tobacco smoke, foods cooked at high temperatures, and combustion byproducts, forming soluble, nontoxic peptide derivatives to be excreted [107]. At present, there are seven families of human cytosolic GSTs: alpha, mu, pi, sigma, omega, theta, and zeta [108]. 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 [109]. 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 [110]. 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 [111–117]. Early studies also demonstrated that the variant GST genes have varying phenotypes associated with the genotypes [118–120].

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 byproducts. Some aromatic amines are classified as definite human carcinogens (group 1) by the International Agency for Research on Cancer (IARC) [121]. There are two known active *N*-acetyltransferase isoenzymes found in humans: NAT1 and NAT2. These isoenzymes share 80–95% homology and have overlapping substrates [122]. The N-acetylation phenotype associated with *NAT2* is quite variable in humans due to 30 alleles deriving from 13 SNPs [103]. 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 either via genotyping [123] or by phenotyping using appropriate substrates, such as caffeine [103]. Like its counterpart, *NAT1* also exhibits a high degree of variability, with 26 reported allelic variants [103], some of which also correlate with enzyme activity, particularly the *NAT1*$*$4 and $*$10 alleles [103, 124].

NAD(P)H:quinine oxireductase (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 [125]. More specifically, NQO1 is involved in oxidative reduction of quinones, nitroaromatics, and azo dyes [125]. It has also been extensively studied for its role in reductive activation of important chemotherapeutic compounds [126, 127]. A common polymorphism involving a C to T transition at base pair 609, *NQO1 C609T* (rs1800566) is associated with loss of NQO1 enzyme activity [128] and has been studied extensively in the context of cancer susceptibility.

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 [129–131], cell cycle control [132, 133], signal transduction [134, 135], epigenetic regulation [136–140] (including one carbon metabolism [141, 142]), histocompatibility genes [143, 144], or those involved with induction of xenobiotic metabolic 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 (rs25487), which confers a three- to four-fold decrease in enzyme repair capacity [145], may result in increased susceptibility to accumulation of radiation damage and, accordingly, cancer. 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 prevented (and still do prevent) random mating across the general global population. The result is differences in allele frequencies of certain genes by race, ethnicity, or geography. This is an important concept to consider 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 non-homogenous genetic makeup of the source population by or within a racial or ethnic group [146, 147], as has been observed for many of the metabolic polymorphisms discussed above [111, 148–151]. 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. 2.7). Consider a hypothetical example devised by Lander and Schork [152], 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 phenotypic expression of an "ability to eat with chopsticks" unless either chopstick use or race/ethnicity is properly controlled for in the analysis.

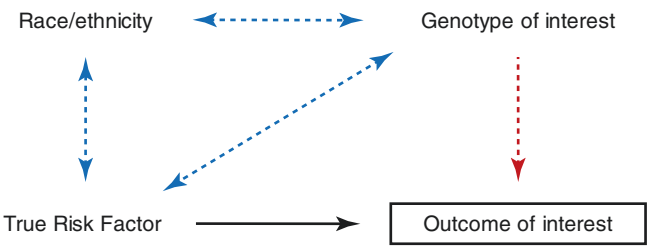

Fig. 2.7 A schematic diagram illustrating population stratification. In population stratification, a true causal risk factor for the outcome of interest, which could be genetic or environmental in nature, is associated with race/ethnicity. Therefore any genotype that is also associated with ethnicity 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. [147])

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—although 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 are 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, particularly when the variant of interest has a relatively low population allele frequency. First order gene–gene interaction of xenobiotic genes 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 [153], 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 [154].

Genome-Wide Association Studies (GWAS)

The advent of high throughput technologies—initially SNP arrays and now whole-genome sequencing—that allow for the conduct of genome-wide association studies (GWAS) have further progressed our understanding of genetic susceptibility to cancer. However, despite early enthusiasm and advances in our

comprehension of genetic cancer risk factors, these technological advances have not thus far lead to the identification of 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 [155]). 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 (i.e., genes or chromosomal regions), most of which were previously unknown [156]. 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) [155, 157].

Epigenetics and Environmental/Occupational Exposure

Our genetic code is not the only biological program capable of interacting with exogenous chemicals and other physical insults. As an added complexity, alterations in our epigenetic configuration may stem from and interact with occupation and environmental exposures. 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 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 [158], which is likely attributable to differences in environmental exposures over the course of time. People are most susceptible to epigenetic dysregulation during prenatal and neonatal development, puberty, and old age [159]. In addition to cancer research, a lot of research now centers around the importance of environmental exposures during intrauterine development in terms of epigenetic reprogramming and its downstream effect on health throughout the life course [160].

Summary

The DNA that we inherit from our parents is the basic blueprint for our existence, encoding the proteins and ncRNA transcripts necessary for life. Interpersonal variability within the genes encoded by our DNA, as well as our epigenetic programing, is what sets us apart from one another by providing phenotypic diversity. In the context of occupational cancer risk, our genetics and epigenetics—particularly (although not limited to) those involved in expression of enzymes involving xenobiotic metabolism or excretion, DNA damage sensing and repair, and inflammatory response to exogenous materials—can interact with each other and with our lifetime environmental and occupational exposures to modulate our risk of developing malignant disease. High-penetrance cancer alleles confer a strong likelihood of developing cancer but are relatively rare and only attributed to about 5% of human cancers. Conversely, low-penetrance genetic variation confer a much smaller level of risk to the individual but are much more common and therefore can have a substantial impact at the population level.

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Mechanisms of Environmental and Occupational Carcinogenesis

3

Scott M. Langevin and Karl T. Kelsey

Environmental and Occupational Carcinogenesis

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 that can potentially take on an invasive phenotype and become a clinically appreciated disease. Major sources of such events include exogenous physical, chemical, and biological exposures stemming from the environment, including those encountered in the occupational setting.

Hanahan and Weinberg 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—or growth of new blood vessels—as a source of oxygen, nutrient, and waste exchange; and activation of invasion—or extension of malignant cells through the basement membrane of the tissue or into other adjacent normal tissue [3]—and metastasis—or movement of malignant cells from their original site to elsewhere in the body [3]. These attributes are largely attained as a result of activation of oncogenes and inactivation of tumor suppressor genes. An oncogene is a gene that can potentially induce cancer under certain conditions, for example by enhancing cell survival or proliferation [3]. A proto-oncogene is a normal-functioning 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 protects the cell from potentially carcinogenic alterations [3], such as through inhibition of proliferation or induction of apoptosis.

From a genetic standpoint, aberrant activation of an oncogene typically acts in a dominant fashion, while inactivation of a tumor suppressor gene generally follows a recessive model. Increased activity or expression of a single allele is sufficient for activation of an oncogene, as it results in increased signaling that can provide a growth or survival advantage. Historically, Knudson's two-hit hypothesis has dictated that 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 or epigenetic inactivation of a second allele. This is because 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]. Aberrant activation or inactivation of an oncogene or tumor suppressor gene can stem from genetic and/or epigenetic changes that can occur as a result of environmental or occupational exposures, contributing to carcinogenesis through facilitation of these hallmark events.

Field Cancerization and Expanding Fields

Human tissues regularly encounter a variety of exogenous and endogenous exposures, which are capable of inducing genetic and epigenetic alterations that will be described in detail later in this chapter. This is particularly true of the epithelium—the lining along the aerodigestive and genitourinary tracts—since these are chronically exposed to a host

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of environmental and occupational carcinogens. The term carcinogen describes any agent that contributes to the development of cancer [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 new 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. 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] (Table 3.1). The short-term consequences may 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.

Table 3.1 Major types of DNA damage

Damage type	Description	Consequence
Small adduct (alkylation)	Covalent attachment of an alkyl groupto 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 reaction of free radicals with DNA	Induction of base-mispairings and DNA strand breaks
Deamination	Hydrolytic reaction resulting in loss of a base	Loss of base and corresponding coding information
DNA strand breaks	Double- or single-strand break in DNA phosphate backbone	Chromosomal breaks, deletion, and genomic instability

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

One source of physical DNA damage is ionizing radiation. This includes high-frequency (i.e., 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]. 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. Ionizing radiation can induce DNA damage in a variety of ways, as depicted in Fig. 3.1. Ionizing radiation can directly damage cells induction of single- and double-strand breaks, as well as damage to the bases, interstrand cross-linkage, and pyrimidine dimer formation [12]. Despite the fact that double-strand breaks occur much less frequently than single-strand 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. Additionally, ionizing radiation can indirectly damage cells—termed the radiation-induced bystander effect—through oxidative lesions induced by free radicals—reactive molecules or ions with unpaired electrons—that form from irradiation of water molecules, as well as generation of reactive oxygen (ROS) species and reactive nitrogen species (RNS), either via activated immune cells responding to ionizing radiation damage in other cells or through direct intracellular communication through transfer of cytokines and ROS/RNS by an adjacent damaged cell [13].

Ultraviolet (UV) light, which is only marginally ionizing, is also capable of inducing DNA damage. It exerts the bulk of its carcinogenic effect through covalent cross-linkage of pyrimidine bases—cytosine (C) or thymine (T)—connecting bases on opposing strands of the double helix, preventing separation of the strands during transcription, and thus inhibiting the transcriptional process. It can also generate UV signature mutations involving C to T transitions (a transition mutation is defined as an interchange between either two purine or pyrimidine bases, whereas a transversion mutation involves a change from a purine to a pyrimidine, or vice versa). This primarily occurs at dipy-

rimidinic or 5-methylcytosine sites, and stimulation of oxidative damage, caused by ROS production through activation of small molecules, including riboflavin, tryptophan, and poryphryin [14–17].

Another form of physical agent that has been increasingly studied in recent years is non-ionizing radiation. In contrast to ionizing radiation, non-ionizing radiation lacks sufficient energy to break atomic bonds [11], so 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 non-ionizing radiation has any biological/physiological effect in human cells, much less if it plays a role in human pathological processes. From a mechanistic standpoint, there is experimental evidence suggesting that prolonged exposure to non-ionizing electromagnetic field radiation (EMF) may induce oxidative stress through activation of pathways that generate ROS [18]. However, in terms of human correlates, this has not been substantiated. There is limited epidemiologic evidence between extremely low-frequency magnetic fields and childhood leukemia, and radiofrequency electromagnetic fields and glioma and acoustic neurofibroma, each of which has been classified as *possibly carcinogenic* (2B) by the International Agency for Research on Cancer (IARC) [19, 20]. Nonetheless, it is important to note that replication of such studies has been very inconsistent, and the literature surrounding their biological implication is extremely conflicting and contradictory [21].

Chemical Carcinogenesis

A chemical carcinogen is a substance with a distinct composition and potential to induce cancer-associated changes in cells. The husband and wife tandem of James and Elizabeth

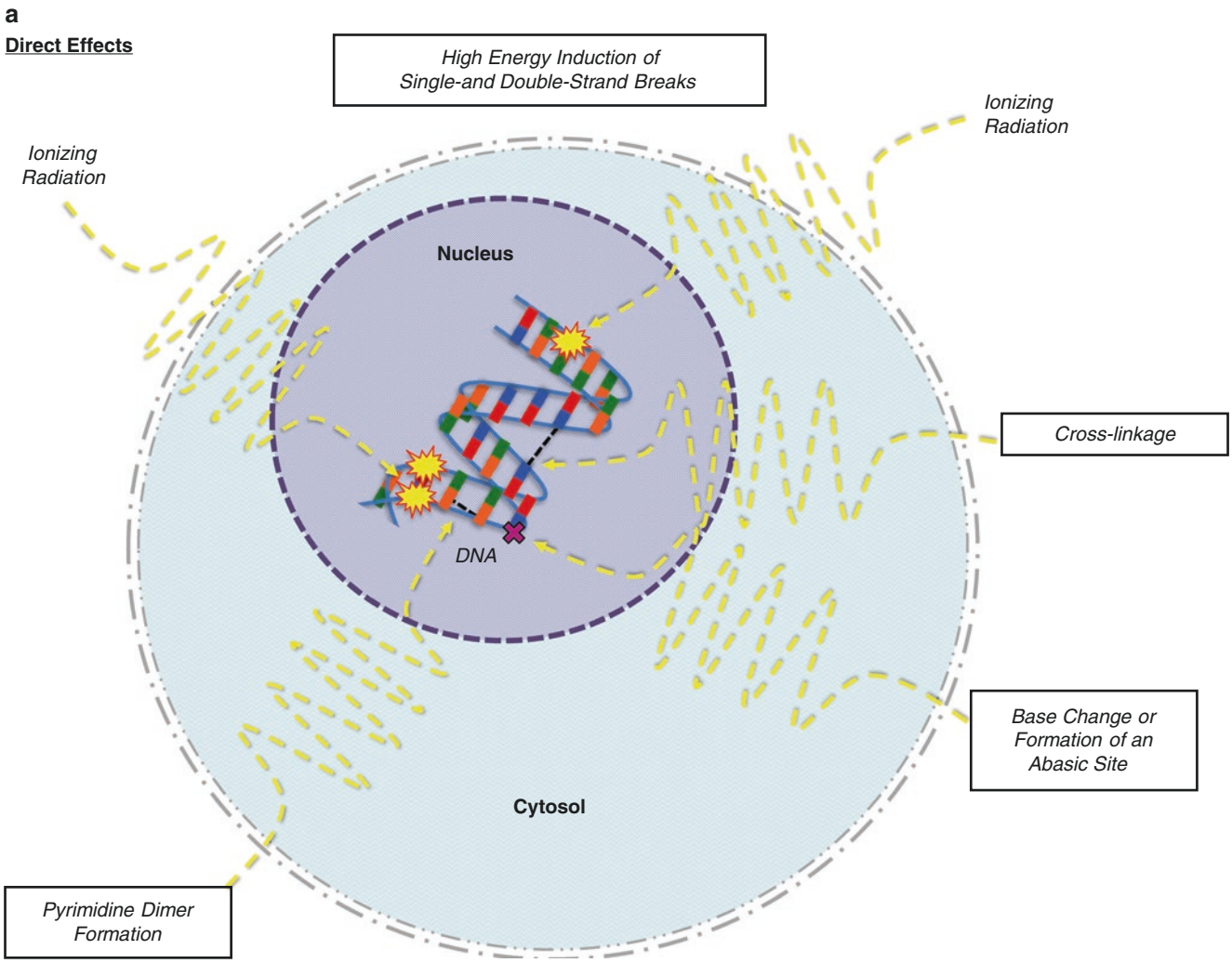

Fig. 3.1 Mechanisms for induction of DNA damage by ionizing radiation. (**a**) Direct effects to irradiated cells, including high-energy induction of single- and double-strand breaks, development of an abasic site or base change, or chemical alterations, including protein or DNA cross-linkage and formation of pyrimidine dimers. (**b**) Indirect or bystander effects stemming from generation of free radicals from endogenous H_2O or an increase in reactive nitrogen and oxygen species cytokine release induced by other damaged cells, either directly transferred by adjacent damaged cells via gap junction or indirectly mediated through immune cell activation

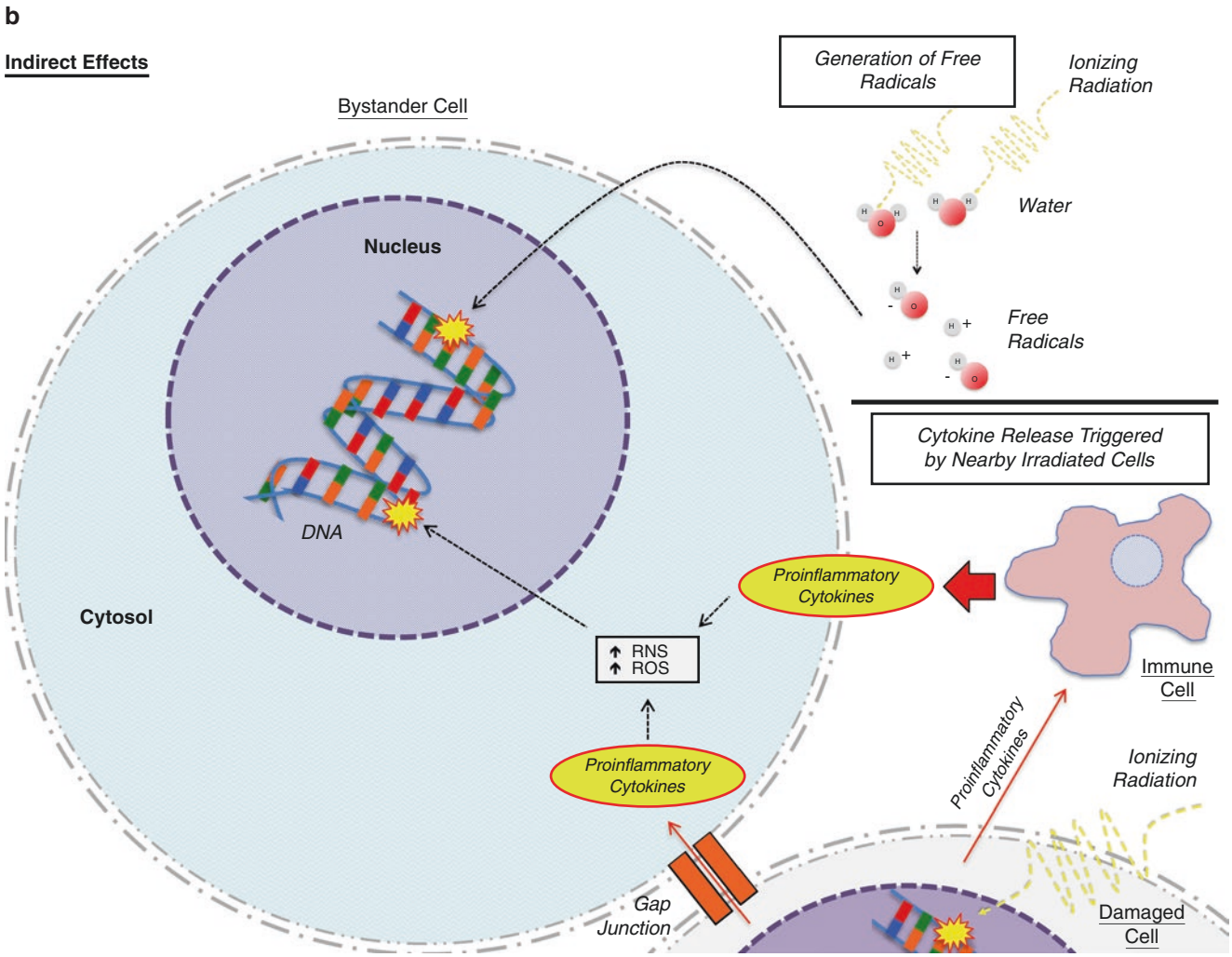

Fig. 3.1 (continued)

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 [22]. Direct carcinogens—also referred to as 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 [23], all of which are directly DNA reactive with no need for further metabolic conversion. Conversely, procarcinogens 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 [24]. They primarily operate by damaging DNA through formation of covalent lesions such as adducts or cross-linkage, oxidative damage stemming from free-radical production, or through induction of epigenetic alterations [24]. In contrast to endogenous carcinogens, which are already internalized, exogenous chemical carcinogens or their reactive metabolites must be capable of entering cells to generate DNA damage, meaning that they must either possess lipophilic properties allowing for passive transport or be actively transported across the cellular membrane [24].

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 adduct 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 sites 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 [24, 25]. This is an important chemical distinction since the ability of a chemical to form stable adducts is associated with increased mutagenicity [26, 27]. 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} [28]. Methyl groups ($–CH_3$) are the most common alkyl group adducted to DNA [29]. Generally speaking, alkylation lesions occurring on a base-ring nitrogen tend to be less mutagenic relative to those occurring on a ring oxygen [30]. These adducts can destabilize DNA leading to apurinic (i.e., degradation of a purine base) or apyrimidinic (i.e., 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 [31]. 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 [32], and may generate double-stranded breaks during the repair process [33, 34].

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 [24]. Both experimental and epidemiological evidence suggest a strong association between DNA adduct formation and cancer development [26, 27, 35–40]. As with small adducts formed by alkylation damage, the location of adduct formation on the DNA molecule matters with respect to mutagenicity [24]. For example, benzo[α]pyrene is a polycyclic aromatic hydrocarbon found in cigarette smoke, well-cooked foods, and combustion products and exhaust fumes [23]. 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, 24]. 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, and can produce conformational changes to the DNA and induce sequence alterations [9, 24].

Additionally, some exogenous chemicals or their metabolic intermediaries are capable of inducing oxidative DNA damage, frequently as a result of byproducts produced during their metabolism. In fact, oxidative damage accounts for a large portion of DNA mutations [41]. This occurs primarily through production of free radicals, such as ROS [42]. 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 damage, including strand breaks and covalent base lesions [42]. However, the predominant lesions induced are 8-hydroxydeoxyguanosine lesions and thymine glycol, which can result in base-mispairings, potentially leading to base-misincorporation mutations [43]. Dioxins and dioxin-like polychlorinated biphenyls (PCBs) are prime examples of such carcinogens for which the carcinogenic properties derive from free-radical production [44].

Up to this point, the majority of carcinogens that have been discussed involve organic chemicals, meaning that the molecules contain carbon atoms. However, several inorganic toxic metals or metalloids are considered by IARC to be definite or probable carcinogens, including nickel, cobalt, lead, vanadium, beryllium, arsenic, and chromium [45–47]. Humans can be exposed to such metals environmentally, such as through diet, pollution, and occupation. They are of interest due to their longstanding biopersistence, since they do not degrade [48], 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 operate through various pathways, some of which include, but are not necessarily limited to, induction of genetic and epigenetic alterations (the latter will be discussed in further detail later in this chapter), deregulation of cellular proliferation and metabolism, aberrant activation of signal transduction pathways, generation of reactive oxygen species and induction of hypoxia pathways [49], or by competitive binding with enzyme-associated metals, such as may be the case with inhibition of zinc-finger DNA repair proteins by arsenic, cadmium, nickel, cobalt, or lead [50].

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 ROS, RNS, and lipid peroxidation [42]. Hydrolysis can create aba-

sic sites or result in deamination [31, 51, 52]. Adducts derived from endogenous reactions, such as production of aldehydes [53] or estrogen metabolites [54], which, as with exogenously derived adducts, are capable of inducing mutations. ROS can produce oxidative lesions, single-stranded breaks, or phosphoglycolates—lesions produced at the sites of radiation-induced DNA strand breaks [42, 55, 56]. RNS, such as nitric oxide or peroxynitrite, can also create oxidative lesions and/or covalent adducts [57]. 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 [42, 58]. Many of these internally generated DNA damaging processes can occur in response to exogenous exposures, particularly in the presence of chronic exposures, such 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

Human genetic information is encoded in DNA, providing the blueprint for 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 [59]. 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 inter-individual 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-strand break repair, and damage tolerance, each of which will be explained in further detail below. 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-alky-guanine and O^4-alkyl-thymine lesions. 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 [60]. 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 [61] or of small single-strand DNA breaks by DNA ligase [62].

Base Excision Repair

Base excision repair (BER) is specific for correction of damaged bases, in particular apurinic or apyrimidinic bases [63, 64]. A key function of this mechanism is the removal of small, non-helix distorting DNA lesions, such as those caused by alkylating agents [9], so 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 [63, 64]. The relevance of BER to cancer is exemplified by heritable germline mutations in the aforementioned *MYH* glycosylase, which is involved in 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, with an elevated risk of colorectal cancer [65].

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 [66, 67]. 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 [66]. 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 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 [66, 67]. 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 [67, 68], which is associated with greater than 1000-fold increased risk for UV-induced skin and ocular cancer [68].

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, pairing of non-complementary 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 [69]. Mismatch repair is a post-replication mechanism that is specific for base-mispairings [69]. 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 [69, 70]. 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 [69]. 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* [71, 72], 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 [71, 72].

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 [73]. 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 [32]. 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 removal and repair of the lesion via a combination of the aforementioned repair mechanisms. Alternatively, global genome repair mechanisms (previously discussed in the NER section) can be used to sense DNA cross-links independent of DNA replication or transcription [32]. Deficiencies in the cross-link damage-sensing Fanconi Anemia pathway results in organ defects, as well as a substantially elevated cancer risk [74], exemplifying the relevance of interstrand cross-link repair to cancer prevention.

Double-Strand DNA Break Repair

As we discussed in an earlier section, double-strand DNA breaks (DSB) represent a major threat to DNA integrity [75], 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 [75]. The former mechanism (non-homologous end joining) simply links the broken ends of the DNA back together, in an enzymatic reaction [75]. 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 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, 75]. 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 [75]. 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 [75]. The importance of double-strand 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-strand 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 [76, 77]. Additionally, some radiation sensitivity syndromes arise as a result of germline mutations in damage-sensing genes involved in DNA double-strand 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-strand break damage and are associated with a substantial increase in cancer susceptibility [78].

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 [79, 80]. 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 [79, 80]. Both of these mechanisms are highly error prone, with potential for increased DNA mutations due to base-mispairing and/or recombination events.

Apoptosis

Finally, as a last resort, a cell that is damaged beyond repair may undergo and orderly, preprogrammed event resulting in apoptosis—or programmed cell death [81]. This is an important process that prevents somatic mutations from being passed on to subsequent generations, which is why acquisition of resistance to apoptosis is considered to be a hallmark of cancer [1, 2].

Genetic Mutations

A number of different types of genetic mutations are possible (Fig. 3.2). These can include point mutations, which affect only a single nucleotide, or insertion or deletion of multiple bases. Recall from the previous chapter that there are 64 different codon combinations that code for 21 possibilities (20 amino acids plus a stop codon), meaning that some codon combinations have overlapping specifications. Therefore, a point mutation can result in three potential scenarios: (1) synonymous—or silent—mutation, where the base change does not result in an amino acid change; (2) non-synonymous—or missense—mutation, where the base change does result in an amino acid change in the polypeptide sequence; or (3) truncation—or nonsense—mutation, which results in substitution of a stop codon for the original amino acid, thus cutting off the remaining polypeptide sequence, and can have dire functional consequences, such as improper functioning or loss of function. Insertion or deletion of bases in the sequence can be further classified as either (1) in-frame, where the number of bases inserted or deleted is a multiple of three, resulting in insertion or deletion of amino acids from the polypeptide without changing the reading frame (i.e., the rest of the sequence remains intact); or (2) frameshift, where the number of inserted or deleted bases is not a multiple of three, thus altering the downstream reading frame and, accordingly, the protein sequence.

From the standpoint of exposure biology, there is evidence that some exposures can produce unique mutational signatures in cancers, as a result of the mechanism through which the exposure induces mutations [82]. For example, exposure to UV radiation preferentially induces C to T or CC to TT mutations at pyrimidine dimer sites [83–85], giving rise to a unique mutational signature in skin cancer [86]. Similarly, specific mutational signatures have also been identified in cancers associated with aflatoxin exposure [87] and those arising in epithelium directly exposed to cigarette smoke [88].

Epigenetics and Cancer

Mutations stemming from DNA damage are not the only form of somatic carcinogenic aberration; epigenetics also play a major role in cancer development. Epigenetics encompass stable and heritable changes that either alter or have the potential to alter gene expression or phenotype [89]. There is mounting evidence that environmental exposures can alter epigenetic regulation of the genome, although the precise mechanisms for many such exposures remain unclear. 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 [90], 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, neonatal, or early development, when cells are still developing increasing

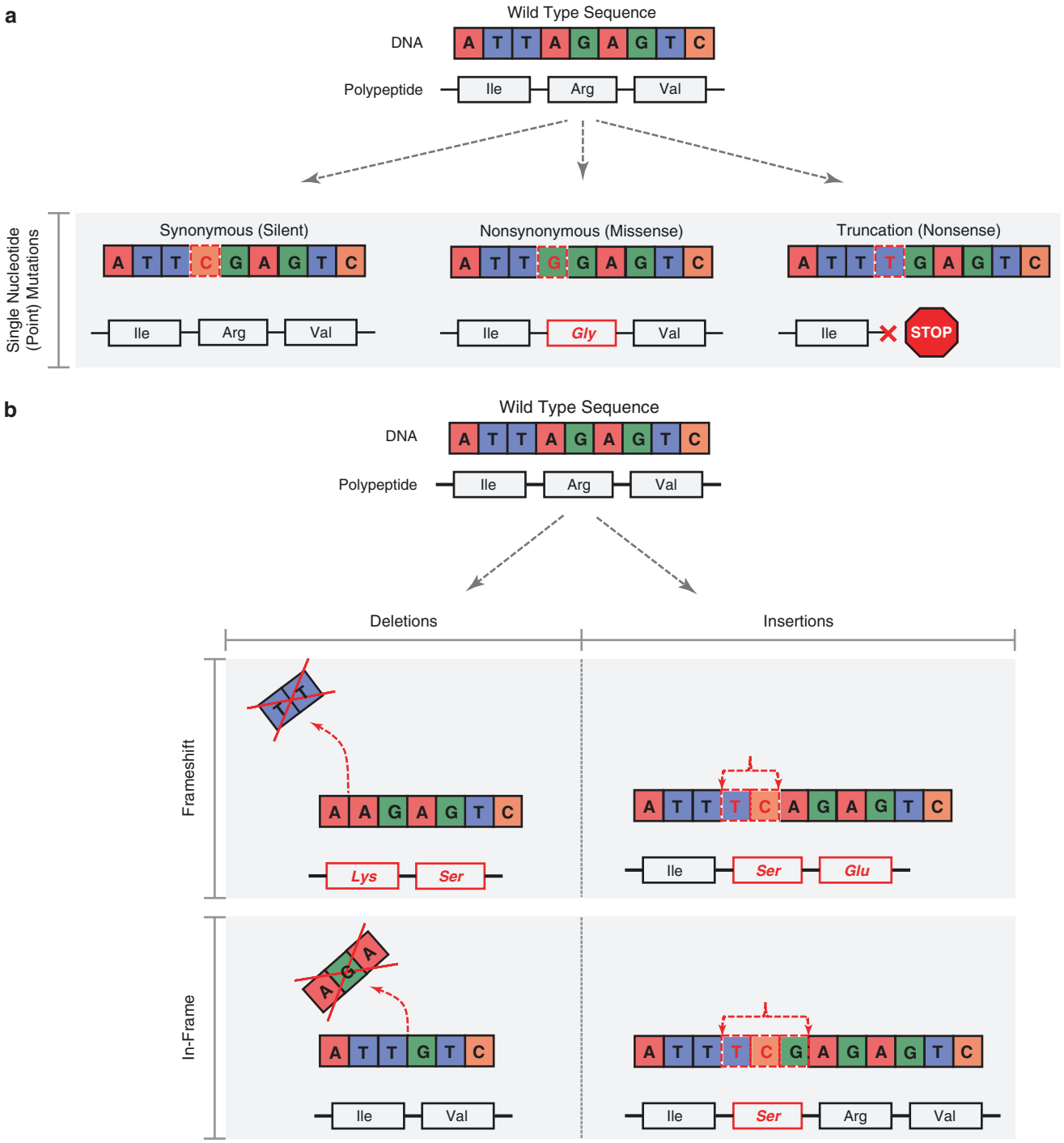

Fig. 3.2 Illustration of different types of mutations, and the respective impact on the associated polypeptide sequence during translation. Panel (**a**) depicts synonymous (silent), non-synonymous (missense) and truncation (nonsense) point mutations. Panel (**b**) depicts frameshift and in-frame insertions and deletions

the chance of dissemination of epigenetic errors throughout the genome, 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 DNA methylation and histone modifications in the context of cancer development.

DNA Methylation and Cancer

It is widely appreciated that cancer development is accompanied by widespread gains and losses of 5-methylcytosine (i.e., DNA methylation), termed hypermethylation and hypomethylation, respectively. 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 (e.g., CpG island, type of repeat sequence, transcription factor binding site, etc.) [91, 92].

Cancer-associated alterations in DNA methylation includes localized hypermethylation of CpG dense regions called CpG islands, particularly in promoter regions of tumor suppressor genes, although localized hypomethylation of oncogene promoters—resulting in their aberrant activation—can also occur. Promoter hypermethylation is generally associated with transcriptional silencing, at least as common as DNA mutation in the inactivation of tumor suppressor genes, and considered to be a major event in carcinogenesis. There are approximately 100–400 hypermethylated CpG islands in the promoter regions of most tumors [93]. Some genes frequently undergo promoter hypermethylation in multiple cancer types, such as *RASSF1A* and *CDKN2A*, while promoter hypermethylation of other genes are cancer-specific [94]. Promoter hypermethylation can affect genes involved in cell cycle control, DNA repair, carcinogen metabolism, cell-cell interactions, apoptosis, and angiogenesis [93, 95]. 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 [93, 95, 96]. It is not yet fully appreciated if the localized hypermethylation observed during carcinogenesis is a stochastic or targeted event, and whether it occurs as a result of failed epigenetic machinery, random biochemical processes, in response to endogenous or exogenous stimuli, or, most likely, a combination these events.

Most cancers are also accompanied by genome-wide hypomethylation, which often starts to manifest as an early event in carcinogenesis and becomes greater as tumors progress [93, 97]. Hypomethylation describes a general loss of methylation, with tumor cells losing between 20 and 60% of their genomic 5-methylcytosine relative to normal tissue [98]. Hypomethylation may be associated with corresponding loss of genomic stability due to nucleosome repositioning as part of reactivation of transposable elements, increasing the risk of chromosomal breaks, translocations, or allelic loss [93, 99, 100]. This is particularly true for hypomethylation of pericentric chromosomal regions, which is characteristic of many cancers and may further increase the probability of chromosomal breakage [99].

Environmental and Occupational Epigenetic Effectors

Numerous environmental and occupational exposures have been associated with altered DNA methylation, including physical agents and organic and inorganic chemical agents, many of which are reported to have a pleiotropic effect. Examples of better-established environmental and occupational modifiers of DNA methylation are described below:

Benzene is a single-ring volatile aromatic hydrocarbon that is a common air pollutant stemming from motor vehicle emissions, gasoline evaporation, cigarette smoke, and industrial exposures, and is classified by IARC as *carcinogenic to humans* (Group 1) [101]. A number of human and experimental studies have observed an association between benzene exposure and global hypomethylation and/or targeted promoter hypermethylation, as recently reviewed by Fenga and colleagues [102]. 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* [103]. Mechanistically, in vitro studies suggest that these effects may, in part, stem from inhibition of DNMT activity by the benzene metabolites hydroquinone and 1,4-benzoquinone [104].

Arsenic is a naturally occurring metalloid that is classified by IARC as *carcinogenic to humans* (Group 1) [105], and been associated with DNA hypomethylation by a number of studies [106, 107]. Arsenic is believed to impact DNA methylation through several mechanisms: (1) during arsenic metabolism, following the reduction of inorganic arsenate (As^{+5}) to arsenite (As^{+3}), arsenite methyltransferase (AS3MT) catalyzes the methylation of arsenite and competitively depletes *S*-adenosylmethionine (SAM)—the primary methyl donor in DNA methylation—to obtain excretable monomethylar-sonic acid (MMA^{+5}); (2) arsenic-induced ROS can result in oxidative lesions that reduce the ability of DNA methyltransferases (DNMTs) to methylate nearby cytosine bases; and (3) arsenic induced oxidative stress depletes reduced glutathione, resulting in an increase in glutathione biosynthesis at the expense of SAM biosynthesis, thus reducing available methyl groups for DNA methylation [108, 109]. In contrast to global hypomethylation, arsenic has also been associated with localized promoter hypermethylation of *p53* [110], *CDKN2*A [111], *DAPK* [112], and *RASSF1A* [111, 113].

Lead is a well-known toxic metal associated with a wide variety of health states, including neurocognitive effects, high blood pressure, chronic kidney disease, and cardiovascular disease. Inorganic lead compounds have also been classified by IARC as *probably carcinogenic to humans* (Group 2A) [114]. Epidemiologic studies have shown a trend toward global DNA hypomethylation [115–118]. This is further supported by experimental studies, which found that lead exposure inhibits expression of DNMT enzymes [119–122].

Cadmium is a toxic metal that is classified by IARC as *carcinogenic to humans* (Group 1) [123]. Interestingly, cadmium exposure induces opposing epigenetic effects, dependent upon the duration of exposure. Short-term exposure to cadmium results in hypomethylation through inhibition of DNMT [124]. However, experimental [124–133] and epidemiologic evidence [115, 134, 135] indicate that prolonged cadmium exposure can result in hypomethylation as a result

of over-compensation of DNMT in response to the initial inhibition.

Histone Modification

As is the case for DNA methylation, environmental and occupational exposures have been reported to alter histone modifications, particularly exposure to metals and metalloids. Nickel is a carcinogenic metal [136] that can actuate de novo methylation of tumor suppressor genes through induction of heterochromatin conformation by suppressing H4 acetylation through interference with HAT enzymes [95, 137–139], alterations in lysine methylation via interference with histone demethylase enzymes [140], and phosphorylation of serine at the tenth position of H3 (H3S10) through induction of the JNK-MAPK pathway [141]. Chromium - a metal that is considered carcinogenic in its hexavalent form [142] - can cause gene silencing via histone acetylation through interactions with histone acetyltranferase (HAT) and histone deacetylase complex (HDAC) enzymes [143], which are the enzymes responsible for adding and removing histone acetylation marks, respectively. Arsenic has been reported to increase dimethylation of lysine at the ninth 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 fourth lysine position on H3 (H3K4), which is associated with a transcriptionally active heterochromatic conformation [144]. However, as with DNA methylation, metals are not the only chemicals capable of inducing histone changes. The industrial organic chemical 1,3-butadiene, which is commonly used in synthetic rubber production and is classified by IARC as *carcinogenic to humans* (Group 1) [145], has been associated with decreases in transcriptionally repressive H3K9 and H3K27 methylation, as well as reduced H3K20 methylation, which is involved in repression of transposable elements, although the precise mechanism driving these alterations is presently unknown [108].

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 resulting in a C to T transition [99]. As a result, most of the human genome is depleted of CpG dinucleotides due to the relative instability of 5-meC [99]. The frequency of C to T methylation-associated transitions varies by tissue-type, probably due to tissue-specific differences in mismatch repair [99]. Repair of a T-G mismatch stemming from deamination can also give rise to a T-A transversion mutation [146]. More than 30% of disease-related germline point mutations occur at CpG dinucleotides [99]. 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 [147]. The risk of p53 mutation at 5-meC is tenfold that of unmethylated cytosine, and CpG dinucleotides in these regions are commonly methylated in normal tissue [147].

Alternatively, DNA methylation can indirectly induce point mutations by enhancing the mutagenic effect of exogenous carcinogens [99]. 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 [148–150]. Similarly, acrolein has an affinity for binding 5-meC, instigating to C to T transitions [151]. Additionally, methylation alters the light absorption wavelength for cytosine, favoring formation of covalent cross-link lesions in skin DNA upon UV exposure [99].

Somatic Mutations in Epigenetic Regulators

Recent large-scale whole-exome sequencing studies [152–162] have revealed a number of commonly mutated epigenetic genes in a wide variety of cancers [163–165]. Counted among these are a number of key regulators of epigenetic marks, including histone acetyltransferases, deacetylases, methyltransferases, and demethylases. While such events do not represent a direct epigenetic alteration, per say, functional mutations of these genes can clearly impact the ability of the cells to maintain the epigenetic status quo, which can in turn result in widespread transcriptional dysregulation.

Inflammation and Reactive Oxygen Species

While inflammation is crucial in protecting our tissues from foreign materials, pathogens and damaged cells, and facilitating wound healing, it can also play a key role in cancer development and progression [2, 166]. There are several reasons for this. Activated immune cells can induce oxidative stress—or an imbalance in reactive radicals relative to our capacity to detoxify them—through production of reactive oxygen species (ROS) and nitrogen species (RNS), which in turn can damage lipids, lipid membranes, enzymes and other proteins, and, perhaps most importantly in terms of lasting effects, DNA [167], although damage to proteins and lipids can also increase susceptibility of the cell to genomic dam-

Table 3.2 Examples of carcinogenic or potentially carcinogenic endocrine disrupting chemicals and the hormones or hormone receptors that they interact or interfere with

Endocrine disrupting chemical	Industrial or pharmaceutical application(s)	IARC classification	Disruption targets	References
Di(2-ethylhexyl) phthalate (DEHP)	Plasticizer	*Possibly carcinogenic to humans (Group 2B)* [174]	PPARα; PPARγ; CAR	[175, 176]
Polychlorinated biphenyls (PCB)	Variable industrial applications	*Carcinogenic to humans (Group 1)* [177]	T3; T4	[178]
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	Industrial byproduct	*Carcinogenic to humans (Group 1)* [179]	via AhR activation: ERα; ERβ; GCR	[180–182]
Dichlorodiphenyltrichloroethane (DDT)	Pesticide	*Probably carcinogenic to humans (Group 2A)* [183]	ERα; ERβ; AR	[184]
Diethylstilbestrol (DES)	Synthetic estrogen	*Carcinogenic to humans (Group 1)* [185]	ERα	[186]

ERα estrogen receptor alpha, *ERβ* estrogen receptor beta, *T3* triiodothyronine (thyroid hormone), *T4* thyroxine (thyroid hormone), *PPARα* peroxisome proliferator-activated receptor alpha, *PPARγ* peroxisome proliferator-activated receptor gamma, *AhR* arylhydrocarbon receptor, *GCR* glucocorticoid receptor, *AR* androgen receptor, *CAR* constitutive androstane receptor

age [168]. Moreover, activated immune cells and/or damaged tissue secrete cytokines and chemokines that can result in stimulation of angiogenesis or growth and proliferation of malignant (or premalignant) cells, as well as pro-survival signals via sustained activation of the pro-inflammatory NF-κB pathway [169].

One such example of environmental or occupational exposure would be inhalation of particulate matter stemming from combustion of organic materials or vehicle exhaust, both of which are classified by IARC as *Carcinogenic to humans* (group 1) [170, 171]. The carcinogenic effect of particulate matter stems, in part, from stimulation of an immune response, resulting in generation of ROS and RNS, along with the pro-cancer signaling described above [169]. This is supported by experimental and epidemiologic evidence for increased inflammation of pulmonary and perivascular tissue, along with increased levels of pro-inflammatory cytokines, as recently reviewed by Falcon-Rodriguez and colleagues [172]. Some of carcinogenic effect from asbestos is also believed to stem from induction of a chronic inflammatory response due to the presence of persistent asbestos fibers embedded in the tissue [173].

Endocrine Disruption

The term endocrine disruptor refers to exogenous chemicals or chemical mixtures that can interfere with the endocrine system, potentially leading to adverse health effects. They can mimic hormones and interact with hormone receptors in a specific or non-specific manner. As such, some endocrine disruptors can have a carcinogenic effect by altering key pathways in hormone-sensitive tissues. Examples of carcinogenic or potentially carcinogenic endocrine disruptors and the endocrine targets that they interfere with are provided in Table 3.2.

Summary Carcinogenesis is a complex multistep process involving an accumulation of genetic and epigenetic changes that alter the phenotype of the cell and imbue a growth or survival advantage that can eventually allow affected cells to develop malignant properties and invade into other tissues. Exogenous physical, chemical, and biological exposures stemming from the environment or occupational setting can induce such somatic genetic and epigenetic changes through a variety of mechanisms. Fortunately, eukaryotic cells have evolved a highly efficient mechanism for repairing such damage, although unfortunately, despite the high-fidelity of the process, mutations still may go unrepaired and become incorporated into the genome. Understanding how physical, chemical, and biological exposures can lead to genetic and epigenetic aberrations is paramount for discerning how occupational exposures can modulate risk for cancer development.

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Head and Neck Cancers

4

Dana Hashim and Paolo Boffetta

Introduction

Head and neck cancers (HNCs) of the lip and oral cavity, pharynx, larynx, salivary glands, and nose or nasal passages predominantly begin in the squamous cells (~90% of all HNCs) [1] that line the moist, mucosal surfaces inside the mouth, the nose, and the throat. Approximately 30–40% of patients with HNC squamous cell carcinomas present with early stage (stage I or II) disease; of those, the 5-year survival is 70–90% with treatment [2]. For most patients, however, HNCs are diagnosed at advanced stages, when treatment is both less effective and highly damaging to organs required for speech and swallowing. In particular, for individuals in countries with limited access to advanced treatment modalities, survival rates for all stages of HNC have been reported to be lower at 30–40% [3–6] compared to the US combined survival rate of 64% [2].

Within the US, the 5-year survival rate has not decreased substantially for the past two decades [7], reaching slightly over half the number of cases diagnosed [2]. The low survival rate is driven mainly by late diagnostic stage and lack of systematic HNC screening protocols. Even after treatment, approximately 30–60% of patients successfully treated for HNC will develop recurrent locoregional cancer [8–11], which is difficult to treat due to effects of prior treatment on tumor cells, as well as the infiltrative and multifocal nature that typically characterizes recurrent disease [12]. Given the highly aggressive, late diagnostic stage, and recurrence-prone clinical characteristics of HNCs, identification of HNC risk factors plays a key role in reducing HNC burden.

The majority of HNCs are due to acquired genotoxic exposure rather than cancers of inherited high penetrance oncogenic mutations. HNC tumors arising in epithelial tissue exposed to the environment and consistent epidemiological evidence demonstrating high attributable HNC risk factors. HNC carcinogenic agents that occur in occupational settings must therefore be understood in terms of their etiology, prevalence within occupations, and risk magnitude to accurately gain clinical and public health consideration in reducing overall exposure between and within countries.

Descriptive Epidemiology

Collectively, HNCs comprise approximately 3.8% of all malignancies and 3.6% of cancer deaths worldwide [13]. An estimated 529,500 cases of lip, oral cavity, and pharyngeal cancers have occurred worldwide in 2013, with 292,300 deaths [13]. Incidence rates of HNC are varied, ranging from 26.3 per 100,000 persons in Melanesia to 2.2/100,000 in Western Africa and 1/100,000 in Micronesia (Fig. 4.1), while the ratio of mortality to incidence is similar across regions [14]. Incidence is very high in both urban and rural areas in India. Other high incidence areas are Eastern, Western, and Southern Europe, Australia, and New Zealand [14]. Rates vary widely even within those countries [15, 16]. In Brazil, mortality rates from oral cavity cancer are stable in both men and women while pharynx cancer is increasing [17]. The diversity in HNC incidence rates are thought to be due to differences in risk factor prevalence, such as tobacco and alco-

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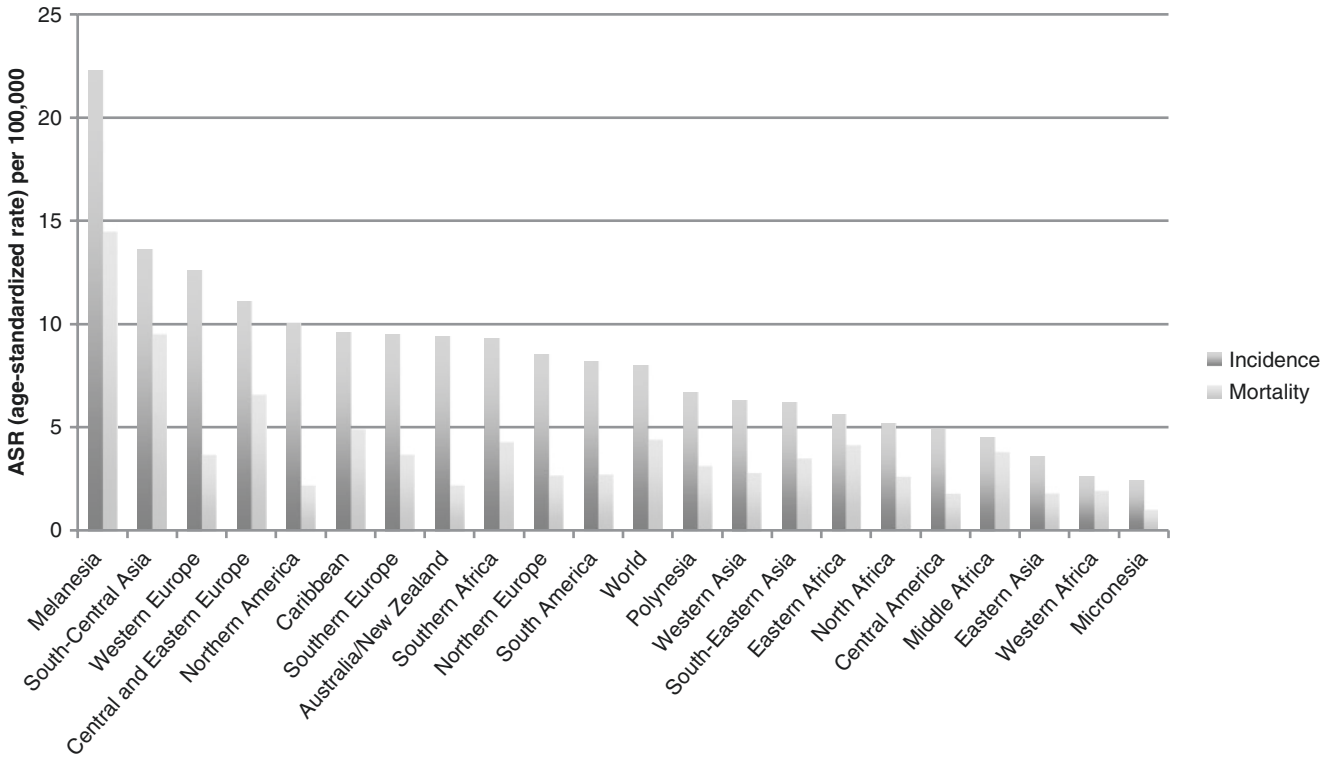

Fig. 4.1 Age-standardized incidence and mortality rates for head and neck cancers (excludes nasopharyngeal cancers) worldwide**.** (Reference: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 10/Jan/2018)

hol consumption, and exposure to chemical agents in some occupations. The contribution inherited susceptibility differences plays a more important role in younger patients than older patients [18].

Nasopharynx Cancer

Nasopharyngeal carcinoma differs from other HNCs in its epidemiology, pathology, natural history, and treatment. 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 [19]. However, incidence is higher in Southern China, Southeast Asia, the Middle East, and North Africa (Fig. 4.2). 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 [20–22]. This can mainly be attributed to changes in environmental risk factors within the Chinese population, such as lower consumption of traditional Chinese-style salted fish both in China [22] and in Chinese-Americans [23, 24]. The World Health Organization classifies nasopharyngeal carcinoma into three histological types: squamous cell carcinoma (Type I), nonkeratinizing carcinoma (Type II), and undifferentiated carcinoma (Type III). Nonkeratinizing and undifferentiated carcinoma are the most common (>90%) in high incidence areas, and squamous cell carcinoma, the most common (>70%) in low incidence regions [24–27]. Keratinizing squamous cancers at this site are uncommon except in the United States, and undifferentiated cancers are the most common nasopharyngeal cancers [27].

Similar to other HNC sites, nasopharygeal cancer incidence rates vary widely among geographic regions and suggests a multifactorial etiology that includes environmental and genetic susceptibility. In southern China, Southeast Asia, the Arctic, and the Middle East/North Africa, incidence may reach 25 cases per 100,000 per year [28]. In the United States and Europe, nasopharyngeal carcinoma is rare (incidence of 0.5 per 100,000 per year), but is more commonly associated

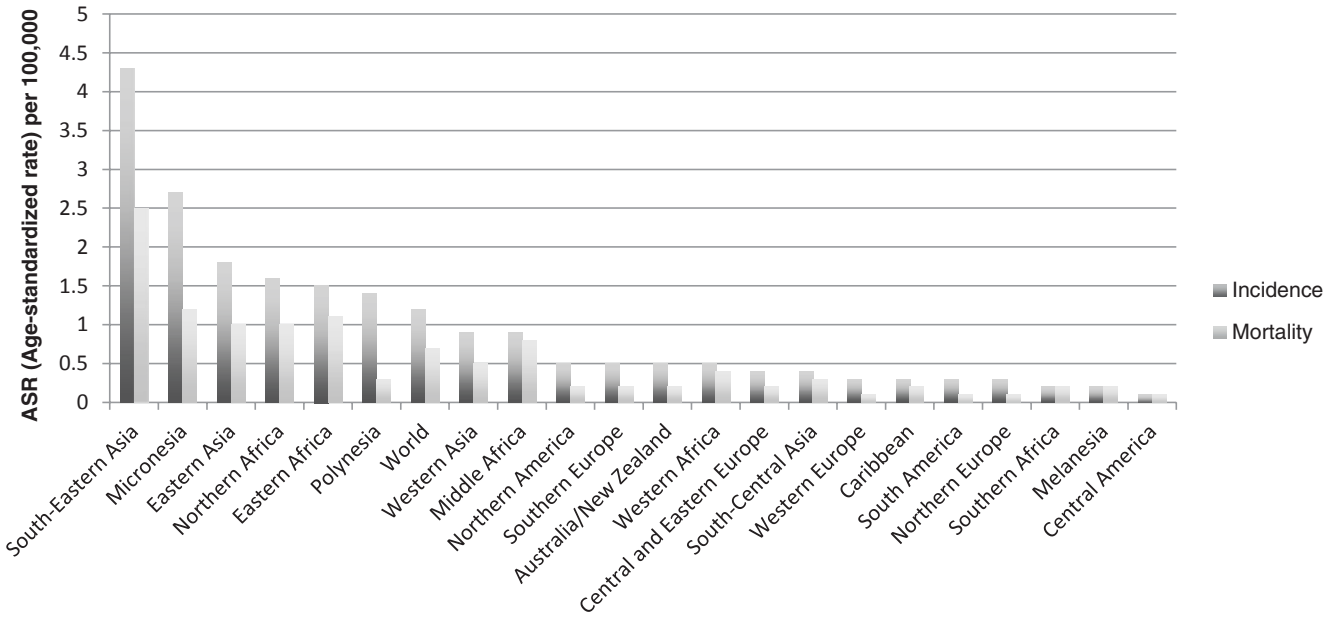

Fig. 4.2 Age-standardized incidence and mortality rates for nasopharyngeal cancers worldwide. (Reference: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 10/Jan/2018)

with alcohol and tobacco usage, which are classic risk factors for other head and neck tumors [29]. Nasal cavity and paranasal sinuses are the least frequent sites of origin for head and neck cancers in the United States. In Asia and South Africa, tumors of these sites occur more commonly than in the United States.

Nonoccupational Risk Factors

In high-income countries, approximately 75% of lip, oral cavity, and pharyngeal cancers are attributable to tobacco smoking and alcohol consumption [30]. In low-income countries, risk factors for lip, oral cavity, and pharyngeal cancers also include the chewing of betel quid with or without tobacco, particularly for oral cavity and oropharyngeal and oral cavity cancers) [31]. Other major global risk factors include the use of pipes to smoke tobacco; the consumption of nitrosamine-rich foods, including salted fish [18] and Epstein–Barr virus (EBV) for nasopharyngeal cancer [18]. In addition, infection with high-risk human papillomavirus (HR-HPV) types (i.e., HPV16 and HPV18) explains 17–56% of oropharyngeal cancers in developed countries and, to a lesser extent (13%), oropharyngeal cancers in less developed countries [32]. Oropharyngeal squamous cell cancer (OPSCC) is increasing in incidence in the United States and other high-income countries [33, 34]. Studies of Scandinavian populations have also increasing incidence of tongue cancer in both male and female young adults [33, 34]. These epidemiologic changes are driven by increasing oral exposure to human papillomavirus (HPV) infection. HPV-positive OPSCC patients are more likely than HPV-negative OPSCC patients to be white, to be younger, and to have better survival [35, 36] both at the time of the primary diagnosis and upon disease recurrence [37].

Other HNC risk factors are linked to environmental exposures, e.g., ultraviolet radiation (UVR) (lip cancer) [38], or deficiencies in dietary intake, e.g., fruits and nonstarchy vegetables (oral cavity and pharyngeal cancers) [39]. Several nonoccupational factors have been found to be consistently associated with increased risks of developing HNC. Agents with sufficient evidence for HNC as agreed upon by experts recruited to the International Agency for Research on Cancer (IARC) monographs are presented in Table 4.1.

Tobacco smoking and alcohol consumption have been recognized as the main causal factors for oral cavity and pharynx tumors, with a consistent dose–response relationship with HNC risk and substantially higher risks in more distal HNC organs [42, 84, 85]. There is also an evident interaction between these two risk factors [86].

Table 4.1 Carcinogenic agents with sufficient evidence in humans

Risk factor	Definition	Range of risk[a]	HNC subsite	References
Lifestyle risk factors				
Alcoholic beverages	>3 drinks/day	1.5–2.8	Oral cavity	[40–44]
	Per 10 g/day increase	1.01–1.3	Pharynx	[45]
	>3 drinks/day	1.7–3.8	Pharynx	[40]
Betel quid with tobacco	Chewers vs. nonchewers	4.0–30.4	Oral cavity	[43, 46–56]
	Chewers vs. nonchewers	1.8–8.0	Pharynx	[47, 57, 58]
Betel quid without tobacco	Chewers vs. nonchewers	2.2–6.9	Oral cavity	[43, 59, 60]
Tobacco smoking	Smoking vs. nonsmoking	1.4–9.7	Oral cavity	[61, 62]
	Smoking vs. nonsmoking	1.5–36.7	Pharynx	[61, 62]
	Over 1 pack/day vs. none	4.0–5.3	All HNC excluding nasopharynx	[62]
	Duration: over 10 years vs. never smoking	1.4–6.5	All HNC excluding nasopharynx	[62]
	30 or more pack-years vs. never smoking	1.9–3.0	Nasopharynx	[63, 64]
Tobacco, smokeless	Chewers vs. nonchewers	4.7–5.1	Oral cavity	[47, 65]
Chinese-style salted fish	Diet includes salted fish vs. does not include salted fish	2.0–4.9	Nasopharynx	[66, 67]
Infectious risk factors				
Human papillomavirus (HPV) type 16	HPV positivity	1.3–24.0	Oral cavity	[68, 69]
	HPV positivity	51	Tonsil	[69]
	HPV antibodies or HPV positivity	38.2–69.0	Oropharynx	[70–72]
Epstein-Barr virus	Epstein-Barr virus infection antibodies	9.4–22.0	Nasopharynx	[73, 74]
Chemical risk factors				
Formaldehyde	>4.0 parts per million (ppm) vs. 0 ppm	1.8	Nasopharynx	[75]
	Residential exposure or job exposure vs. no exposure	1.3–5.5	Nasopharynx	[26, 76–79]
Radiation risk factors				
X-radiation, gamma-radiation	Excess relative risk (ERR) or excess odds ratio (EOR) per Gy	2.4–4.5	Salivary glands	[80–83]

[a]Confidence intervals do not include 1

A pooled analysis of case-control studies has shown the carcinogenic associations of involuntary smoking on head and neck anatomical sites, particularly pharynx and larynx [87]. Although the evidence is limited, secondhand exposure to tobacco smoke in homes and work place is also associated with oral cavity and pharynx tumors. While some studies report a higher risk of HNC among those ever exposed to secondhand smoke, many are not able to adjust for other factors that influence cancer or secondhand smoking exposure, including other sources of secondhand smoke exposure [88, 89]. Other studies adjusting for confounding factors and pooling multiple data sources [87] did not find strong evidence of an association. Among never tobacco and alcohol users, all the odds ratios (OR) were elevated for >15 years of exposure at home or at work for head and neck cancers overall and separately for cancer of the pharynx, and only at work for cancer of the larynx [87]. An important risk factor associated with both HNC and secondhand smoke exposure is low socioeconomic status. Both prevalence and incidence of oral cavity and pharynx cancer is higher among groups of low socioeconomic status [90, 91].

Although uncommon in Western countries, betel quid chewing is widespread in much of the Indian subcontinent, East Asia, and countries of the Asian Pacific and is a major risk factor for lip, oral cavity, and pharyngeal cancers for a large proportion of individuals globally. Betel quid chewing prevalence has been reported to vary from 33.8% among in rural Sri Lanka [92] to 76.8% in the Solomon Islands [93]. Risk has been associated with chewing of betel quid with or without tobacco [18, 31]. Betel quid is placed in close contact with the oral mucosa and absorbed, similar to tobacco snuff, and consists of a combination of betel leaf, areca nut, slaked lime, and sometimes includes tobacco and/or other spices and herbs [92]. Both tobacco and nontobacco products are commercially available in India and are considered carcinogenic to humans [94, 95].

Recent decreases in tobacco and betel quid use have resulted in a decrease in the overall incidence of oral cavity cancers in

most parts of the world. However, the incidence of oropharyngeal cancers has been increasing, especially among individuals in high-income countries, hypothesized to be due to non-regressing HR-HPV infection [96, 97]. Human papillomavirus (HPV), particularly HPV16, is associated with oropharyngeal cancer. Increasing the vaccination coverage by HR-HPV prevention program efforts for young men and women is expected to control the rise of oropharyngeal cancers among young individuals. Immunization against the most common HR-HPV types can prevent a large proportion of HR-HPV-related cancers (in some cases, approximately 80–90%), especially for oropharyngeal cancers [96]. Increasing incidence of tongue and tonsil tumors seen in the under 45 years has been attributed to increasing prevalence of HPV infection in developing countries, practice of oral sex, and number of sexual partners [96, 98]. Though many of the recently vaccinated age group have yet to reach middle age, the increasing the coverage of HR-HPV prevention programs may be effective at controlling the increasing trend of oropharyngeal cancers by controlling exposure to HPV. Immunization against the most common HR-HPV types is expected to prevent a large proportion of HR-HPV–related cancers (in some cases, approximately 80–90%), especially for oropharyngeal cancers, which are predominantly caused by HPV type 16 [15].

Other factors with limited evidence related to HNC have also been reported. Consumption of fruit and vegetables is inversely associated with HNC risk [39]. Individuals with BMI < 18 are at increased risk of all HNCs or by subsite (including oral cavity, pharynx, and larynx) [99–101]; periodontal disease and regular gum bleeding, as well as daily mouthwash use have been shown to be independent risk factors for oral cavity and pharynx cancer [102, 103], even after adjusting for education attained, a global proxy for socioeconomic status [104].

Although HNCs share tobacco smoking as a common risk factor, two unique non-occupational agents are strongly associated with nasopharyngeal cancer alone: Epstein–Barr virus, Chinese-style salted fish. Long-term consumption of salted fish starting in childhood is an important cause of nasopharyngeal cancer in the Chinese population [18, 95]. While there is sufficient evidence of an association between Epstein–Barr virus and nasopharyngeal cancer, other cofactors must also be present for carcinogenesis [24, 105, 106]. Other factors also associated with nasopharynx cancer are residential exposure to formaldehyde [107] can previous chronic ear or nose diseases, such as chronic rhinitis or otitis media [108, 109]; active and passive smoking [18, 108–112]; use of Chinese nasal oil and traditional herbal medicine [110, 113].

Occupational Risk Factors

There is some evidence that known carcinogens can also play a role in HNC risk within occupations, including asbestos, strong acid mists, polycyclic aromatic hydrocarbons, textile dust, working in the rubber industry, metal working fluids, and man-made vitreous fibers [114–119]. Whether the relationship is causal remains inconclusive due to small sample size population, very few conducted studies, and inconsistent associations between HNC risk and specific occupation. In addition to discussing established HNC occupational risk factors, this chapter therefore provides an overview of suspected occupational causes of HNCs with limited evidence.

Some studies have investigated the relationship between occupation and oral cavity and pharynx cancer. Tables 4.2 and 4.3 describe 20 case-control and 24 cohort studies, which reported an association between specific occupations and industries and oral cavity and pharyngeal cancer. Several occupations, work in specific industries, and exposure to specific agents have been screened for their carcinogenic potential.

Oral and Pharyngeal Cancers

Occupations and Agents with Less Than Sufficient Evidence

Formaldehyde

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

Results of available studies on oral and pharyngeal cancers and the relationship to occupational formaldehyde exposure are inconsistent and no clear association could be established [118, 159]. Three of the four case-control studies examining the association of formaldehyde exposure in oral and pharyngeal cancer did not report any risks or were inconclusive [76, 125, 129, 136, 159]. However, these studies were small and retrospective, relying on questionnaires for exposure assessment.

Cohort studies provide conflicting results on the relationship between formaldehyde occupational exposure and oral and pharyngeal cancers. A cohort study of workers from ten US formaldehyde production or utilization plants found elevated standardized mortality ratios (SMRs) of 443 ($p < 0.05$) for oropharynx cancer in those exposed to cumulative doses of

Table 4.2 Case-control studies on occupation and cancer of 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 [120], 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. [121], United States, 1975–1978	232 women with oral and pharynx cancer residents in certain central North Carolina counties	502 controls matched by admission date, age, race, and county of residence (from the same institutions as cases; and from death certificate lists).	Employment in textile, apparel, and hosiery industries. It was examined also with 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)		
	(156 from 5 hospital and 99 from death certificates)	Controls were not eligible if they had a diagnosis of mental disorder, neoplasms of oral cavity or pharynx, esophagus or larynx, or other noninfectious oral or pharyngeal diseases		**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)		

Vaughan et al. [76], 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		
				9-Jan	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		
				19-May	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		
				19-May	16 (40)	0.9 (0.4–1.8)		
				20+	15 (22)	1.3 (0.6–3.1)		
Oreggia et al. [122], 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 of 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 professionals 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)		
				Electricians	2 (2)	5.5 (0.7–40.2)		
				Railwaymen	2 (1)	5.7 (0.6–51.3)		

(continued)

Table 4.2 (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
Franco et al. [107], 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 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 [123], 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, gender	Jobs were broadly classified into 31 industrial and 59 occupations classified via the US Census Bureau. Never/ Never considering all years and induction period (excluding 15 years before diagnosis). Here is presented only the odds ratios equal or higher than 1.5 for both situations "all years" and "induction period"	**Occupation/ Industry**		**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)
				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, 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, fisheries	6 (11)	1.6 (0.5–5.3)		
				Other machine operators in lumber, 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 laborers in lumber, wood-product manufacturing	8 (18)	1.6 (0.6–4.7)		
				Occupation/ Industry		**OR (Induction period)**		
				Writers, entertainers, 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)		

(continued)

Table 4.2 (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
				Food service in transportation, 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, fisheries	6 (11)	1.6 (0.5–5.4)		

				Other machine operators in lumber, 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)		
				Other transportation workers in transportation communication	8 (9)	1.5 (0.6–4.0)		
				Handlers, cleaners laborers in lumber, wood-product manufacturing	8 (18)	1.6 (0.6–4.7)		
Haguenoer et al. [124], France, 1983	283 men with nose (n = 14), lips (n = 16), oral cavity (n = 64), pharynx (n = 114), and larynx (n = 54), other and multiple sites (n = 21)	Two controls per case were chosen from patients without cancer in general hospitals in the same geographical area, matched by age, gender, ethnic group,	Types of occupation classified in 11 groups		**Oral cavity**			
				Mining	11 (11)	3.5 ($p < 0.5$)		
				Building industry	12 (14)	1.9 ($p \geq 0.5$)		
				Metal work, mechanics	13 (22)	1.2 ($p \geq 0.5$)		
				Agriculture	1 (7)	0.3 ($p \geq 0.5$)		
				Road transport	4 (10)	0.8 ($p \geq 0.5$)		
				Shipping and seamen	3 (9)	0.5 ($p \geq 0.5$)		
				Textile industry	2 (5)	0.7 ($p \geq 0.5$)		
				Wood work	2 (3)	1.3 ($p \geq 0.5$)		
				Road works	5 (5)	2.2 ($p \geq 0.5$)		
				Service	11 (39)	0.5 ($p \geq 0.5$)		
				Others	1 (3)	0.7 ($p \geq 0.5$)		
	cancer diagnosed in first semester 1983 in a regional cancer center in North of France	area of residence, and smoking and alcohol drinking history			**Pharynx**			
				Mining	17 (28)	1.4 ($p \geq 0.5$)		
				Building industry	21 (23)	2.0 ($p < 0.5$)		
				Metal work, mechanics	16 (42)	0.7 ($p \geq 0.5$)		
				Agriculture	4 (15)	0.5 ($p \geq 0.5$)		
				Road transport	6 (15)	0.8 ($p \geq 0.5$)		
				Shipping and seamen	5 (10)	1.0 ($p \geq 0.5$)		
				Textile industry	12 (11)	2.4 ($p < 0.5$)		
				Wood work	4 (1)	–		
				Road works	5 (6)	1.8 ($p \geq 0.5$)		
				Service	20 (67)	0.5 ($p < 0.5$)		
				Others	5 (10)	1.0 ($p \geq 0.5$)		

(continued)

Table 4.2 (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. [125], 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.	**Occupation**			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,
				Service workers	15 (36)	2.7 (1.0–4.6)		
				Working proprietors	3 (1)	14.7 (1.0–206.5)		
				Cooks, waiters, bartenders	3 (3)	10.3 (1.3–81.2)		
				Service workers	3 (4)	5.9 (1.0–35.4)		
				Production and related workers, transport equipment	69 (235)	2.3 (1.1–5.0)		
				Chemical processers and related workers	4 (2)	8.3 (1.3–55.0)		
				Tailors, dressmakers, sewers	3 (8)	6.8 (1.4–38.7)		
				Machinery fitters and assemblers, precision instrument makers (except electrical)	18 (43)	2.0 (1.0–4.0)		
				Plumbers and pipe fitters	6 (5)	5.0 (1.8–21.5)		
			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.	**Activity branch**				naphthalene, sulfuric acid, formaldehyde, dusts, gases, solvents were conducted, but all RR had 95% confidence intervals included 1
				Railway equipment production	3 (2)	7.7 (1.0–63.2)		
				Building industry	29 (67)	2.5 (1.3–4.5)		
				Restaurant, bars, hotels	6 (4)	14.5 (2.8–75.7)		
				Social services	10 (26)	2.8 (1.1–6.7)		
				Recreational and cultural private services	3 (1)	34.6 (2.3–524.0)		

			A job-exposure matrix for 13 agents which are or may be related to respiratory cancer and three nonspecific exposures was applied to this data base. Here is presented only the odds ratios OR with 95% confidence intervals excluded 1					
Vaughan and Davis [126], 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.	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 year before diagnosis	12	0.5 (0.2–1.2)		
				Employment for 10 or more year taking place at least 15 year before the reference date	No information	1.5 (0.4–5.5)		
			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					

(continued)

Table 4.2 (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. [127], United States, 1984–1985	1114 incident cases of the oral cavity and oropharynx (762 men, 352 women) of ages 18–79 years	1268 controls (837 men, 431 female) 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). There were 14 suspected high-risk jobs, also a list of employment categories were examined according to specific anatomic sites. Ever/Never employment or job were 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, etc.	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, etc.	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)		
				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, etc.	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)		

(continued)

Table 4.2 (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	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. [128], Germany, 1988–1991	100 incident cases of oral cavity cancer	400 randomized control	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. [129], Sweden, 1988–1990	Incident cases of cancers of 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 as a stratified by age and region 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, 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)		

					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. [130], Sweden, 1980–1988	410 cases (276 men, 134 women) of squamous cell carcinoma of oral cavity diagnosed and reported to Cancer Registry in four most northern counties in Sweden	410 controls matched by age, sex, and of same county as cases	A questionnaire covered lifetime occupational history up to date of diagnosis and were asked about exposure for some agents. All occupations were classified according to the Nordic Working Classification system	**Occupations (10 or more subjects)**		OR		
				Secretary and typist	4 (10)	0.4 (0.1–1.3)		
				Miner, 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)		
				Pesticides all	49 (43)	1.2 (0.7–1.8)		
				Phenoxyacetic acids	20 (12)	1.7 (0.8–3.5)		
				Herbicides, others	4 (6)	0.7 (0.1–2.4)		

(continued)

Table 4.2 (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
				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)		
Marchand et al. [131], France, 1989–1991	206 incident cases of hypopharynx cancer in men recruited from 15 hospital 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) were 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		
				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. [132], Cuba, 1996–1999	200 incident cases of oral cavity and oropharynx (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 and other	35 (30)	1.94 (0.87–4.33)		
Coble et al. [133], 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**			Adjusted for age, smoking, and alcohol consumption. *P*-value for trend: dusts 0.5; metals 0.2; solvents 0.03	
				Agriculture industry	36 (64)	1.4 (0.8–2.6)		
				Sugarcane industry	16 (13)	3.4 (1.2–9.4)		
				Sugarcane farmers	14 (10)	4.4 (1.4–13.6)		
				Pharynx				
				Agriculture industry	24 (64)	1.6 (0.8–3.2)		
				Sugarcane industry	5 (13)	1.0 (0.3–3.8)		
				Sugarcane farmers	3 (10)	0.8 (0.2–4.0)		
				Oral cavity and pharynx				
				Dusts				
				None	119 (197)	1.0		
				Low	25 (51)	0.5 (0.3–1.0)		
				Medium	60 (70)	1.3 (0.7–2.1)		
				High	82 (94)	1.1 (0.7–1.7)		
				Metals				
				None	234 (350)	1.0		
				Low	20 (23)	1.1 (0.5–2.6)		
				Medium	24 (32)	1.2 (0.6–2.5)		
				High	8 (7)	2.7 (0.7–10.6)		
				Solvents				
				None	205 (321)	1.0		
				Low	28 (33)	1.0 (0.5–2.1)		
				Medium	41 (54)	1.6 (0.9–2.9)		
				High	12 (4)	3.2 (0.8–12.6)		

(continued)

Table 4.2 (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
Menvielle et al. [134], 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**			RR adjusted by alcohol intake, smoking, and occupational exposures: asbestos, coal dust (ever/never) and formaldehyde (maximal probability of exposure)	
				Never manual	27	1.0		
				Ever manual	174			
				Adjusted				
				Age		3.50 (2.14–5.73)		
				+ alcohol and		2.65 (1.51–4.66)		
				tobacco				
				+ occupational		1.84 (0.97–3.48)		
				exposure				
Andreotti et al. [135], Brazil, 1999–2001	325 incident cases of oral cavity and pharynx (274 men, 51 women) from 7 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**			Adjusted for age, smoking, and alcohol consumption.	Analysis conducted only with men workers. Reported only the occupation or industry with RR statistically significant
				Ever exposed	26 (12)	2.45 (1.14–5.27)		
				≥10 years	21 (3)	7.90 (2.03–30.72)		
				≥10 years and ≥20	19 (3)	7.38 (1.88–28.98)		
				latency years				
				Vehicle repair worker				
				Ever exposed	14 (7)	2.10 (0.78–5.68)		
				≥10 years	13 (1)	26.21 (2.34–294.06)		
				≥10 years and ≥ 20	11 (1)	24.46 (2.10–284.60)		
				latency years				

Vlajinac et al. [136], Serbia and Montenegro, 1998–2000	100 incident cases (89 men, 11 women) of oropharynx (including base of tongue, neoplasm of palate, neoplasm of 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. [137], United States, 1982–1988	1522 men of upper aero-digestive and respiratory cancers (241 oral and pharynx)	1522 controls matched on age and smoking, selected from hospital visitors with a cancer suspicion and those who were screened as outpatients in 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, alcoholic drinks per week and year of enrolment	
				Wood dust exposure				
				Never	188 (1153)	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 (1153)	1.0		
				Occasionally	28 (262)	0.68 (0.44–1.06)		
				Regularly	21 (107)	1.27 (0.76–2.14)		

Table 4.3 Cohort studies on occupation and cancer of 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. [138], France	1374 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. [139], United States	26,561 workers (22,553 men; 3130 women) first employed in 10 formaldehyde-producing or -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.	Several tumors		**Oral cavity and pharynx**	**SMR**		Black women were excluded from analysis because of small numbers ($n = 26$). SMR based on U.S. national rates.
					White men			
				18	Exposed	96 (57–152)		
				3	Nonexposed	54 (11–157)		
					White women			
				0	Exposed	–		
				0	Nonexposed	–		
					Black men			
				3	Exposed	–		
				3	Nonexposed	–		

		Measures of exposure to formaldehyde used in the analysis included level or intensity, duration, average, cumulative or peak exposure, presence of particulates, and measures			Intensity of exposure (white men)			NS = non-statistically significant
				2	0	89 (NS)		
				1	>0 to <0.1	30 (NS)		
				4	0.1–0.4	59 (NS)		
				14	0.5–1.9	130 (NS)		
				0	≥2.0	–		
					Lip			
					Cumulative formaldehyde exposure			
				0	0 ppm-year	–		
				1	≤0.5 ppm-year	477 (NS)		
				0	0.51–5.5 ppm-year	–		
				1	>5.5 ppm-year	764 (NS)		
		that excluded recent exposures from the exposure index			**Tongue**			
					Cumulative formaldehyde exposure			
				0	0 ppm-year	–		
				0	≤0.5 ppm-year	–		
				2	0.51–5.5 ppm-year	96 (NS)		
				0	>5.5 ppm-year	–		
					Gum, floor, 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	–		

(continued)

Table 4.3 (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
					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. [140], United States	11,030 workers (2088 men, 9022 women) 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 exposed	All tumors			**SMR**		Workers who were employed only in clerical or administrative positions were excluded fro the analysis.
				4	**Oral cavity**	343 (118–786)		
				0	White men	–		
				4	White women	485 ($p < 0.01$)		
				0	Non-white men	–		
				0	Non-white women	–		
				2	Plant 1	306 (NS)		
				2	Plant 2	886 ($p < 0.01$)		
				0	Plant 3	–		
					Latency period			
					(3 months–9 years)			
					Duration of exposure			Reported here only risk estimates for oral cavity and pharynx tumors. NS = non statistically significant
				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	357 (NS)		
					Latency period			
					(20+ years)			
					Duration of exposure			
				0	3 months-3 year	–		
				1	4–9 y	315 (NS)		
				1	10+ year	654 (NS)		
				2	Overall	705 ($p < 0.01$)		
					Year of first exposure			
				4	1955–1962	440 ($p < 0.01$)		
				0	1963–1970	–		
				0	1971–1978	–		
				2	**Pharynx**	359 (NS)		
				1	White men	239 (NS)		
				1	White women	86 (NS)		
				0	Non-white men	–		
				0	Non-white women	–		
				1	Plant 1	100 (NS)		
				0	Plant 2	–		
				1	Plant 3	–		
					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	233 (NS)		
					Latency period			
					(20+ years)			
					Duration of exposure			

(continued)

Table 4.3 (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
				0	3 months–3 years	–		
				0	4–9 years	–		
				0	10+ years	–		
				0	Overall	–		
					Year of first exposure			
				1	1955–1962	76 (NS)		
				1	1963–1970	273 (NS)		
				0	1971–1978	–		
Lynge and Thygesen [141], Denmark	Cohort included people aged 20–64 years at the census on 9 November 1970. Ten year folllow-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		**Occupation/ Industry**	**RR**		Here were reported only RR with 95% confidence interval excluded 1
				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, painter in metal industry	1.95 (0.05–10.92)		
				6	Skilled workers, painter in paint workshop	3.30 (1.21–7.18)		
				0	Skilled workers, painter/other industries	–		
				3	Self-employed, painter in paint workshop	1.73 (0.34–5.07)		
				10	All painters	2.27 (1.09–4.18)		

Gardner et al. [142], United Kingdom	14,017 men employed in six of formaldehyde-producing or -using plants (7660 first employed before 1965, 6357 first employed after 1964); mortality follow-up until end of 1989	Exposure to formaldehyde was on the basis of recorded titles of jobs undertaken by each of the men before 1982.	All tumors		Employed before 1965	**SMR**		Here reported only the risks for oral cavity and pharynx cancer
				3	Oral cavity	137 (28–401)		
				7	Pharynx	147 (59–303)		
					Employed after 1964			
				1	Oral cavity	190 (5–1059)		
				0	Pharynx	–		
		Exposures have been qualitatively classified after detailed discussions on past working conditions						
Johnson [143], United States	Cohort with 10,841 members of meatcutters union in Baltimore (6906 men, 3935 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 department	Men		
						1.7 (0.8–3.2)		
						Women		
						0.5 (0.0–2.6)		
Pukkala et al. [144], Finland	Cohort of persons born in Finland during 1906–1945. Follow-up 1971–1985 detected 3178 cases (2369 in men, 809 in women) of cancer of lips, tongue, oral cavity, and pharynx	Occupations were coded at Statistics Finland using a modified Nordic Classification of Occupations	Oral cavity (lips, tongue), pharynx		**Tongue (men only)**	**SIR**	SIR adjusted for social class	We reported here only SIR with 95% confidence interval excluded 1
				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)		

(continued)

Table 4.3 (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
					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	1.71 (1.39–2.08)		
					Pharynx (men)			
				3	Electronics and telefitters	7.81 (1.61–22.8)		
				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. [145], United States	3929 men with potential exposure to formaldehyde for at last 6 months between 1960–1987 at an automotive iron foundry; mortality follow-up until end of 1989. An internal referent population of 2032 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		Oral cavity and pharynx	**SMR**		Reported only risks for oral cavity and pharynx cancer. Reference group for RR estimates consists of white nonsmokers with non exposed to formaldehyde and cumulative silica exposure in first quartile
				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)		
					Quartil 3 + Quartil 4	1.16 (0.20–6.51)		
					Non-White	4.41 (1.004–22.7)		
					Ever smoking	1.00 (0.23–6.84)		

					Silica			
					Quartil 2	0.43 (0.02–4.54)		
					Quartil 3	0.48 (0.06–4.00)		
					Quartil 4	0.37 (0.06–2.91)		
Coggon and Wield [146], England and Wales	Cohort of men, 4018 butchers and 2062 cooks identified from 1961 census; mortality follow-up until end 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)		
Boffetta et al. [147], Denmark, Finland, Norway, Sweden	6296 workers employed >1 year in 9 factories (3685 rock-slag wool; 2611 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)		
Innos et al. [148], Estonia	6786 workers (3723 men, 3063 women) employed for at least 6 months in two large furniture factories employed between 1946–1988; cancer incidence follow-up between 1968–1995	Medium and high exposure to wood dust; employment duration: <10 years, 10–19 years, ≥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		
				0	Pharynx	0		
					Women			
				4	Oral cavity	1.84 (0.50–4.71)		

(continued)

Table 4.3 (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
				0	Pharynx	0		
					Medium exposure			
				2	Oral cavity	2.47 (0.30–8.91)		
				0	Pharynx	0		
					High exposure			
				2	Oral cavity	1.61 (0.19–5.81)		
				0	Pharynx	0		
					<10 years			
				1	Oral cavity	0.75 (0.02–4.20)		
				–	Pharynx	–		
					10–19 years			
				0	Oral cavity	0		
				–	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. [149], Sweden	25,049 men butchers or meat workers from 1960–1970; follow-up for incidence 1971–1989	Three categories: butchers in the meat industry, butchers employed in other industries, non-buchters in meat industry	Oral cavity and pharynx			**SIR**	Relative risk adjusted for age, calendar period, geographic 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. [150], 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
				1733	Men	1.05 (1.00–1.10)		
				31	Women	1.64 (1.11–2.33)		
					Men	**RR**		
					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			
				1150	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)		
Marsh et al. [151], United States	7328 workers (6859 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		**Cancer**	**SMR**		
				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, other mouth	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)		

(continued)

Table 4.3 (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
				10	Long-term (1+ year)	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	9-Jan	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 to <1	2.35 (1.17–4.21)		
				4	9-Jan	1.81 (0.49–4.63)		
				5	10+	3.65 (1.18–8.52)		
					Cumulative exposure			
				6	>0 to <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 to <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 to <1	2.19 (0.80–4.77)		

				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 to <1	2.58 (0.70–6.61)		
				2	1+	2.50 (0.30–9.03)		
Brown et al. [152], 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 (6662), men employed in paint and varnish plants (5741), women lacquerers (974), women glazers (882), women artists (2136); 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		**Men**	SIR		
				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)		
Coggon et al. [161], United Kingdom	14,014 men employed in six of formaldehyde-producing or -using plants, each individual was followed starting at the latest of January 1, 1941; mortality follow-up until 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.	All tumors	Total cohort (1941–2000)		**SMR**		This study is an update of the cohort of Gardner et al. [142]. See above in this Table. Here 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)		

(continued)

Table 4.3 (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
		Exposure to formaldehyde was classified as: background (<0.1 ppm), low (0.1–0.5 ppm), moderate (0.6–2.0 ppm), high (>2.0 ppm), and unknown		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. [153], United States	11,039 workers (2015 men, 9024 women) exposed to formaldehyde in three garment manufactures who had been working for at least 3 months 1955–1977. Mortality follow-up until end of 1998	Workers of the cohort were compared with the USpopulation. Exposure assessment considered duration of employment, latency and first year exposed	All tumors			**SMR**		This study is an update of the cohort of Stayner et al. (1998). See above in this Table. Here 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. [75], United States	Cohort of 25,619 workers (22,493 men, 3126 women) employed in 10 US formaldehyde-producing or -using plants prior 1966; mortality from solid cancers 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,	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. [139]. See above in this Table. (*) 95% confidence interval does not includes 1
				13	Non exposed	0.99 (0.58–1.71)		
				49	Exposed	1.01 (0.77–1.34)		
						RR		
					Intensity (ppm)			
				13	0	2.42 (*)		
				18	>0 to <0.5	1		
				16	0.5 to <1.0	2.41 (*)		
				15	≥1.0	1.89 (NS)		

		by industrial hygienists, and defining average intensity, peak of exposure, cumulative exposure, duration of exposure			*Peak (ppm)*			(NS) 95% confidence interval include 1
				13	0	2.08 (NS)		
				15	>0 to <2.0	1		
				11	2.0 to <4.0	1.07 (NS)		
				23	≥4.0	1.83 (NS)		
					Cumulative (ppm-year)			
				13	0	1.98 (NS)		
				25	>0 to <1.5	1		
				12	1.5 to <5.5	1.59 (NS)		
				12	≥5.5	1.74 (NS)		
					Duration (years)			
				13	0	1.87 (NS)		
				27	>0 to <5	1		
				16	5 to <15	1.74 (NS)		
				6	≥15	0.95 (NS)		
Ji and Hemminki [154], 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 end of 2000	Occupation was coded according to national adaptations of the Nordic Occupational Standard Classification of Occupation. Were defined 53 occupational groups	Tongue, oral cavity, pharynx		**Men (1960 Census)**	**SIR**		Reported here only occupations with SIR statistically significant
					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)		
					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			

(continued)

Table 4.3 (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
				8	Artistic	3.83 (1.63–6.94)		
				14	Mechanics	2.27 (1.24–3.62)		
				9	Hairdressers	2.49 (1.13–4.39)		
Pardue et al. [172], 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, 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		
				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		
				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	Never	1		
				1.8	Ever	1.8 (0.7–4.9)		
Krstev et al. [155], United States	Cohort of all workers employed at the US Coast Guard shipyard workers (4413 men; 289 women) 1950–1964; mortality follow-up until 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			**SMR**	Adjusted for age, sex, and race	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
				18	**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. [156], United States	7345 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 unspecified, floor of the mouth, and pharynx			**SMR**		
				Tongue				
				5		1.08 (0.55–2.53)		
				Gum and other oral 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. [157], 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 × mean level of exposure in the occupation) for every 5-year birth cohort	Oral cavity and pharynx (excluding nasopharynx)		**Men**	**SIR**	SIR adjusted for age, calendar period, and social class. Reference total Finnish population. RR included age, calendar period, socioeconomic status, and all 3 occupational exposure (high, middle, low)	SIR reported here only for equal or higher than 1.2 and 95%CI statistically significant. RR reference category: no occupational exposure.
				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, 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)		

(continued)

Table 4.3 (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
				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			
				37	Chlorinated hydrocarbons	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)		
					Men and Women			
					High level of cumulative exposure	**RR**		
				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. [158], Denmark	3.22 million Danish born 1925–1973 and aged ≥30 years in the incidence period 1994–2003		Oral cavity and pharynx			**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	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)		
					Bohemian	1.80 (1.15–2.82)		
				20	Service	0.92 (0.83–1.03)		
				517	Manual	1.00		
				1022	Agricultural	0.31 (0.23–0.42)		
				47	Unknown	0.95 (0.81–1.12)		
				182	**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

0.5 parts per million-years (ppm-years) or less. However, a study of mortality for industrial workers found SMRs below 100 for those exposed to higher cumulative dose levels [160]. An expanded follow-up to this study by [75] found mortality risk ratios for oral cavity cancer to be >2.0 were for average intensity exposure levels, although no dose–response effect was detected. In a cohort study of six formaldehyde-producing companies in the United Kingdom [142] increased SMRs were found for oral and pharyngeal cancers. Elevated SMRs for oral and pharyngeal cancers have also been found among workers exposed to formaldehyde in the automotive iron foundry [142], chemical workers [161], furniture workers [148], and in a plastics producing plant [151], although positive results from the latter study may have been driven by the inclusion of nasopharyngeal cancers, which are known to be associated with formaldehyde exposure. Stayner et al. [140] conducted a mortality cohort study in garment manufacturers, as workers in this industry are potentially exposed to formaldehyde, noting an SMR of 343 (95% CI 118–786) for oral cavity cancers. An extension of this cohort until 1998 [153] confirmed increased risks 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. Another cohort study of chemical agent exposure [157] did not find any increased risk for Finnish workers at the lowest, middle, or highest exposure levels to formaldehyde for oral cavity and pharyngeal cancer.

Other formaldehyde-exposed professionals exposed during preservation of human tissue, such as pathologists, anatomists, medical laboratory technicians, embalmers, and funeral directors [162–166] show elevated risks of cancer, but paradoxically decreased risks of oral and pharyngeal cancer. In a meta-analysis of cohort studies on formaldehyde and cancer risk; industrial workers had a RR of 1.09 (95% CI 0.75–1.23) for oral cavity and pharynx and 0.96 (95% CI 0.75–1.23) for professionals [167].

Wood Dust and Wood Industry Work

Many case-control studies have reported an association between oral/pharyngeal cancers and wood dust or jobs in wood-related work found decreased risks or null associations [76, 107, 124, 125, 129, 135, 137, 148, 152]. Although a few studies have found risks ranging from 1.5 to 2.0 for pharyngeal cancer [123, 127, 136], the magnitudes of association have not been consistent; two case-control studies [130] observed a RRs of 5.5 for wood/wood-product workers (RR 5.5, 95% CI 1.2–25.0), while a cohort study of United States Coast Guard shipyard woodworkers [155] detected a high risk (RR 6.20, 95% CI 2.27–13.50). In Finland, two cohort studies did not reveal any risks of oral and pharynx cancer in woodworkers [149, 157]. 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 [129], however, after subdividing smoking habits into eight increasing cumulative tobacco classes, low RR associated with exposure to wood dust persisted. Collectively, the conducted studies utilized different risk exposure methods ranging from specific agent exposure to job titles and industries, no clear relationship between woodwork and oral/pharyngeal cancers has been found for either retrospective or prospective studies. Furthermore, there has been no evidence of a dose–response relationship with exposure level or duration of exposure, decreasing the likelihood that inhalation of wood dust is causally related to HNC site-specific cancers.

Leather Dust and Leather Industry Work

While some studies showed evidence of oral and pharyngeal cancer in leather industry workers [120], three subsequent case-control studies reporting specifically on the leather industry or exposure to leather dust showed less emphatic results. Case-control studies from Brazil [161], Italy [125], and Sweden [110] did not find a statistically significant positive relationship for exposure to leather dust while a cohort study in Finland [157] reported increased risk of oral and pharynx cancer 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 having sufficient evidence for carcinogenicity for humans, (Group 1) [168, 169], no conclusive association can be assumed based on the available case-control and cohort studies that include oral and pharyngeal cancer.

Cotton Dust and Textile Work

Studies on the relationship between cotton dust exposure or textile work and oral and pharyngeal cancer have shown inconsistent results and do not support a causal relationship. A case-control study of women in the United States [121] 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 not found in France [124] for pharyngeal cancer (RR 2.4, 95% CI 1.0–5.7) or in Italy [125] for oral cancer (RR 2.5, 95% CI 0.5–9.9). Similar studies have also supported null associations for textile dust exposure or textile work [123, 127, 129, 135, 157, 161].

Welding Fumes and Welding as an Occupation

Many different welding methods involve exposure to carcinogenic agents, such as irritant gases, chromium, polycyclic aromatic hydrocarbons, and metal dust. However, exposure to welding fumes has been inconclusive for associations with oral cavity and pharyngeal cancers. A case-control study in

Sweden [129] found excess risk of pharynx cancer (RR 2.26, 95% CI 1.09–3.69) in workers exposed to welding fumes for more than 8 years. However, for another case-control study in Sweden [130], 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 [123, 125, 127, 135] and cohort studies [154, 155]. The IARC working group deemed evidence on welding inadequate [170].

Diesel Engine Exhaust and Vehicle Repair Mechanics

The IARC working group found sufficient causal associations between diesel engine exhaust and lung cancer, however there were too few studies on HNCs to support a relationship [171]. Boffetta et al. [150] conducted a cohort study to evaluate diesel engine emission exposure in a Swedish population and found a general SIR of 1.64 (95% CI 1.11–2.33) for oral and pharynx cancer in women, but no risk for men. Using a job-exposure matrix, exposure was categorized according to probability and intensity as low, medium, and high. Positive RR were observed, but without a dose–response effect. A cohort study in Finland [157] detected increased risks of mouth and pharyngeal 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 [123] 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 nasopharyngeal tumors together. A case-control study in Brazil on vehicle mechanic work [135] found increased risks, particularly when considering >10 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. Vehicle mechanics in repair and diesel and gasoline exhaust services are potentially at increased risk of contracting oral and pharyngeal cancer, but more studies are needed to confirm this relationship.

Other Occupations

Several other occupations, industries, and agents have been linked to oral cavity and pharyngeal cancer.

Exposures in meat industry, such as viruses, nitrosamines, and polycyclic aromatic hydrocarbons may contribute for elevated cancer risks. Increased RRs for oral and pharynx cancer have been found in butchers in both cohort and case-control studies [122, 143, 149], however results were not significant. In contrast, Coggon and Wield [146] in a cohort study in England and Wales found deficit risks for oral and pharynx cancer in butchers.

Studies on man-made mineral fibers and HNCs have shown conflicting results [129, 131, 138, 147]. A cohort study of workers at a man-made mineral fibers (MMMF) factory in France found SIRs of 3.0 for oral and 1.4 for pharynx cancer, both not statistically significant [138]. A Scandinavian cohort of employees in nine factories producing rock-slag wool and glass wool [147] found increased HNC risk 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).

Asbestos is a Group 1 carcinogen, which is under scrutiny for HNCs due to the exposure route. The largest studies have been conducted using retrospective cohorts from time periods when exposure was common among insulation workers. While one case-control study found increased risks were found for those with cumulative low or cumulative high exposure [131, 157], previous case-control studies did not find increased risks of HNCs associated with asbestos [125, 127, 129]. A cohort study of construction workers also showed inconsistent results, finding an RR 1.7 (95% CI 0.9–3.3) for those with moderate exposure to asbestos, but lower risk for those with high exposure (RR 0.5, 95% CI 0.1–5.2) [172].

Cooks, waiters and bartenders, as well as workers at restaurants, bars and hotels have shown consistently increased risks of oral and pharynx cancer through some case-control and cohort studies [129, 144, 157]. However, the main hypothesis for these increased risks is the higher prevalence of heavy tobacco smoking and alcohol consumption among these workers. These circumstances require further studies before a definitive view can be taken on their possible role in the causal chain for the disease.

Several other occupational agents that are carcinogenic for other cancer sites, such as chromium, nickel, lead, iron, cadmium, phenoxy acids, solvents, cement dust, asphalt, pesticides, and aliphatic and alicyclic hydrocarbons have been studied by exposure level or by proxy in using occupational job title. In general, these increased risks were based in small number of observed cases, providing imprecise results.

Nasopharyngeal Cancer

Fourteen case-control and eight cohort studies examining the association between occupation or exposure to some agents and nasopharyngeal cancer. Formaldehyde and wood dust showed strong evidence of carcinogenicity to the nasopharynx; however, the association for other agents and occupations was inconclusive.

Formaldehyde

The first epidemiological evidence suggesting an association between exposure to formaldehyde and nasopharyngeal cancer found increased SMRs for different formaldehyde exposure levels among workers in ten plants producing or using formaldehyde [139]. Animal models had indicated nasal squamous cell carcinomas occurring in rodents submitted to formaldehyde vapor inhalation [173, 174]. A case-control study found increased RRs for longer exposure durations [76] and long induction period (25 or more years since first exposure) [175]. Increased nasopharyngeal cancer death rates were observed in a cohort of formaldehyde-industry workers by Hauptmann et al. [75], an update of the Blair et al. cohort [139]. This cohort revealed an exposure–response effect for peak and cumulative exposure to formaldehyde, but not for average exposure intensity or duration.

The study by Haptmann et al. [75] 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 [156, 176, 177]. Some criticisms on the Haptmann et al. [75] 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 [156]. However, as pointed out by Cogliano et al. [177], 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 the most recent IARC evaluation [118, 178] and formaldehyde was listed as known human carcinogen in the 12th Report on Carcinogens of the US National Institute of Environmental Health Sciences [179].

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 [168, 180].

In another case-control study of the Malaysian-Chinese population [181] found RR 2.36 (95% CI 1.33–4.19) for those exposed once to wood dust, and RR 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 nasopharygeal cancer have found increased risks [26, 126, 182, 183]. However, Vaughan et al. [184] did not find any evidence that exposure to wood dust increased the risk of nasopharyngeal carcinoma, as the modest association disappeared after adjusting for potential exposure to formaldehyde. Also Siew et al. [185] did not find any indication that wood dust and formaldehyde increased the risk of nasopharyngeal cancer in a large cohort of Finnish men born from 1906 to 1945. A study of four Nordic countries found the HR in the highest cumulative exposure category of wood dust ($\geq$28.82 mg/m^3 -years) was 16.5 (95% CI 5.05–54.1) however neither nose nonadenocarcinoma nor nasopharyngeal cancer could be linked to wood dust exposure [186].

In a pooled reanalysis of four American cohorts and one British cohort of wood-related industries [187] excess risks of nasopharyngeal cancer were found for all combined wood workers (SMR 2.4, 95% CI 1.1–4.5) and furniture workers (SMR 2.9 95% CI 1.2–5.9). Mortality risk from nasopharyngeal 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 have considered there is sufficient evidence that human exposure to wood dust is carcinogenic to the nasopharynx [156]. This was reaffirmed in a recent revision [169].

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. Li et al. [188] conducted a case-cohort study in Shanghai that suggested the possibility of nasopharyngeal cancer risk among those exposed to cotton dust. A RR 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. However, a dose–response relationship was not observed for exposure duration.

Some studies have suggested that cotton dust is a possible carcinogen for the nasopharynx [186], but results have been largely conflicting or have shown inconclusive results for cotton dust exposure [181, 189, 190]. The IARC classify cotton dust and working in textile industry as possibly carcinogenic to humans (Group 2B) [191], signifying limited evidence for a causal relationship for nasopharyngeal cancer.

Other Occupations

Evidence linking nasopharynx cancer to other occupational risk factors is less definitive, as the number of studies is limited. Further studies are needed for all these occupational factors to elucidate the role of these risk agents and occupations in nasopharyngeal cancer risk.

Fumes, smoke, and chemicals: Henderson et al. [192] in a case-control study found increased risks of nasopharynx cancer for fumes, smoke, and chemicals, but not for dusts. Yu et al. [190], found increased risks for smoke and chemical fumes, but for dusts. Armstrong et al. [181] did not find risks for exposure to chemicals, fumes, or dusts.

Chlorophenols: Chlorophenols are classified by IARC as possibly carcinogenic to humans—Group 2B [193]. A series of case-controls studies have found relationships between exposure to chlorophenols and nasopharynx cancer. Hardell et al. [194] found about a sevenfold risk of nasopharyngeal and nasal cancer analyzed together for exposure to chlorophenols in the wood industry. Mirabelli et al. [195] 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. [108] found increased risks of nasopharyngeal squamous cell carcinoma in people exposed to chlorophenol (RR 2.2, 95% CI 1.1–4.3).

Industrial heat and combustion products: Two case-control studies have examined the effect of industrial heat on nasopharynx cancer. Henderson et al. [192] found increased risks, around 1.5, but these were not statistically significant. Armstrong et al. [181] also found increased risks of nasopharynx cancer for heat exposure of RR 1.23 ($p = 0.02$), after adjustment for wood dust, diet, and cigarette smoke. Increased risks of nasopharyngeal cancer were also found for exposure to combustion products in a case-control study in China [190] with RR 2.7 ($p < 0.05$) for those with occasional exposure and RR 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.

Organic solvents: A case-control study in Taiwan [26] explored the effect of organic solvents on nasopharynx cancer, but risks were low, imprecise, and no dose–response effect was detected.

Cutting oil: Zhu et al. [108] 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).

Concluding Remarks

The efforts to decrease major occupational risks factors for HNCs depend on the knowledge of potential carcinogens agents present in a particular occupation in different industry settings and the effective surveillance and prevention of workers' exposure to these agents.

HNCs collectively and by subsite have a low incidence compared to more common cancers, making prospective studies with the adequate sample sizes needed to for precise estimations difficult. Furthermore, occupational exposures may suffer from misclassification biases due to lack of exposure measurement instruments given birth cohort time periods and lack of exposure surveillance in particular industries or countries. The definition of occupational exposure also differs for each study, ranging from occupational job title, industry title, to exposure level. For an occupational study adequately determined occupational risk, exposure level, intensity, duration, and induction should be taken into consideration. Major confounders such as tobacco smoking and alcohol smoking, must be adjusted for, as most occupations are associated with lifestyle habits and choices.

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.

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Cancers of the Gastrointestinal Tract (Esophageal, Gastric, and Colorectal Cancer)

5

Miguel Santibañez and Juan Alguacil

Introduction

This chapter reviews the occupational risk factors of cancer of the esophagus, stomach, and the colon and the rectum. Preliminary, the general epidemiology of these neoplasms is briefly reviewed, along with the main histological subtypes and nonoccupational risk factors associated, to put the data on occupational risk factors in a broader context.

Regarding occupational risk factors, the occupational exposures classified as carcinogenic by International Agency for Research on Cancer (IARC) for which occupational epidemiologic studies exist in relation to selected locations, are described in first place. Lastly, other occupational exposures for which epidemiological studies also exist, especially if they have been included in systematic reviews or meta-analysis, are presented.

Epidemiology of Esophageal Cancer

Esophageal cancer (EC) is probably one of the most geographically and sex variable tumors in the world. It is also marked by large differences in incidence within geographical areas and marked changes in incidence over time, suggesting a predominant role of environmental factors under a multifactorial etiology model of action, in which it has not yet been possible to identify all the risk factors involved in its etiology [1, 2].

Along with pancreatic cancer, EC has the worst survival of all cancers. Because the survival of esophageal cancer is so low, mortality and incidence rates are comparable, assuming mortality as a good indicator of the real magnitude of the problem. The incidence rates between countries worldwide vary more than for any other cancer, with a difference of more than 50 times between the countries of high and low incidence. Most developed countries show annual incidence rates of less than 10 per 100,000 inhabitants, while in some developing countries, such as Iran, it is the most common cancer [1].

According to estimated Age-Standardised incidence and mortality Rates (ASR-W) as assessed by GLOBOCAN 2012, it would be worldwide in tenth place in incidence and eighth place in mortality with an incidence ASR (W) of 5.9 per 100,000; and a mortality ASR (W) of 5 per 100,000 [3].

In men it would be in 6th place in incidence and mortality with an ASR (W) of 9 and 7.7, respectively whereas in women it would be in 13th place in incidence with an ASR (W) of 3.1, and in 10th place in mortality with an ASR (W) of 2.7 [3].

OC is more common among men in most parts of the world, particularly in some European countries such as France and Spain, where the sex ratio may reach 6.5:1.0 [2].

Morphologically and etiologically, two major types are distinguished: esophageal "Squamous Cell Carcinoma (SCC)" and "ADenoCarcinoma (ADC)," which account for over 90% of EC [1, 4, 5].

The squamous cell carcinoma is the most frequent type in most areas, and usually shows stable or decreasing incidence trends [6]. Most epidemiological studies have identified tobacco smoking and alcohol drinking as the main risk factors in Western (industrialized) countries for esophageal carcinomas with squamous cell differentiation. They frequently carry G:C > T:A mutations of the TP53 gene. There is a three- to eightfold increase in the risk of esophageal cancer in individuals who consume 40–100 g of alcohol per day, and there are multiplicative effects if they also smoke [7]. Other causes include or chronic mucosal injury through hot beverages or low fruit and vegetable intake or malnutrition [8], but the very high incidence rates observed in Iran and some African and Asian regions remain inexplicable [4].

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Esophageal carcinomas with glandular differentiation (ADC) are typically located in the distal esophagus and occur predominantly in white males of Western countries, showing a marked increasing incidence in many industrialized countries [6]. This is paralleled by rising rates of gastric adenocarcinoma of proximal origin (proximal/cardia gastric cancer). Regarding the adenocarcinoma variety, the most important etiological factor is chronic gastroesophageal reflux leading to Barrett type mucosal metaplasia, the most common precursor lesion of adenocarcinoma [4]. Nowadays obesity is considered also as strongly associated [9]. Smoking has been identified as another major risk factor but the association is not as strong as for the squamous cell variety, while for alcohol the association is uncertain [4, 7, 10].

Certain occupations and occupational exposures are known to influence EC risk, but whether risk varies according to histological type specifically (SCC or ADC) remains unknown. Jansson et al. [11] in 'The Nordic Occupational Cancer Study', found that the risk of EC was elevated, particularly among those who served as waiters or food workers, whereas those who worked as teachers were at reduced risk. However, histological type had little influence on specific increases or decreases on risk. In contrast, Santibañez et al. [12], results in a hospital-based case-control study in eastern Spain, suggest that some occupational exposures may specifically increase the risk of esophageal SCC or ADC, while other exposures such as asbestos may increase the overall risk of EC. Higher association were found by Vaughan et al. [13], in a USA population-based case-control study between tetrachloroethylene exposure and SCC subtype, although none of associations yield statistical significance. When possible, in this chapter associations specifically by histological subtypes for the occupational exposures below will be presented.

Occupational Exposures and EC

Dry Cleaning and Tetrachloroethylene

Tetrachloroethylene (Perchloroethylene), is one of the most important chlorinated solvents worldwide. Between the 1950s and 1980s, the most important use of tetrachloroethylene was in dry cleaning and in smaller amounts was used as a degreaser in multiple processes. Since the 1990s, the largest use has been as a feedstock for the synthesis of fluorocarbons. According to the last published monograph by IARC in 2014 (IARC monographs, Vol 106, 2014), tetrachloroethylene is probably carcinogenic to humans (Group 2A IARC). There is sufficient evidence in experimental animals for the carcinogenicity of tetrachloroethylene, but there is still limited evidence in humans for the carcinogenicity of tetrachloroethylene, with the highest epidemiological evidence link for cancer of the bladder.

For EC, first studies characterized exposure by employment in occupation or industry categories related, and were included in several reviews [14, 15]. Two studies of mortality were cited in both reviews, in which two cohorts of dry cleaning workers were identified, mainly exposed to this product [16, 17]. Both studies found a significant association. However, in their analysis, studies did not control the confusion correctly and it cannot be ruled out that this association was biased by strongly confusing variables such as alcohol or tobacco. Thus, the IARC has included dry cleaning within the possibly carcinogenic industries/occupations (Group 2B) for EC, in its Vol 63, year 1995 monograph (IARC monographs, Vol 63, 1995 [18]).

None of the cohort studies of dry-cleaning workers above, assessed exposure to tetrachloroethylene directly. More recently, statistically significant increases in mortality from cancer of the esophagus were observed in two cohort studies of dry-cleaning workers in the USA, with a larger increase among the longest-employed workers [19, 20]. No increase in incidence of cancer of the esophagus was found in the Nordic dry-cleaners study, which controlled for social class as a proxy indicator of tobacco and alcohol consumption [21]. A study of aircraft manufacturing workers in the USA who were also exposed to trichloroethylene reported a non-significant increase in mortality from EC [22].

Regarding case-control studies, two small case-control studies provided information on the association of EC with potential exposure to tetrachloroethylene: one evaluated employment in dry cleaning and reported a nonsignificant positive association [13], while the other assessed exposure to tetrachloroethylene, but had no exposed cases [23].

Rubber Industry and Nitrosamines

In the review performed by Kogevinas et al. [24] considering papers published after 1982, four cohorts reported an increased risk for EC [25–28]. A small excess of EC was also observed in the British rubber industry [29] and Chow et al., in a cohort of men using the Cancer Environment Registry of Sweden [30] reported a statistically significant Standardised Incidence Ratio (SIR) of 4.7 among workers in vulcanizing shops within the rubber industry. In Poland, Szymczak et al. [31] reported a significant excess risk among rubber footwear workers. In contrast, in a cohort mortality study in England and Wales and Scotland, no association for EC was found [32, 33].

In this context, occupational exposures in the rubber-manufacturing industry were considered firstly by IARC Working Groups in 1981 and 1987. In the last monograph published in 2012, the IARC Working Group concluded that there was some evidence for an excess risk of cancer of the esophagus among workers in the rubber-manufacturing

industry, based on the published cohort studies described above (IARC monographs, Vol 100F-36, 2012 [34]). However, the evidence for this cancer site according to IARC would be limited because the IARC Working Group noted that in none of the studies, adjustments were made for tobacco or alcohol use. In contrast, there is sufficient evidence in humans for stomach cancer and other cancer sites such as urinary bladder, lung, leukemia, or lymphoma, so occupational exposures in the rubber-manufacturing industry are considered carcinogenic to humans (Group 1 IARC).

Regarding exposure to nitrosamines, Straif et al. in 2000 [35] published a retrospective cohort study of mortality in workers in this industry, in which semiquantitative exposure to nitrosamines was assessed. An association was found with a relative risk (RR) of 2.7; 95%CI (0.7–11.5) for exposures of medium intensity and a RR of 9.1; 95%CI (2.1–38.8) for the high-intensity exposures. This study did not control either for alcohol or tobacco. Lastly, some studies show an association between nitrosamines in the diet and this cancer although the evidence is insufficient and in any case less to its association with stomach cancer [36].

Carbon Black

According to IARC last update (IARC monographs, Vol 93–6, 2010 [37]), carbon black is possibly carcinogenic to humans (Group 2B) with the higher evidence of association for lung cancer. Industrial exposure to carbon black has occurred in the carbon black production industry and in several user industries, including the rubber, paint, and printing industries.

With respect to EC, there are several studies focusing on carbon black production industry, where carbon black was the dominant exposure in the industrial environment, as studies developed in the UK [38], the USA [39], and Germany [40], with a range of Standardised Mortality Ratios (SMR) between 1.15 and1.62. None of associations among these studies for EC yield statistical significance. An Italian study developed with dockyard workers who transported bags containing carbon black as study population [41], also showed a positive statistically no significant SMR: SMR 1.62; 95%CI (0.44–4.15).

Two publications also exist which are drawn from the same population [42, 43] corresponding to a Canadian community-based multi case-control study which specifically include carbon black among the exposures analyzed as assessed by a team of chemists and industrial hygienists who examined detailed job histories obtained by questionnaire. In this Montréal study there were 99 cases of EC, of which 63 were squamous cell carcinoma (SCC). A separate analysis was conducted and published that focused on this site only [42], showing a statistically significant positive association for exposure to carbon black, with 11 exposed cases and an overall odds ratio (OR) of 2.1; 95%CI (1.0–4.3) adjusted for several confounding variables including alcohol and tobacco smoking. Association increased when restricting to SCC: OR 3.4; 95%CI (1.0–4.3).

Mists from Strong Inorganic Acids Including Sulfuric Acid

Strong inorganic acid mists may be produced as a result of the use of inorganic acids, including sulfuric acid, which is used in production processes for the manufacture of fertilizers, soaps, or rayon, for the cleaning of metals, in the refining of petroleum products or as electrolytic in batteries. There is sufficient evidence in humans for the carcinogenicity of mists from strong inorganic acids. According to the last IARC volume 100F-33 monograph published in 2012, mists from strong inorganic acids cause cancer of the larynx, and also, a positive association has been observed for lung cancer (Group 1 IARC) (IARC monographs, Vol 100F-33, 2012 [34]).

Parent et al. [42], in their Canadian community-based case-control study found a statistically significant positive association for exposure to sulfuric acid with 15 exposed cases and an overall OR of 2.2; 95%CI (1.2–4.3), adjusted for several confounding variables including alcohol and tobacco smoking.

The oldest studies, based on occupations and death certificates, present mixed results. For example, Blair and Mason [44] show an association that has not been confirmed in previous studies [30, 45].

Exposure to Dust and Fibers

As in the case of Gastric Cancer, some of the occupational published studies on the risk of EC have focused on exposure to different dusts (mainly silica dust) and fibers such as asbestos, and found associations for industries and/or occupations with higher exposure to these agents.

Silica Dust, Crystalline

The IARC monograph about crystalline silica in the form of quartz or cristobalite (Vol 100C-14) include 14 studies on the risk of EC. Among these 14 reports, five had RR >1.0, and nine with RR ≤1.0 (IARC monographs, Vol 100C-14, 2012).

In three out of the five reports with RR >1.0, the associations are particularly elevated: Wernli et al. [46] reported a hazard ratio (HR) of 15.80; 95%CI (3.5–70.6) among Chinese textile workers exposed for over 10 years to crystalline silica dust. Pan et al. [47] reported an overall HR of 2.75;

95%CI (1.44–5.25) with a clear exposure-response trend with years of exposure in Chinese refractory brick workers. Yu and Tse [48] reported an overall SMR of 2.22; 95%CI (1.36–3.43), and an SMR of 4.21; 95%CI (1.81–8.30) among caisson workers.

Asbestos, All Forms

Association and causality between all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) and mesothelioma and cancer of the lung, larynx, and ovary is well established and all forms of asbestos are carcinogenic to humans (Group 1 IARC) (IARC monographs, Vol 100C-11, 2012).

Some evidence for cancer of the Esophagus exist. Regarding Cohort studies, Selikoff and Seidman [49] found an SMR of 1.61; 95%CI (1.13–2.40) among a cohort of 17,800 asbestos insulation workers across the USA and Canada.

Berry et al. [50] found a SMR of 2.08; 95%CI (1.07–3.63) among a cohort of over 5000 male and female asbestos-exposed factory workers in the UK, but with no consistent relation to exposure. In contrast, a cohort of nearly 400,000 Swedish construction workers found evidence for a positive association between asbestos exposure and adenocarcinoma of the esophagus. RR increased to 1.7; 95%CI (0.5–5.4) among those with "moderate" exposure with respect to no asbestos exposure, and to 4.5; 95%CI (1.4–14.3) among those workers with "high" asbestos exposure, suggesting a positive dose–response relationship [51].

Hein et al. [52] found a SMR of 1.87; 95%CI (1.09–2.99) in a cohort of 3072 workers exposed to chrysotile in a South Carolina asbestos textile plant (1916–1977) followed up for mortality through 2001.

Other cohort studies of various groups occupationally exposed to asbestos—asbestos miners and millers, asbestos cement workers, friction products workers, and "generic" asbestos workers—yield generally nonpositive results for cancer of the esophagus or positive statistically no significant associations ([53–56]). These studies are available in Table 2.6 of the 100C IARC monograph at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.6.pdf.

The Institute of Medicine (IOM) conducted in 2006 a meta-analysis of 25 cohort studies and reported a summary RR of 0.99; 95%CI (0.78–1.27) for any exposure to asbestos versus no exposure. The IOM also examined the RR of "high" versus no exposure, and calculated a no statistically significant summary RR in a range between 1.35 and 1.43 [57].

Li et al., have conducted and published in 2016 [58] a more recent meta-analysis of cohort studies on EC and asbestos exposure. According to their inclusion criteria, 20 cohort studies were included. Overall pooled standardised mortality ratios (meta-SMR) was 1.24; 95%CI (1.13–1.38), with little evidence of heterogeneity among studies. Being male, exposure to chrysotile or mixed asbestos, working at textile industry, long study follow-up (≥20 years), Asia, Europe, and America cohorts with larger cohort size (>500), and high-exposure group all contribute to significantly higher SMR.

Regarding case-control studies, Parent et al. [42] in their Canadian community-based case-control study found an OR of 1.4; 95%CI (0.8–2.4) for any exposure to chrysotile asbestos with 21 exposed cases. When restricting to SCC, association strengthened and reached statistical significance: OR 2.0; 95%CI (1.1–3.8) but with a no consistent dose–response trend. Santibañez et al. [12] in the Spanish hospital-based case-control study found for all histological types of EC combined and for SCC and ADC subtypes separately, a threefold increase in risk with a dose–response trend, with an overall OR for exposure >0.26 fibers/cm^3 of 3.46; 95%CI (0.99–12.10). Other studies such as the community-based case-control study in Sweden by Gustavsson et al. [59] found an association between exposure to asbestos and laryngeal cancer, but not for EC.

Other Dusts

Minder and Beer-Porizek in 1992 [45] documented an association in "carpenters and wood workers" for EC. Gustavson et al., in 1998 [59], found an OR of 2.16; 95%CI (1.15–4.05) for exposure to high intensity of "all dusts in general." However, for specific exposures to metal dust, wood dust, or textile industry or leather industry dusts, these ORs were close to unity and not significant. The specific exposures of metal and wood dusts were also evaluated by Parent et al. [42] with the same results. However, in this study, a significant increased risk was obtained for exposures to iron compounds and mild steel dust. Dement et al., in a cohort mortality study in the USA published in 2003 did not find an association for male carpenters, with a SMR of 1.1; 95%CI (0.5–2.2). In contrast, Jansson et al., in their cohort cancer incidence study in Sweden among male construction workers published in 2005 [51], found a RR 2.2; 95% (0.3–15.9) for esophagus SCC in relation to high exposure to wood dust as assessed by a job exposure matrix (JEM). For adenocarcinoma, statistically significant increases were observed among "carpenters and joiners": OR 9.69, 95%CI (1.32–70.81) in a Spanish Hospital-Based Case-Control study [12].

Polycyclic Aromatic Hydrocarbons (PAHs)

Exposure to polycyclic aromatic hydrocarbons (PAHs) has been suggested as a risk factor for developing esophagus SCC [60, 61].

PAHs are a group of compounds that are formed by incomplete combustion of organic matter, including vegetation, fossil fuels, and oil products. PAHs are found in soil, water, air, and food. They are very widespread environmental contaminants, so exposure to PAHs, that may occur through inhalation, ingestion, or percutaneous penetration, is not necessarily from occupational origin. Common sources of exposure to PAHs in addition to occupation are for example food and tobacco smoking.

They are composed of two or more condensed aromatic rings, and whereas some of them are recognized as carcinogenic, other are not classified as carcinogenic. Benzo[a] pyrene is the most common PAH to cause cancer in human, and is recognized as carcinogen (Group 1 IARC) based on the sufficient evidence for the carcinogenicity of benzo[*a*] pyrene in experimental animals (IARC monographs, Vol 100F-14, 2012 [34]). Recently, IARC also classified diesel engine exhaust (an important source of exposure to PAHs) as carcinogenic to humans (Group 1 IARC), based on sufficient evidence that exposure is associated with an increased risk for lung cancer (IARC monographs, Vol 105, 2013 [62]).

In relation to occupational exposure to PAH and EC, statistically significant associations were found by Gustavsson et al. [59], for occupational high exposure to PAHs and esophageal SCC: OR 1.9; 95%CI (1.1–3.2). Suggestions of excess risk for EC have been also reported by [63]. Results from Parent et al. [42] would not be totally contradictory, because for some of the analyzed PAHs there were slight associations, although they did not reach statistical significance.

In relation to occupations related to this exposure, increased risk among Swedish chimney sweeps [64–66], among French road-paving workers [67], and among workers exposed to combustion products [68] had been reported.

Other Occupational Exposures

Santibañez et al., found a significant increase in risk of esophageal ADC for high exposure to "volatile sulfur compounds", which includes exposure to gases such as sulfur dioxide, hydrogen sulfide, mercaptans, dimethylsulfide, and dimethyldisulfide [12]. Sulfide dioxide is a chemical compound very commonly used in the production of pulp, and previously a Canadian cohort mortality study had found a statistically significant SMR among pulp and paper industry workers in Canada [69]. However, when these authors published data on the incidence of esophageal cancer in 2001, the association was not confirmed, attributing the discrepancy to a diagnostic misclassification between esophageal and gastric cancer after the use of more accurate morphological and topographic data [70]. No evidence of increased mortality due to EC in relation to sulfur dioxide exposure was either found in a cohort study of 5613 pulp and paper industry workers from 12 different countries developed by IARC [71]. Workers in the chemical industry, metal industry, or foundries are also commonly exposed to volatile sulfur compounds. Most of the epidemiological studies on EC in these groups did not show positive associations, but a Swiss study based on death certificates, although it did not find associations for the rest of professions related to the metallurgical industry, found a positive association for foundry workers [45]. Another historical cohort study also found a significant SMR for these workers in New Zealand [72]. As these occupations also share other exposures such as polycyclic PAHs, asbestos… that would be highly correlated with volatile sulfur compounds and also involved in the associations for EC, it deserves further investigation.

EC mainly of the squamous cell type, has been well documented as a second cancer among breast cancer patients treated with adjuvant radiotherapy [73, 74]. Regarding occupational exposure to ionizing radiation and EC, it has been poorly studied but some evidence exist [12, 75, 76].

Lee et al. [77] evaluated the risk of adenocarcinomas of the esophagus or stomach associated with farming and agricultural use of pesticides in a population-based case-control study in eastern Nebraska, USA. No association was found with farming or ever-use of insecticides or herbicides, or with individual pesticides. Santibañez et al., did not find either statistically significant associations in eastern Spain [12].

Epidemiology of Gastric Cancer

In spite of the decreasing incidence and mortality observed in many parts of the world, gastric cancer (GC) is still a major Public Health problem. According to estimated age-standardised incidence and mortality rates (ASR-W) as assessed by GLOBOCAN 2012, it would be worldwide in sixth place in incidence, seventh place in 5-year prevalence, and fourth place in mortality; with an incidence age-standardised rate [ASR (W)] of 12.1 per 100,000; a 5-year prevalence of 29.6 per 100,000, and a mortality ASR (W) of 8.9 per 100,000 [3].

In men it would be in fourth place in incidence and 5-year prevalence with an incidence ASR (W) of 17.4 and a 5-year prevalence of 39.7 per 100,000; and in third place in mortality with an ASR (W) of 12.8 [3].

In women it would be in sixth place in incidence with and ASR (W) of 7.5; and in fifth place in mortality with and ASR (W) of 5.7 [3].

GC is also related to one of the highest cancer burdens, as measured by disability-adjusted life years lost [78, 79].

Its etiology is clearly multifactorial, being both environmental and genetic factors involved [79–81].

Helicobacter pylori is estimated to cause 65–80% of all GC cases, or 660,000 new cases annually and these numbers may be underestimated [82, 83]. It must be remarked that at least in Western countries, *H. pylori* is a major risk factor for only distal/non-cardia GC but not for proximal/cardia GC [79].

Interaction between *H. pylori* and gastric mucosa is a complex phenomenon and as yet little understood. In most cases, this microorganism does not cause any pathology but in some cases, it causes serious lesions in the mucosa and as it was mentioned above, is the main epidemiological risk factor for distal/non-cardia GC, with a RR of approximately 6 for this type. It appears that characteristics of the infecting strain in relation to existence of virulence factors such as cytotoxin-associated gene A (cagA), or the host, or factors in the environment, or a combination thereof might radically modify the carcinogenicity of *H. pylori* [84–87].

In relation to its histological classification, adenocarcinoma is by far the most common type of GC (approximately 90%) [79]. The two major histological subtypes of adenocarcinomas proposed by Laurén in 1965 are accepted and commonly used. According to Laurén classification, lesions are classified into one of the two major types: intestinal or diffuse. Tumors that contain approximately equal quantities of intestinal and diffuse components are called mixed carcinomas. Carcinomas too undifferentiated to fit neatly into either category are placed in the indeterminate category [4].

In contrast with the decreasing incidence time trend of the intestinal subtype, an increase in the number of cases of diffuse is observed, with an approximate 3.7% increase per year in the USA [80, 88].

On the other hand, the stomach is divided into several anatomic subsites, including the cardia (roughly the top inch of the stomach), fundus, body, pylorus, and the antrum. These areas are distinguished by anatomic demarcations, histologic differences, or both. Additionally, epidemiological studies and reviews, have usually distinct between adenocarcinomas arising from the cardia (cardia GC) and other parts of the stomach (non-cardia GC), as they have also shown different epidemiologic patterns and causes.

Nowadays, the varying epidemiology of GC across disease histological subtypes and anatomical subsites suggests that the GC is not merely a single disease, and may be better described as different individual diseases. New molecular evidence also supports this notion [80, 89, 90]. So, what has emerged more recently is a further stratification between gastric adenocarcinoma with intestinal histology of proximal origin [cardia and gastro esophageal junction (GEJ)] and intestinal gastric adenocarcinoma of distal origin in body and antrum (non-proximal, non-cardia, non-diffuse), as well as diffuse histology [80].

In summary, three main GC subtypes are currently distinguished: (1) proximal/cardia, (2) distal/non-cardia, and (3) diffuse; and significant differences between them are recognized in terms of environmental and genetic risk factors and clinical management.

Differences Between Intestinal Gastric Adenocarcinoma of Distal/Non-cardia Versus Proximal/Cardia Origin

Intestinal type of proximal origin seems to have a 3:1 male predominance whereas distal intestinal type shows a nearly 1:1 ratio of incidence of men to women [80, 91].

H. pylori infection is carcinogen for the development of distal/non-cardia GC. In contrast, infection with *H. pylori* appears to be protective for the development of proximal GC (which is also comprised of GEJ and distal esophageal adenocarcinoma) [92, 93]. The explanation is that severe atrophic gastritis and reduced acid production, a common consequence of chronic *H. pylori* infection, reduces the risk of gastroesophageal reflux disease (GERD) significantly [80, 94]. Supporting this explanation, obesity and GERD are associated with proximal GC but not with distal GC [79].

The review of time trends of GC incidence has revealed changes not only between the two different Lauren subtypes of adenocarcinoma, but rather between the proximal and distal GC of intestinal subtype. As well as the diffuse subtype, there is an annual increase of intestinal gastric adenocarcinoma of proximal origin in contrast to the declining of the intestinal gastric adenocarcinoma of distal origin [80, 88].

In addition to H. pylori infection, environmental risk factors that seems to be more related for distal GC include tobacco and alcohol consumption [79] and dietary factors such as low consumption of fruits and vegetables [95] and high salt intake [96].

Physical activity [97] and high fiber intake [98] seem to be protective, whereas radiation for example seems to be a risk factor for all GC subtypes [79].

Diffuse Gastric Adenocarcinoma Versus Intestinal Non-cardia Gastric Adenocarcinoma

Intestinal gastric adenocarcinoma of distal/non-cardia origin is characterized by a multistep progression initiated by chronic inflammation, progressing through chronic gastritis, intestinal metaplasia, and dysplasia. Diffuse GC has no known precursor lesion. Diffuse GC pathway may present a common precursor event in their development related to mutation or epigenetic silencing of the E-cadherin gene, in contrast with chronic inflammation and gastric atrophy that characterizes intestinal non-cardia GC [79, 80].

Occupational Exposures and GC

Most studies in occupational health did not report results separately for the GC types described above, so in this chapter the decision to combine information on overall GC is made, although information about GC types considered separately has also been made when possible.

Exposure to Dust and Fibers

Most of the occupational published studies on the risk of GC have focused on exposure to different dusts (mainly minerals) and fibers such as asbestos, and have found associations for industries and/or occupations with higher exposure to these agents. These exposures were already highlighted in a review carried out by Cocco et al., in 1996 [99] on occupational risk factors and GC, and were further confirmed in another review carried out by Raj et al., in 2003 [100]. A study [101] that studied 3260 workers (1639 exposed to different dust) for 50 years showed a hazard ratio (HR) of 1.77 for GC. Aragones et al. [102] also evidenced these associations for occupations performed between 1971 and 1989, and Santibañez et al. [103] found that some dust may increase the risk of the diffuse subtype of GC whereas other dusty occupations, such as "miner," and specific exposures such as asbestos may increase the risk of the intestinal subtype of GC.

The most convincing explanation is that, after inhalation, insoluble dust particles like silica in the metal, glass, ceramic, or stone industry (marble, granite, etc...) may be cleared by the lung and then swallowed. In the stomach, these agents would act as irritants, promoters, or carcinogens directly [99].

The evidence of association for different types of specific dust and fibers is discussed below:

Silica Dust, Crystalline

Crystalline silica is one of the most common types of particulate mineral pollutants. There is sufficient evidence in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite in relation to cancer of the lung and it has been classified as Group 1 by IARC in 2012 (IARC monographs, Vol 100C-14, 2012).

Cancers other than that of the lung have not been as thoroughly researched. In the IARC monograph, 40 reports with information on cancer of the stomach were reviewed, 18 had RR > 1.0 (including three significantly elevated), and 22 with relatives risks ≤1.0 (including two significantly reduced). More recently, Lee et al. [104] have conducted a systematic review and meta-analysis published in 2016, searching for articles on occupations involving silica exposure and GC studies up to December 2014. According to their selection criteria, 29 articles, including 9 case-control and 20 cohort studies, were analyzed. Their study included metaregression and subgroup analysis in relation to histological confirmation status, study design, and industries. The overall meta-analyzed OR was 1.25; 95%CI (1.18–1.34). Heterogeneity of studies was attenuated after metaregression by industry. Both heterogeneity and publication bias were partially attenuated after subgroup analyses and higher overall effects were observed in the mining and foundry industries, supporting a significant relationship between occupational crystalline silica exposure and GC.

Asbestos (All Forms)

In the monographs published in by the IARC (IARC monographs, Vol 100C-11, 2012), the Working Group noted a positive association between exposure to asbestos and GC, supporting two large and well performed meta-analyses published previously [105, 106].

Fortunato and Rushton have published in 2015 [107], a new meta-analysis restricting to cohort studies. The sources of heterogeneity were also explored through subgroup analyses and metaregression [107]. Thirty-seven papers were identified according to their inclusion criteria and cancer incidence data were extracted for 15 separate cohorts from 14 papers. The overall pooled standardised mortality ratio (meta-SMR) for GC was 1.15; 95%CI (1.03–1.27) with heterogeneous results across studies. Statistically significant excesses were observed in North America and Australia but not in Europe, and for generic asbestos workers and insulators. Meta-SMRs were larger for cohorts reporting a SMR for lung cancer >2 and cohort sizes <1000.

New results from the prospective Netherlands Cohort Study [108], and a Chinese miner/miller cohort [109] support this association.

Regarding case-control studies, a study from Poland [110] found an OR for GC of 1.5; 95%CI (0.9–2.4) for workers ever exposed to asbestos, and of 1.2; 95%CI (0.6–2.3) for workers with 10 or more years of exposure to asbestos. Cocco et al., in 1994 [111] reported in Italy an OR of 0.7; 95%CI (0.5–1.1) for workers ever exposed to asbestos, and of 1.4; 95%CI (0.6–3.0) for those with 21+ years of exposure to asbestos. Santibañez et al., found a significantly increased risk for intestinal subtype in men in the highest category of asbestos exposure [103].

Overall, the results based on the IARC monograph and the meta-analysis support that asbestos is associated with a moderate increased risk of GC.

Coal Dust

In relation to GC, some evidence of association between work in coal mines and GC exist [102, 112–117]. In addition, the studies that have controlled the confusion have not found substantial changes when adjusted for different variables such as diet and socioeconomic level [112, 113]. In these studies, the dust generated in the workplace is assumed as the causal agent, but coal dust contains a number of carcinogens including polycyclic aromatic hydrocarbons (PAHs), metals such as cadmium or chromium and silica. The lack of studies analyzing the exposure based on specifying levels to these agents, makes difficult to clarify to what extent, each of these components may be carcinogenic.

Wood Dust

Wood dust is carcinogenic to humans (Group 1) according to IARC last monograph with sufficient evidence in humans for cancer of the nasal cavity and paranasal sinuses and of the nasopharynx (IARC monographs, Vol 100C-15, 2012).

In relation to GC, published studies show mixed results and evidence is inconclusive.

Cocco et al., in 1998 and 1999 did not find an association in the USA [118, 119] in their census-linked case-control studies for gastric cardia and overall stomach cancer respectively, whereas other north American and Canadian studies based also on death certificates found positive results [120–122].

A pooled analysis of updated data from five cohort studies from the UK and the USA [123] did not find an association. Stellman et al. [124] in their US prospective study of men enrolled in the American Cancer Society Cancer Prevention Study II found a RR of 1.3; 95%CI (1.0–1.9) based on self-reported wood dust exposure, but the same study for wood-related occupations found a RR of 1.1; 95%CI (0.6–1.9). Innos et al. [125] in a retrospective cohort study of furniture workers in Estonia, did not find significant associations in relation to exposure to wood dust based on industrial hygiene surveys and work history in men or women.

A large Danish study based on cases of cancer notified to the Danish Cancer Registry linked to information on employment kept on another nationwide registry found a twofold increase in the risk of GC related to occupations in basic wood processing. However, there was no correlation with sinonasal cancer rates and the absence of an increased risk for GC in trades in which a high risk for sinonasal cancer is seen was interpreted as it indicates that wood dust was not of etiological importance for GC [126]. Dement et al. [127] in a cohort mortality study in the USA did not find an association, whereas Jansson et al., in their cohort cancer incidence study among Swedish male construction workers published in 2005, found a RR of 4.8; 95%CI (1.2–19.4) for proximal/cardia gastric adenocarcinoma, in relation to high exposure to wood dust as assessed by a JEM, but not for distal/non-cardia gastric adenocarcinoma: RR 1.2; 95%CI (0.4–3.6) [115]. Pukkala et al. [128] in the Nordic countries and Arias Bahia et al. [129] in Brazil, did not find associations in their cohort studies based on census and registries.

Regarding case-control studies based on direct interviews, in a case-control study on occupational exposures and GC in Spain published in 1991, an increased nonsignificant risk was observed for wood and furniture workers (OR 1.76) [113]. More recently, Santibañez et al. in 2012 have found some statistically significant associations also in Spain between the diffuse adenocarcinoma subtype and wood-related occupations and a significant association for "wood dust" exposure as assessed by Finish job-exposure matrix (FinJEM) but without evidence for a dose–response pattern.

Rubber Industry and Related Occupational Exposures

The IARC Working Group concluded in 2012 that there was evidence of an excess of GC among rubber-manufacturing workers (IARC monographs, Vol 100F-36, 2012 [34]) and occupational exposures in the rubber-manufacturing industry are carcinogenic to humans (Group 1 IARC).

The multiple genetic and cytogenetic effects observed among workers employed in the rubber-manufacturing industry provide strong evidence to support genotoxicity as one mechanism for the observed increase in cancer risks. However, due to the complexity and changing nature of the exposure mixture and the potential interactions between exposures in the rubber-manufacturing industry, other mechanisms are also likely to play a role. While it is clear that exposure to some agents in the rubber-manufacturing industry has been reduced over time, the results of recent cytogenetic studies continue to raise concerns about cancer risks.

In relation to GC, the risk seems to be more confined to mixing, milling, and compounding. On the basis of this evidence, carbon black, PAHs, asbestos, or talc have been considered as the possible carcinogenic specific agents. The role of nitrosamines on the risk of GC seems to be less conclusive and nitrosamines are unlikely to be a major risk factor for GC in this industry. Straif et al., in 2005 [35], coinciding with other studies have not found an association for GC, although the same study did find strong evidence of association for esophageal cancer.

Mists from Strong Inorganic Acids Including Sulfuric Acid

As it was mentioned previously, mists from strong inorganic acids cause cancer of the larynx and are classified as Group 1 by IARC (IARC monographs, Vol 100F-33, 2012 [34]).

Manufacture of phosphate and nitrate has been categorized as potentially related to exposure to strong inorganic acids (sulfuric acid mists). In this sense, the historical cohort mortality study from Sweden among 1756 male workers at a nitrate fertilizer plant, showed a slightly increased SIR for GC of 1.50 for 27 men hired before 1960 [130]. In a factory complex in Russia where both phosphate and nitrate fertilizers were manufactured, Bulbulyan et al. [131] reported a statistically significant increase for GC mortality for men in the sulfuric acid tower department: 11 deaths, SMR 2.04; 95%CI (1.02–3.66). In contrast, Al-Dabbagh et al. [132] in the UK, Rafnsson and Gunnarsdóttir [133] in Iceland, or Fandrem et al. [134] in Norway, did not find associations.

Case-control studies of GC, and other sites are available in Table 2.2 of the 100F-33 IARC monograph at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-28-Table2.2.pdf. In two studies from the USA an increased risk for GC was found associated with exposure to sulfuric acid, which was derived from a job-exposure matrix (JEM) applied to the occupation and industry indicated on the death certificates [118, 119].

Polycyclic Aromatic Hydrocarbons (PAHs)

As discussed above for EC, there is no doubt about the potential carcinogenic effects of some PAHs (IARC monographs, Vol 100F-14, 2012 [34]).

Indirect evidence in humans may suggest that GC is associated with higher exposure to PAHs, since tobacco smoking, a major source of PAHs, is associated with higher risk of GC in last meta-analysis, or exposure to diesel exhaust has also been associated with GC [115].

Based on occupational studies that have evaluated PAHs and GC, the association remains unclear. The epidemiological results in relation to GC are contradictory, and there are again, as usual in occupational epidemiology, studies with positive and negative results.

In the meta-analysis carried out by Partanen and Boffetta in 1994 [135], there was an excess risk for roofers (exposed to bitumen fumes and previously often to coal-tar fumes). This excess was interpreted by the authors as mainly associated with exposure to high intensities of PAH, although other agents, including asbestos, were also suggested. Later, there was no clear suggestion of an association between employment in jobs entailing exposure to bitumen and mortality from GC among European asphalt workers [136]. Occupational exposure to oxidized bitumens and their emissions during roofing are considered as group 2A and occupational exposure to straight-run bitumens and their emissions during road paving are considered as group 2B according to the last monograph by IARC published in 2013 (IARC monographs, Vol 103, 2013 [137]).

In contrast, Stucker et al. [67] in French asphalt workers, found a nonstatistically significant higher rate of GC in road-paving workers than their nonexposed counterparts: SMR = 2.2; 95%CI (0.8–4.7).

Friesen et al., found no evidence that oil-based metal working fluids (PAH component) were associated with risk of GC in an auto worker cohort [138].

Liao et al., in 2014 [139], examined prediagnostic urinary concentrations of 1-hydroxypyrene glucuronide (1-OHPG), a PAH metabolite, in 153 gastric cancer cases and 306 matched controls within the Shanghai Women's Health Study. Increasing concentrations of 1-OHPG (μmol/mol Cr) appeared to be associated with elevated risk of GC: Q3 vs. Q1 adjusted OR 1.91; 95%CI (1.02–3.60), but not within the highest category of 1-OHPG: Q4 vs. Q1 adjusted OR 1.34; 95%CI (0.72–2.50), so no clear dose–response relationship was observed.

Hexavalent Chromium Compounds

There are various hexavalent chromium-containing substances and overall, they are known as hexavalent chromium compounds. Hexavalent chromium or chromium VI Cr(VI) compounds are carcinogenic to humans (Group 1) according to IARC last monograph (IARC monographs, Vol 100C-9, 2012) with sufficient evidence in humans for cancer of the lung. The main route of exposure is inhalation, and hexavalent chromium compounds are used in a number of industries, such as leather tanning, chrome plating, cement work, and stainless steel welding and manufacturing.

In 2015 [140], Welling et al., have published a systematic review and meta-analysis, identifying 56 cohort and case-control studies on GC and specific Cr(VI) exposure, or work in an occupation associated with high Cr(VI) exposure including chromium production, chrome plating, leather work, and work with Portland cement. The overall meta-analyzed OR was 1.27; 95%CI (1.18–1.38). In a subgroup analysis, studies that were positive for lung cancer (with lung cancer RR estimates ≥1.5), which may indicate higher exposures, produced a slightly higher summary RR for GC than the full meta-analysis: OR 1.41; 95%CI (1.18–1.69).

The issue of whether Cr(VI) causes GC not only in exposed workers, but also in people who ingest Cr(VI) in drinking water, cannot be ruled out. US Environmental Protection

Agency (US EPA) is considering regulating Cr(VI) in drinking water based on its potential carcinogenicity in the gastrointestinal tract, and California has recently established the first drinking water standard for Cr(VI) in the USA [140].

Pesticides

Recently, IARC has published a monograph as volume 112, assessing the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (IARC monographs, Vol 112, 2017 [141]). The insecticides tetrachlorvinphos and parathion were classified as "possibly carcinogenic to humans" (Group 2B). The insecticides malathion, diazinon, and glyphosate were classified as "probably carcinogenic to humans" (Group 2A) with limited evidence for non-Hodgkin lymphoma, prostate, leukemia, and lung cancer. In addition, IARC has assessed the carcinogenicity of the insecticides lindane and 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT), and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). These assessments have been published as Volume 113 of the IARC Monographs [142]. Lindane has been classified as "carcinogenic to humans" (Group 1) with sufficient evidence for non-Hodgkin lymphoma. DDT was classified as Group 2A and 2,4-D as Group 2B.

Regarding GC, the association between pesticide exposure and GC found in some studies has not been confirmed in others [77, 99, 100, 143–145].

Thus, in a case-control study published by Ekstrom et al., in 1999 [143], an association for gastric adenocarcinoma with herbicides attributable to exposure to phenoxyacetic acids was found: OR 1.70; 95%CI (1.16–2.48). However, another case-control study in Nebraska [77] has found no association for gastric adenocarcinoma and exposure to insecticides or herbicides including pesticides classified as nitrosatable (capable of forming N-nitroso compounds when reacting with nitrates). Santibañez et al., in 2012 [103] found significant associations for gastric diffuse adenocarcinoma in some agricultural-related occupations, as well as in their analysis with FinJEM: OR for the highest level of exposure to pesticides 10.39; 95%CI (2.51–43.02); p trend = 0.02, although the specific association for pesticides was not maintained when the analysis was restricted to exposures older than 15 years of duration.

Other Occupational Exposures

According to the last IARC monograph published in 2016, there is sufficient evidence in experimental animals for the carcinogenicity of inorganic lead compounds so this exposure is classified as Group 2A (IARC monographs, Vol 87, 2006 [146]). Some case-control studies for the risk of GC are reported in the monograph, and inorganic lead compounds are considered as an agent with limited evidence in humans for GC. In contrast, "X-radiation, gamma-radiation," are carcinogenic agents with sufficient evidence in humans in relation to GC (Group 1 IARC) according to the latest monograph by IARC published in 2012 (IARC monographs, Vol 100D-7, 2012 [147]).

Shiftwork that involves circadian disruption is probably carcinogenic to humans (Group 2A IARC), based on experimental studies and limited evidence on human breast cancer risk (IARC monographs, Vol 98–8, 2010 [148]). Night shift work and GC risk has been recently evaluated in the MCC-Spain study. In this population-based case-control study no clear evidence concerning an association was found [149]. A non-significant association with ever having had worked in permanent night shifts (≥1 year) was found: OR 1.2; 95%CI (0.9–1.8), but there was no association with ever having had worked in rotating night shifts: OR 0.9; 95%CI (0.6–1.2), and no clear dose–response trends were obtained.

Christensen et al., in 2013 [23] evaluated GC in relation to occupational tetrachloroethylene exposure in a Canadian case-control study in Montreal using a combination of subject-reported job history and expert assessment. A non-statistically significant increased risk of GC was found (two exposed cases: OR 2.1; 95%CI 0.3–17).

Epidemiology of Colorectal Cancer

The distribution of cancer of the rectum, parallels the distribution of colon cancer. Thus, colorectal cancer (CRC) is one of the leading causes of cancer and cancer-related mortality worldwide and a major health problem in industrial countries. Highest incidences of CRC are recorded in developed countries, while rates in developing countries are lower, but increasing over time in that which are witnessing an economic advancement [150, 151].

According to estimated age-standardised incidence and mortality rates (ASR-W) as assessed by GLOBOCAN 2012, it would be worldwide in fourth place in incidence, third place in 5-year prevalence, and fifth place in mortality; with an incidence age-standardised rate [ASR (W)] of 17.2 per 100,000; a 5-year prevalence of 68.2 per 100,000, and a mortality ASR (W) of 8.4 per 100,000 [3].

In men it would be in second place in incidence with an incidence ASR (W) of 20.6; and in third place in 5-year prevalence and mortality with a 5-year prevalence of 75.3 per 100,000 and mortality ASR (W) of 10 [3].

In women it would be in second place in incidence and 5-year prevalence with and incidence ASR (W) of 14.3 and a 5-year prevalence of 61.2 per 100,000; and in third place in mortality and with and ASR (W) of 6.9 [3].

Colon cancer most commonly occurs sporadically and is estimated to be inherited in 5–15% of cases [152, 153].

Most of the biological features are shared among cancer of the colon and the rectum. The predominant histological type of both colon and rectum cancer is adenocarcinoma, which is usually preceded by a polyp or adenoma, and less frequently by nonpolypoid dysplastic mucosa.

The variation in incidence within countries, along with the increase in the developing countries that are undergoing economic growth, or the rapid rise of CRC showed in studies of immigrant populations from low- to high-risk areas, have suggested a strong environmental influence on CRC pathogenesis [150, 154]. The adoption of a Western life style, along with increasing life expectancy and population growth are supposed to be responsible for the increases [150, 155].

Overall, the risk increase of CRC is 12% for each 100 g/day increase of red and processed meat intake. The new epidemiological evidence support that milk and whole grains may have a protective role against CRC, whereas the evidence for vegetables and fish as protective factors for CRC is still less convincing, and intakes of fruits or legumes were not associated with colorectal cancer risk according to the last update of the evidence of the WCRF-AICR Continuous Update Project [156].

Physical activity has consistently been associated with decreased risk of CRC, with consistent reports in studies of occupational activity, leisure activity, and total activity [157, 158]. Obesity and diabetes would also be associated with CRC [157].

In relation to other medical conditions, patients with ulcerative colitis and Crohn's disease are at increased risk of CRC [159].

Smoking cigarettes had originally not been associated with an increased risk of CRC. However, some of the more recent studies show an association, which is convincing according to last reviews [157]. In addition, cigarette smoking has been consistently associated with a higher risk of colorectal adenomas, precursors of cancers (Giovannucci et al. [160]; IARC monographs, tobacco smoking, Vol 100E-6, 2012 [161]).

Regarding alcohol, WCRF panel concluded in 1997 that "high alcohol consumption probably increases the risk of cancers of colon and rectum" and that is likely to be related to total ethanol intake, irrespective of the type of drinking. Based on more recent reviews, heavy alcohol is consistently associated with CRC [162] and the risk of CRC seems to increase 7% for each 10 g/day increase of ethanol intake in alcoholic drinks [156].

Occupational Exposures and CRC

Most studies in occupational health did not report results separately for the two locations, so in this chapter the decision to combine information on these two sites (colon and rectum) is made, although information about the two sites considered separately has also been made when possible.

Asbestos

Asbestos is the most classical occupational exposure studied in the literature in relation to CRC. The last monograph published by IARC in 2012 evaluating asbestos, include this location and review 41 occupational cohort and 13 case-control studies (IARC monographs, Vol 100C-11, 2012). Association and causality between all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) and mesothelioma and cancer of the lung, larynx, and ovary is well established and all forms of asbestos are carcinogenic to humans (Group 1 IARC). With respect to CRC, the evaluation of IARC conclude that "Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum. For cancer of the colorectum, the IARC Working Group was evenly divided as to whether the evidence was strong enough to warrant classification as sufficient."

Occupational cohort studies of asbestos and colorectal cancer are available in Table 2.7 of the 100C IARC monograph at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.7.pdf. The majority of cohort studies found evidence for an association between asbestos exposure and CRC, with a minority of cohort studies which have not found associations [52, 163–167]. Recently, Paris et al., support also an association between occupational exposure to asbestos and colon cancer incidence in men in the French Asbestos-Related Diseases Cohort (ARDCo-Nut) [168].

In relation to case-control studies, studies from the Nordic countries, and several US studies report statistically significant associations [169–173], whereas other US studies have not found such evidence [174, 175].

Wood Dust

Overall, epidemiological evidence did not support an association between exposure to wood dust and CRC. The pooled analysis of updated data from five studies from the UK and the USA published by Demers et al., in 1995 [123], reported a borderline protective association for rectum (ICD code 153): RR 0.8; 95%CI (0.6–1.0). Stellman et al. [124] in their US prospective study found a null association for Colon (ICD code 153): RR 1.0; 95%CI (0.8–1.3) and a positive nonsignificant association for rectum: RR 1.3; 95%CI (0.8–2.0) based on self-reported wood dust exposure. Innos et al. [125] in their retrospective cohort study of furniture workers in Estonia, reported positive nonsignificant associations for colon and rectum cancer separately. In contrast, Dement

et al. [127] in their US cohort mortality study found a statistically significant RR of 1.5; 95%CI (1.1–2.1) for rectum. Pukkala et al. [128] in the Nordic countries and Arias Bahia et al. [129] in Brazil, did not find either statistically significant association for colon or rectum.

Diesel and Gasoline Engine Exhausts

As it has been commented previously, IARC had classified in 2013 diesel and gasoline engine exhaust as carcinogenic to humans (Group 1 IARC), based on sufficient evidence that exposure is associated with an increased risk for lung cancer (IARC monographs, Vol 105, 2013 [62]).

Mixed results have been published for CRC. In a large multisite population-based case-control study of occupational exposures and risks for various cancers in Canada [176], an increase in risk of colon cancer was found for long-term high exposure to diesel engine exhaust: OR 1.7; 90%CI (1.2–2.5), and for long-term high exposure to gasoline engine exhaust and cancer of the rectum: OR 1.6; 90%CI (1.1–2.3). However, it must be noted that in this study 90%CI were used (at the 95% level, most of the intervals would have included unity) and that the group of controls comprised only hospital cancer patients at other sites. In the same framework of the Canadian multisite population-based case-control study [176], Goldberg et al. [171] reported an OR for substantial exposure to diesel engine exhaust of 2.1; 95%CI (1.1–3.7) when cancer controls were including but population-based controls were also used, comprising a pooled group of cancer and population controls.

In contrast, Fang et al., in 2011 [177] in another Canadian case-control study reported elevated risks for colon cancer: OR 1.54; 95%CI (1.01–2.25) for ever employment as a taxi driver/chauffeur, while other occupational titles, including bus drivers, heavy goods vehicles drivers, and locomotive operators, showed no association. No specific assessment of exposure to diesel or gasoline exhaust was carried out. Previously, in [178], Decouflé et al., reported a OR protective for colorectal cancer: OR 0.60 (24 exposed cases; $p = 0.04$) [CI not provided].

Pesticides

Cancer of the colorectum was studied by Lee et al. [179] in the Agricultural Health Study, with a total of 305 incident cases of cancer of the colorectum (colon, 212; rectum, 93) diagnosed during the study period (1993–2002). Among the 50 pesticides examined, most of them were not associated with CRC risk. However, chlorpyrifos use showed significant exposure-response trend (p for trend = 0.008) for rectal cancer, rising to a 2.7-fold; 95%CI (1.2–6.4) increased risk in the highest exposure category. Aldicarb was associated with a significantly increased risk of colon cancer (p for trend = 0.001), based on a small number of exposed cases, with the highest exposure category resulting in a 4.1-fold increased risk; 95%CI (1.3–12.8).

Tetrachloroethylene

As it has been commented previously, tetrachloroethylene is probably carcinogenic to humans (Group 2A IARC), with the highest epidemiological evidence link for cancer of the bladder. (IARC monographs, Vol 106, 2014).

Regarding CRC, Paulu et al., conducted a population-based case-control study including 326 cases of CRC to evaluate the relationship between CRC and tetrachloroethylene-contaminated drinking water in Massachusetts [180]. The adjusted ORs for CRC were modestly elevated among ever-exposed subjects, and did vary substantially as more years of latency were assumed: OR 2.0; 95%CI (0.6–5.8) for 13 years of latency. Adjusted ORs for rectal cancer among ever-exposed subjects were more elevated than the corresponding estimates for colon cancer: OR 3.1; 95%CI (0.7–10.9) versus OR 1.5; 95%CI (0.3–5.8) for 13 years of latency, respectively.

In the Canadian case-control study published by Christensen et al., in 2013 [23] in relation to occupational tetrachloroethylene exposure, nonstatistically significant increased risks were found for colon cancer (three exposed cases; OR 1.8; 95%CI 0.3–11), or rectal cancer (one exposed case; OR 1.1; 95%CI 0.1–13).

Other Occupational Exposures

Oddone et al., published in 2014 [181], a literature review and meta-analysis of papers regarding the risk of colorectal cancers in workers of several industrial branches classified according to International Standard Industrial Classification (ISIC) codes. A homogeneous pattern of association between colorectal cancer and industrial branches did not emerge from this review. However, interesting results which deserve further research were presented. Based on their results, the estimated crude excess risk fraction attributable to occupational exposures ranged from about 11% to about 15%.

Pooled RR for colorectal cancer was increased and statistically significant for workers occupied in repair and installation of machinery (ISIC code 33, RR 1.40, 95%CI: 1.07–1.84). Authors explain that this interesting result was entirely driven from two articles published in 1977 and 1978 on the same cohort of Italian shipyard laborers, exposed to asbestos [182, 183].

Tannery and fur industry workers (ISIC code 15) showed to have a significant increased risk: RR 1.70; 95%CI (1.24–2.34), while results for iron and steel workers (ISIC code 24) showed a pooled RR of 1.32; 95%CI (1.07–1.65).

Results of borderline significance were observed for "manufacture of chemicals and chemical products workers (ISIC code 20)" with a pooled RR of 1.27; 95%CI (0.92–1.76) and "rubber and plastic (ISIC code 22) industries": pooled RR 1.30; 95%CI (0.98–1.71).

Overall, their results pointed out increased risks for industries with a wide use of chemical compounds, such as leather, basic metals, plastic, and rubber manufacturing, besides workers in the sector of repair and installation of machinery exposed to asbestos.

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Pancreatic Cancer

6

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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]. In 2012, it was estimated that 338,000 men and women were diagnosed with pancreatic cancer and 331,000 died of the disease [2]. Although there have been improvements in the diagnosis and prognosis of pancreatic cancer, these changes are minor [3]. Although smoking is the only established nonheritable risk factor for pancreatic cancer, only approximately 30% of the cases can be attributed to smoking [4]. Despite the inconclusive results, obesity, diabetes, alcohol consumption, chronic pancreatitis, diet, physical inactivity, and genetics have also been suggested as risk factors for pancreatic cancer [5, 6]. Given this poorly understood etiology, prevention of this deadly disease remains a challenge.

Etiological studies of pancreatic cancer have encountered 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; approximately 12% of pancreatic cancer cases have been estimated to be attributable to occupational exposures [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 also include 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 6.1 (cohort studies) [9–64] and Table 6.2 (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 3637 deaths from 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. [15]

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Table 6.1 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 3637 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. [23], USA	From the third National Cancer Survey Interview Study of 7518 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	2485 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 3847 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 8666 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 [22], USA	A cohort of 21,829 workers with 5 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. [18], 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. [16], 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. [14], UK	The mortality experience of 5969 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. [17], 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
Lynge [19], 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 3390 males and 1069 females were included in the study	records	3	RR = 0.59 for workers employed in manufacture of phenoxy herbicides

Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Bond et al. [15], Texas, USA	A general mortality survey was done on a 5% random-start systematic sample ($N = 1666$) 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. [41], Texas, USA	A retrospective cohort mortality study of 1008 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. [40], 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. [21], California, USA	A retrospective cohort mortality study ($n = 1919$) 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 [20], 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. [43], USA	A PMR study in 1401 commercial pressmen	Occupational records	18	PMR = 162 for those employed as commercial pressmen for more than 20 years
Coggon et al. [28], Finland	A mortality study of 5784 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 [27], 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
Wong [42], USA	A cohort of 7676 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 1074 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. [38], Detroit, USA	1766 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

(continued)

Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Smulevich et al. [39], 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. [26], 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. [33], 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. [29], Italy	The mortality of 2926 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. [34], New York, USA	Mortality study in a 1964–1970 cohort of 1013 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. [36], 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 [32], 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
Lanes et al. [35], South Carolina, USA	Mortality study of a cohort of 1271 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. [31], UK	A cohort study of 7660 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. [37], 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. [25], 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(158–1140) for workers exposed to ethylene chlorohydrin

Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Asp et al. [45], USA	An 18-year follow-up for mortality and cancer morbidity in a cohort of 1909 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. [58], Canada	A mortality study to December 1989 of a cohort of 2222 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. [57], 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 3022 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 2050 male and 1924 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
Enterline et al. [54], England	A mortality study of 2802 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 [56], 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. [55],	A mortality study of 3211 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

(continued)

Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
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. [53], Italy	A mortality study of 1388 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. [52], Italy	A PMR of 1043 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. [51], Finland	Cancer incidence among 3922 male and 1379 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
Hooiveld et al. [59], Netherlands	A mortality study of 1167 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 6830 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 1332 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

Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Alguacil et al. [50], 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	4420 men and 2143 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
*$P < 0.05$

vreported an increased risk of pancreatic cancer (SMR = 233) among chemical workers. Wen et al. [41] reported an elevated risk among oil refinery workers (SMR = 167). Ott et al. [21] 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 [25] 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 1315 other-cause-of-death cases as controls observed an odds ratio (OR) of 1.4 for people working in the chemical and allied industries [73]. 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 [68]. One case-control study of 625 pancreatic cancer cases and 1700 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 [75]. A population-based case-control study in Iowa by Zhang et al. [83] 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 2050 male and 1924 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. [82] observed an increased risk of pancreatic cancer associated with processing vinyl and polyethylene. Another nested case-control study by Garabrant et al. [69] 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

Table 6.2 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. [75], 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 [71], 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. [72], 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. [73], 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. [74], Illinois, USA	2444 pancreatic cancer deaths	3198 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. [76], 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. [68], 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. [69], 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	1700 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

Table 6.2 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Results	Comments
Selenskas et al. [82], 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
Kauppinen et al. [77], Finland, 1984–1987	595 incident cases with a response rate of 47%	1622 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 2487 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. [67], 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	1825 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. [70], Shanghai, China, 1990–1993	451 incident cases with a response rate of 78.2%, 37% histologically confirmed	1552 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 manufacturers, 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 6.2 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Results	Comments
Alguacil et al. [65, 66], 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. [83], Iowa, USA, 1985–1987	376 incident cases (202 males and 174 females) with a response rate of 88%	2434 population-based controls (1601 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. [81], 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

*$P < 0.05$

including 595 cases and 1622 controls reported an elevated risk associated with occupational exposure to solvents (including aliphatic and aromatic hydrocarbons) [77]. Two meta-analyses reported an elevated risk of pancreatic cancer associated with occupational exposure to chlorinated hydrocarbons [7, 85]. One examined 32 specific agents and found that chlorinated hydrocarbon solvents and related compounds had a meta-risk ratio (MRR) of 1.4 (95%CI: 1.0–1.8) [7]. Another one applied hierarchical Bayesian methods using both job title and exposure data; they observed a more than twofold increased risk of pancreatic cancer associated with occupational exposure to chlorinated hydrocarbon compounds (MRR = 2.21, 95%CI: 1.31–3.68) [85]. A recent hospital-based case-control study in Spain further supports a positive association between exposure to chlorinated hydrocarbon solvents and pancreatic cancer, but the association seemed stronger for ductal adenocarcinomas of the pancreas (OR = 4.11, 95%CI: 1.11–15.23), with a significant positive trend in risk with increasing duration of exposure (P for trend = 0.04) [81].

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) [40]. Another PMR study in a bearing plant also reported an increased risk of pancreatic cancer [38]. A death certificate mortality study in Illinois reported an elevated risk of pancreatic cancer among metal workers [74]. Acquavella et al. [24] examined a metal work cohort ($n = 3630$) and found an excess in the mortality rate of pancreatic cancer. Ji et al. [70] 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 [22] 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 [7]. 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]. For example, exposure to polycyclic aromatic hydrocarbons (PAHs), a class of chemicals including hundreds of compounds, was found in metal manufacturing industries such as aluminum production industry and iron and steel foundry [87]. While earlier meta-analyses showed a nonsignificant increased risk of pancreatic cancer associated with occupational exposure to PAHs [7, 85], subsequent studies supported a positive association between PAHs and pancreatic risk [88]. 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 1401 commercial pressmen showed a significant PMR of pancreatic cancer among those employed 20 years or longer [43]. Similar results were found in another study of printing pressmen [89]. The Third National Cancer Survey of 7518 incident cancer cases found an elevated risk of pancreatic cancer associated with printing workers [23]. Wingren et al. [90] 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 [75]. 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. [50] 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 might 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 [26]. 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 [68]. 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 [83]. A recent hospital-based case-control study in Spain found an approximately twofold increased risk associated with diesel engine exhaust and two to threefold increased risk among truck drivers [81]. Workers in these occupations may be heavily exposed to motor exhaust, which contains PAHs that have been classified as human carcinogens [91] and have been linked to an increased risk of pancreatic cancer [7, 85, 88]. 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 [38, 85, 92].

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 65 years old [93]. A case-control study involving 625 pancreatic cancer cases and 1700 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 [65]. A hospital-based case-control study in France reported an increased risk of pancreatic cancer associated with textile industry [76]. 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 [83]. A population-based case-control study in Shanghai China also found an elevated risk among female textile workers [70]. It has been speculated that the excessive risk associated with textiles workers may be related to exposure to spinning oils or textile dusts [68]. In contrast, a cohort study in Shanghai China reported that occupational exposure to cotton dust and endotoxin in the textile industry was associated with a reduced risk of pancreatic cancer [94].

Other Occupations and Industries

In addition to the abovementioned industries and occupations that 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 [70, 76]. It was unclear whether the association was due to exposures to silica dusts, asbestos, or other industrial dusts [68, 93]. Several solvent-related occupations or industries such as mechanics [33, 65, 68, 80], leather tanners or other leather industries [29, 43, 73, 76], and dry cleaners [71] 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 [69, 95, 96], 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, 83]. In the absence of exposure to environmental hazards, lifestyle risk factors, such as lack of physical activity [97, 98], may play a role in the development of pancreatic cancer among these workers. While occupational physical activity was associated with a reduced risk of pancreatic cancer based on a meta-analysis of four prospective cohort studies [99], another study found that a reduced risk of pancreatic cancer associated with occupational exposure to physical activity became null after adjusting for body mass index (BMI), suggesting that the observed reduced risk associated with occupational physical activity may be due to confounding factors [94]. 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 [83].

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 a minimum level of health. Employed individuals tend to be healthier than the general population that 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 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 a result, 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. Thus, many studies were likely unpublished because they were unable to detect meaningful associations. For this reason, pooling of data from projects and replication of studies is very important.

Fourth, nonoccupational risk factors may play a synergistic role with occupational factors in the risk of pancreatic cancer. Integration of occupational and nonoccupational risk factors would provide a more precise profile for predicting individuals' risks. 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 [100]. After cessation of cigarette smoking, the risk remains elevated for a minimum of 10 years [100]. 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 [101]. This pooled analysis also indicated that risks after more than 15 years after smoking cessation were similar to that for never smokers [101], 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 [102]. However, very few studies have investigated the association between passive smoke and pancreatic cancer risk. Results from the limited studies have provided mixed results [103–106].

Alcohol Consumption

Based on the results from most case-control and cohort studies, 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 [107]. However, a positive association between heavy alcohol consumption and pancreatic cancer has been suggested by studies that collected detailed information on alcohol consumption [108–119]. 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 [120].

Coffee Consumption

Since McMahon et al. [121] in 1981 reported a strong positive association between coffee consumption and risk of pancreatic cancer, numerous studies have subsequently investigated the relationship and have provided inconsistent results. A meta-analysis of 14 cohort studies conducted in 2011 showed a significant inverse association between coffee consumption and risk of pancreatic cancer [122]. A subsequent meta-analysis including 37 case-control studies and 17 cohort studies suggested a nonsignificant increase of such risk associated with coffee consumption [123]. A recent updated meta-analysis including 20 cohort studies reported a protective effect of high coffee consumption for pancreatic cancer risk (OR = 0.75; 95%CI: 0.63–0.86) [124].

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) [125]. A 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 [126]. It was estimated that approximately 12.8% of pancreatic cancers in men and 11.5% in women could be attributed to overweight/obesity [4]. A meta-analysis confirmed that both general and abdominal obesity were associated with increased pancreatic cancer risk [127].

Nutrition

Although studies linking dietary intake and risk of pancreatic cancer have provided inconclusive results, a majority of studies have suggested a reduced risk of pancreatic cancer associated with high fruit and vegetable intake [98, 128–132]. 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 [133–138]. High fat and red meat intake was associated with an increased risk of pancreatic cancer in some studies [98, 139–141] but not in others [132, 136, 142, 143]. A meta-analysis of 11 prospective studies found a positive association between pancreatic cancer incidence and processed meat consumption [144]. However, subsequent cohort studies did not support such findings [145–147]. A large cohort study detected no association between intakes of red and processed meat and risk of pancreatic cancer, but the study found that poultry consumption was associated with an increased risk of pancreatic cancer [145]. Another cohort study suggested that processed meat sources of dietary nitrate and nitrite might be associated with pancreatic cancer among men only [147]. A recent large cohort study reported that low meat eaters and vegetarians and vegans had lower

mortality for pancreatic cancer compared with regular meat eaters [148]. Frequent nut consumption had been inversely associated with risk of pancreatic cancer in women [149, 150]. Findings from the latest meta-analysis supported that fruit and vegetable intake was inversely associated with the risk of pancreatic cancer [151]. Furthermore, another study suggested that 0–12% of pancreatic cancer cases could be prevented by increasing fruit or folate intake [152].

Diabetes

Diabetes has been considered to be associated with the risk of pancreatic cancer, but 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. The risk was inversely correlated with the duration of diabetes with the highest risk found among patients diagnosed within less than a year [153]. Several studies reported that type I and type II diabetes doubled the risk of pancreatic cancer [154–156]. The United States National Cancer Institute estimates that diabetes is associated with a 1.8-fold increased risk of pancreatic cancer in Hispanic men and Asians compared to whites and blacks [67]. Pancreatic cancer risk decreased with the duration of diabetes, but a 30% excess risk persists for those with more than two decades of diabetes diagnosis [70]. Oral antidiabetics or insulin use were associated with a reduced risk of pancreatic cancer [67, 70].

Pancreatitis

Chronic pancreatitis is another established risk factor for pancreatic cancer. A six-country historical cohort study consisting of 2015 subjects with chronic pancreatitis reported 1.8% 10-year and 4.0% 20-year cumulative risks of pancreatic cancer [157]. About 4% of chronic pancreatitis patients developed pancreatic cancer [158]. The risk of pancreatic cancer associated with pancreatitis was two times higher among people who were younger than 65 years old compared to those who were 65 years or older [159]. Patients with hereditary pancreatitis a rare, autosomal-dominant disease that usually occurs at a young age had a risk that was 50–60 times greater than expected [160].

Helicobacter pylori

Studies have shown that *Helicobacter pylori* infection, a major risk factor associated with pancreatic cancer, has an estimated population attributable fraction of 4–25% [152]. According to a recent follow-up study, these results were not supported [161].

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 the insidious nature of early stage signs and symptoms as well as the relatively inaccessible 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 such as the bile duct, the mesenteric and celiac nerves, the pancreatic duct, and the duodenum [162]. 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. As a result of tumor invasion of the celiac and mesenteric plexus, the pain may take on a gnawing nature. Besides abdominal pain, patients with pancreatic head cancer usually suffer from jaundice caused by biliary tract obstruction that can increase levels of conjugated bilirubin and alkaline phosphatase. As a result, the patient's urine darkens. In addition, the stool may be pale from decreased stercobilinogen in the bowel. On rare occasions, a pancreatic tumor may 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 [163]. In addition to ductal adenocarcinomas, a number of histological types of pancreatic cancer have been recognized, including 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 [163].

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 [164, 165]. Due to its lack of sensitivity and specificity, this antigen is not useful in screening asymptomatic patients [162].

Global gene expression studies of pancreatic cancers have suggested several potential new serum markers for pancreatic cancer. One such marker is the macrophage inhibitory cytokine 1 (MIC1) [166]. Elevated serum MIC1 antigen levels significantly outperformed CA 19–9 and other tumor markers in distinguishing patients with resectable pancreatic cancers from healthy controls [167]. In addition to MIC1, gene products of *osteopontin* [168], *tissue inhibitor of metalloproteinase-1* [169], and *mesothelin* genes [170] have also been suggested as potential novel tumor markers of pancreatic cancer.

Using pancreatic juice as a potential source of biomarkers of early stage pancreatic cancer has attracted significant interest [171, 172]. 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 [173]. However, pancreatic juice can only be obtained during an invasive endoscopic procedure. Thus, 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 [174]. Pancreatic cancer develops from normal ductular epithelium through a sequential worsening of precursor lesions that can be identified through histology and genetic testing [175, 176]. 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 [175, 177, 178]. The p16 tumor suppressor gene is inactivated in more than 80–90% of pancreatic cancer cases at an intermediate stage [179]. 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 [174, 180, 181].

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 [182]. However, the carriers of these genetic disorders in the general population 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 mechanisms such as aberrant DNA methylation, oxidative effects, impaired DNA repair pathways, and abnormal activation of receptors, transcription factors, and cell cycle proteins [183]. While major advances have been made to better understand the interaction between environmental factors and genetic susceptibility to human cancers, the gene–environment interaction for pancreatic cancer has not yet been fully evaluated. There are currently several studies investigating the association between genetic polymorphisms and risk of pancreatic cancer.

Genetic Susceptibility

Studies using candidate gene approaches have mainly focused on genes in the following pathways: carcinogen metabolism [184–193], DNA repair [186, 194–199], inflammatory response [200, 201], alcohol-metabolizing enzymes [202, 203], methylation [117, 202–206], and protease inhibitors [191, 207–209]. 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 [175]. However, studies suggested that the combination of *GSTT1-null* and *GSTP1*-codon 105 Val variants significantly increased the risk for pancreatic cancer [193]. Individuals who were heavy smokers and carried *GSTT1*-null genotype significantly increased their risk of pancreatic cancer compared to non-smokers with *GSTT1*-present genotype [185]. Heavy smokers with the *CYP1A2*∗1F(A-163C) C allele or *NAT1* rapid alleles experienced a significantly elevated risk of pancreatic cancer as compared to never smokers carrying non-at-risk alleles [188].

A case-control study conducted at the MD Anderson Cancer Center investigated genetic variants in glucose metabolism genes and risk of pancreatic cancer in 1654 cases and 1182 controls [210]. 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 [202, 203]. Miyasaka et al. [203] 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. [202] 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. [197] 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 [186, 196, 198]. 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) [195] or cross different pathways (i.e., XRCC1 with GSTT1/GSTM1) [194] in relation to pancreatic cancer risk.

A case-control study from Mayo Clinic of 1354 Caucasian pancreatic cancer patients and 1189 healthy Caucasian controls investigated 1538 SNPs in 102 inflammatory pathway genes [201]. 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 the San Francisco Bay Area suggested that proinflammatory gene polymorphisms in combination with proinflammatory conditions might influence pancreatic cancer development [200].

Suzuki et al. [117] 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. [206] 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 [204].

Recently, genome-wide association studies (GWAS) among the population of European ancestry identified common SNPs in several genomic regions (i.e., 1q32.1, 2p14, 3q28, 5p15.33, 7p14.1, 7q32.3, 8q24.21, 9q34.2, 12q24.31, 13q22.1, 16q23.1, 17q24.3, 22112.1) that are associated with pancreatic cancer risk [211–214]. A GWAS from China identified five significant genomic regions (5p13.1, 10q26.11, 21q21.3, 21q22.3, and 22q13.32) that are associated with risk of pancreatic cancer [215]. A Japanese GWAS reported three significant loci (6p25.3, 7q36.2, and 12p11.21) associated with pancreatic cancer risk [216]. 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 survival rate, often claiming the life of its victims within the first year. From previous studies, a wide array of contributing occupational and nonoccupational risk factors has been suggested. Some of these include smoking, excessive alcohol consumption, obesity, physical inactivity, diabetes, chronic pancreatitis, nutritional considerations, and complex genetic predispositions and interactions. Further studies and data pooling may help gain a better understanding of such risk factors, ultimately leading to effective awareness and prevention programs.

Since delays in early diagnosis may contribute to poor prognosis, misclassification of initial symptoms may be prevented and earlier diagnosis accomplished through the use of specific molecular markers. Thus, the identification and implementation of pancreatic tumors markers has potential to be an important diagnostic tool.

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Sinonasal Cancer

7

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Introduction

Sinonasal cancer, the cancer of the nose and paranasal cavities (ICD 10 codes C30.0 and C31.0 to C31.9), is rare. The incidence is below 2/100,000 persons per year, shows clear differences between countries, and is higher in men than in women [1]. There has 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 minor role [2, 4].

Anatomically, the sinonasal region is located in the midportion 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; 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 respiratory mucosa (referred to as the Schneiderian membrane) begins at the mucocutaneous junction. The nasal cavity with the turbinates and the paranasal sinuses is 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 1 cm anterior to the choanal orifice where the nasal cavity leads into the anterior opening of the nasopharynx.

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 gives an overview and discuss epidemiological studies on sinonasal cancer dealing with epidemiological evidence for various occupational risk factors, exposure characteristics, tumor pathology, findings from experimental and human studies contributing to understanding of 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

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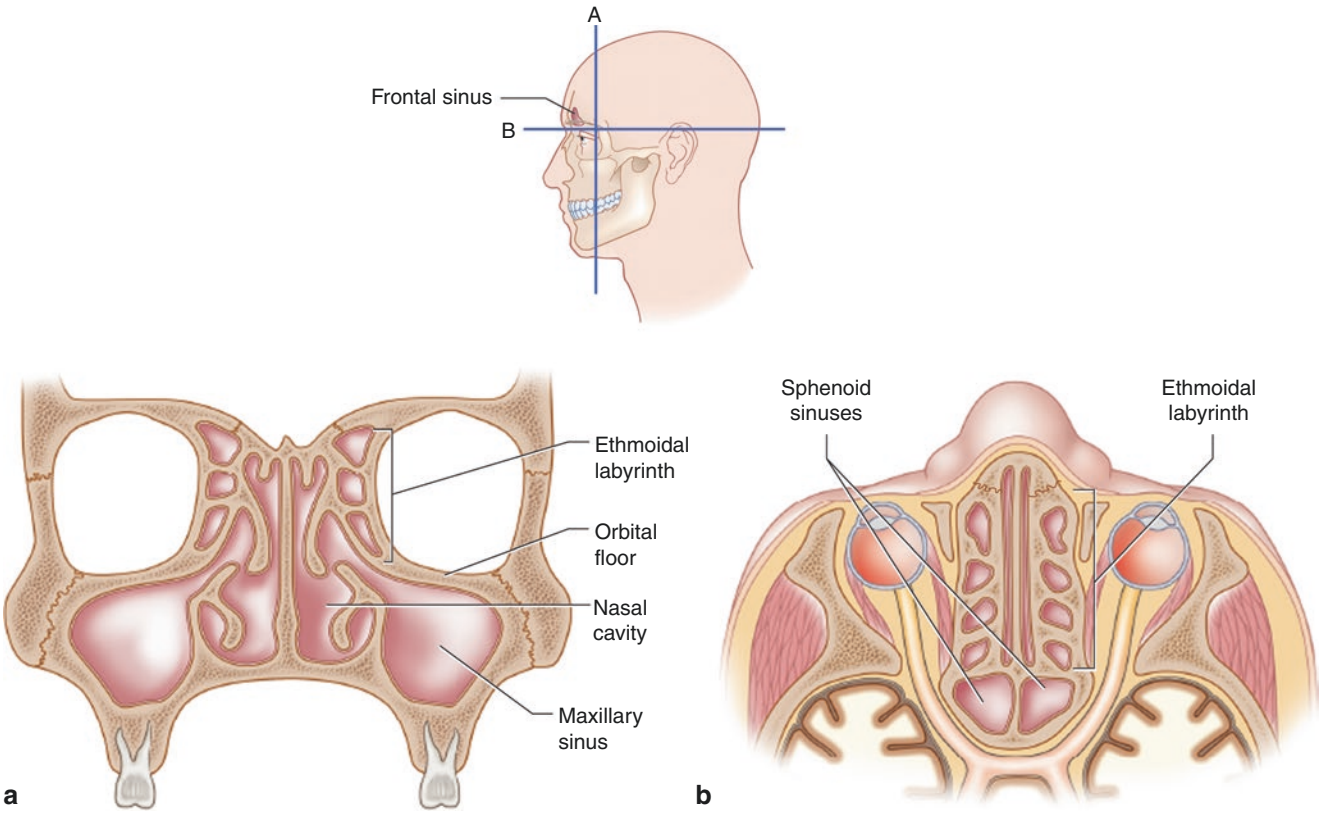


Fig. 7.1 Nasal cavities and paranasal sinuses shown in (**a**) coronal and (**b**) transverse sections. The orientation of the sections is illustrated in the middle where the frontal sinus is also shown. The ethmoidal labyrinth is a frequent target of sinonasal adenocarcinoma. (Adapted from Gnepp [5])

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 countries and even within countries from one region to another [1, 7] For example, age-standardized incidence rates among men during 2003–2007 in some European countries were 0.8–1.5 in France, 0.2–1.2 in Italy, 1.0 in Denmark, 0.8 in the Netherlands, 0.6 in Norway, 0.4–0.6 in the UK, 0.3–0.8 in Germany, 0.6 in Finland, and 0.6 in Sweden. In the US, the incidence rate was 0.7 among colored people and 0.6 among white people. The corresponding rates in each country were lower for women [1]. The two main histological types of sinonasal cancer, squamous cell carcinoma, and adenocarcinoma, have somewhat different etiologies and epidemiology. The 5-year relative survival of sinonasal cancer is 45–60% in both Europe and the US [8–13].

Occupational Risk Factors

Several occupational exposures can increase the risk of sinonasal cancer. According to the most recent reviews of human carcinogens compiled by the International Agency for Research on Cancer [4, 14–16], wood dust, leather dust, nickel compounds, radium-226 and radium-228 and their decay products, and work in a specific isopropanol production can cause sinonasal cancer. Positive associations have also been observed between sinonasal cancer and exposure to hexavalent chromium (chromium VI) compounds, to formaldehyde, and work in the textile industry, although the evidence remains limited in humans [17]. There is limited epidemiological evidence for formaldehyde and sinonasal cancer as opposed to nasopharyngeal cancer, for which the association with formaldehyde exposure is well documented (IARC Group 1) [4, 18]. Table 7.3 provides exposure characteristics for agents evaluated as carcinogenic to humans by IARC (Group 1) [4].

All occupational exposures associated with risk of sinonasal cancer, except for "shoe and leather work," are relatively prevalent exposures worldwide. For wood dust, it has been estimated that approximately 3.6 million workers in the European Union were exposed to wood dust on a regular

basis in 2001–2003; worldwide the numbers are hundreds of millions [2, 19]. Similarly, several millions of 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 [20].

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 use 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.

A key source of information is a pooled reanalysis of 12 case-control studies on sinonasal cancer conducted in seven countries [21–23] with sufficient statistical power to realistically examine the risks according to histological type, sex, work, exposure level, and exposure duration. These studies were selected based on 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 3136 controls (2349 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 analyses from the pooled dataset focused on the associations with wood dust [21], formaldehyde, silica, textile dust, coal dust, flour dust, asbestos, man-made vitreous fibers [23], and various occupations and industries [22]. An analysis was also conducted restricted to the eight European studies included in the pooled dataset, dealing with exposure to wood dust, leather dust, and formaldehyde [24]. 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 are presented and discussed when they add relevant information.

Wood Dust

The causal role of exposure to wood dust in the genesis of sinonasal cancer, first suggested in the 1960s [61], has long been unambiguously established by numerous epidemiological studies carried out in populations with different geographical origins and having been exposed for different periods and in several fields of activity [2, 4, 15].

Wood dust exposure is present in many industries; the typical high exposure industries or tasks are furniture industry, cabinetmaking, and joineries [2, 4]. Wood dust exposure levels in various industries in the past and more recently are 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 [19, 62].

Demers and coworkers [21] analyzed the pooled data from the 12 case-control studies presented above and summarized in Table 7.1 taking levels of wood dust into account. Seven categories of woodworkers were investigated. The levels of exposure to wood dust were classified into four 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 [21] revealed a sizeable relative risk of adenocarcinoma (Fig. 7.2). The study showed a high relative risk in men working in a wood-related job (odds ratio [OR] 13.5; 95% confidence interval [CI] 9.0–20.0). This relative 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 for men. As in 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

Table 7.1 Main characteristics of the 12 case-control studies included in the pooled analyses by Demers et al. [21], Leclerc et al. [22], Luce et al. [23], and 't Mannetje et al. [24]

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
China (Shanghai)/ Zheng et al. [25]	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. [26], Luce et al. [27–29]	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. [30]	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. [31]	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. [32]	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

Table 7.1 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Italy (Biella)/ Magnani et al. [33]	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
Italy (Vigevano)/ Merler et al. [34]	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	Men: 29
			Women: 5	Women: 10
			Men + Women: 21 (69/6)	
The Netherlands/ Hayes et al. [35, 36]	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	Formaldehyde	Men: 91 (25/55)	Men: 195
	Job titles and industries coded SICM of US Census and tasks with the US DOT		Women: –	Women: –
	Job history reviewed and classified according to level and probability of WD exposure and formaldehyde (blinded to case-control status)			
Sweden/Hardell et al. [37]	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	Referents of a previous study of soft tissue sarcoma and lymphoma
			Men: 44 (7/70)	Men: 541
			Women: –	Women: –
USA (Virginia, North Carolina)/Brinton et al. [38, 39]	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)	Men: 181
			Women: 67 (17/52)	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)	Men: 108
			Women: 38 (3/41)	Women: 70

(continued)

Table 7.1 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
USA (Seattle)/ Vaughan and Davis [40]	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)	Men: 327
			Women: 20 (5/35)	Women: 225
Pooled analysis of 12 international case-control studies IARC/Demers et al. [21], Luce et al. [23]	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 studies above	Controls of the 12 studies above
	Job-exposure matrix		Men: 680 (25/48)	Men: 2349
			Women: 250 (10/40)	Women: 787
Pooled analysis of eight European case-control studies/'t Mannetje et al. [24]	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: 1464
			Women: 104 (11/39)	Women: 241

AC adenocarcinomas, SCC squamous cell carcinomas, WD wood dust
[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

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. [41]	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. [42]	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 [43]	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 [44], Fukuda et al. [45]	Postal questionnaire	Woodworking (carpenters, joiners, furniture workers, and other woodworkers)	Diagnosed between 1982 and 1986 in all Hokkaido hospitals, aged 40–79	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

Table 7.2 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Nordic/Hernberg et al. [46]	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)	
Hong Kong/Ng [47]	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. [48], Olsen and Jensen [49], Olsen and Asnaes [50], Olsen [51]	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: 1631
			Women: 180 (8/66)	Women: 834
Germany/Pesch et al. [52]	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. [53, 54]	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. [55]	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

(continued)

Table 7.2 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Japan/Takasaka et al. [56]	Complete history of experience in woodworking and detailed tasks	List of occupations (forestry worker, coal miner, nickel worker, wood sawyer, chipper-men, 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 oto-rhinolaryngological diseases, matched for sex, age, and date of admission
			Men: 107 (6/80)	Men: 413
			Women: –	Women: –
USA/Caplan et al. [57], Mirabelli et al. [58], Zhu et al. [59]	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: 1910
	Estimation of exposures by industrial hygienist		Women: –	Women: –
Nordic/Siew et al. [60]	Occupational history Exposure assessment by job-exposure matrix	Wood dust and formaldehyde	AC: Men: 393 Women: – Other nasal cancers: Men: 2446 Women: –	Five controls per case randomly selected in the population, matched for year of birth and country: 14197

AC adenocarcinomas, SCC squamous cell carcinomas

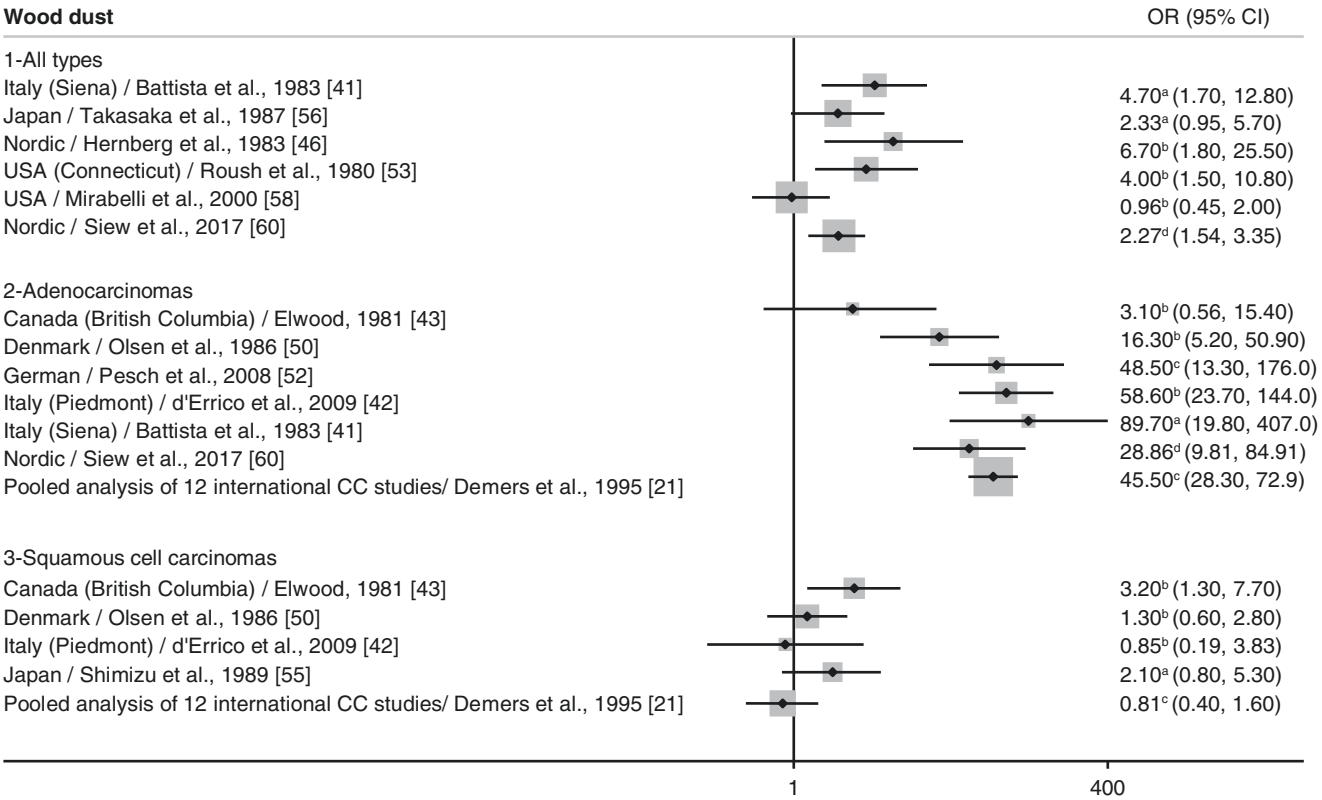


Fig. 7.2 Exposure to wood dust. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95% CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. OR odds ratio, 95% CI 95% confidence interval. 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, [d]High cumulative exposure (>28 mg/m^3-years)

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 [21] were more ambiguous for squamous cell cancers than for adenocarcinomas (Fig. 7.2). The risk for women was approximately doubled, particularly for women who had worked in moderately or highly exposed jobs. An exposure–effect relationship was evident for 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 neither related to being exposed at the job nor to the intensity or the duration of exposure. Overall, the risk estimates for squamous cell carcinomas were distinctly lower than those for adenocarcinomas.

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 mortality was also found in cohorts of woodworkers, but there was no information available on histological type. Demers and coworkers [63] performed a pooled analysis of five cohorts of workers exposed to wood dust. They found 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), 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 initiated their employment before 1940 and whose exposure had started 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 (10 out of the 11 deaths from sinonasal cancer). A more recent record-linkage study in Finland, with incidence data on histological type, found excess risks of nasal cancer overall (RR, 1.59; 95% CI, 1.06–2.38), and of nasal squamous cell carcinoma (RR, 1.98; 95% CI, 1.19–3.31) among men exposed to wood dust. Relative risks were not reported for adenocarcinomas, due to the small number of cases [64].

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 association between exposure to wood dust and the onset of this histological form and is very clear and the association is over tenfold stronger for adenocarcinomas than for squamous cell carcinomas. This result is supported by a recent meta-analysis [65].

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 in particular 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.

Since recently, a large part of the sinonasal adenocarcinoma cases included in the published studies were related to exposure to hardwood dusts, and the case-control studies in which the type of wood used was evaluated confirmed the suspicion of a stronger association with hardwood dust than with softwood dust [4, 26, 52]. 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, 66]. However, a recent large register-based case-control study in the Nordic countries demonstrated a clear excess risk of nasal adenocarcinoma related to exposure to softwood-dominated mixed wood dust; this was, however, without adjustment for tobacco smoking as a potential confounder [60].

Nevertheless, 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.

Regarding the levels of exposure to wood dust, there are no studies with evidence for a safe level concerning the carcinogenic effect. However, data from epidemiological studies with information on exposure–response relations [2, 42, 66–68] suggest that health effects at exposure levels below 1 mg/m^3 may be less significant as opposed to higher exposure levels [68] (Fig. 7.2 and Table 7.3).

Table 7.3 Exposure characteristics for agents causally related to sinonasal cancer (SNC)

	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 safe level for carcinogenicity, but confirmed risk of nonmalignant respiratory effects for exposures below 1 mg/m^3	IARC [67]
				Demers et al. [66]
				d'Errico et al. [42]
				IARC [4]
				Siew et al. [60]
				SCOEL [68]
Nickel compounds	Not specified	Nickel refining industry	No clear exposure–response relationships reported	IARC [20]
		Hydrometallurgy	Airborne nickel concentrations >1 mg/m^3 found in earlier studies, lower in recent years	IARC [4]
		Electrolysis workers		
		Calcining workers		
"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 [69]
		Boot and shoe repair	Increased for both light and heavy exposure, and increased for 5 and 10 years of exposure	Merler et al. [34]
				d'Errico et al. [42]
				Straif et al. [15]
				IARC [4]
Tobacco smoking	Squamous cell carcinoma	–	Exposure–response relationships observed in several studies (duration, intensity)	IARC [70]
			No clear threshold values	't Mannetje et al. [24]
				IARC [71]

Only agents evaluated as carcinogenic to humans by IARC (Group 1) are included
[a]The evaluation is based on studies including workers predominantly exposed to hardwood dust

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 UK [72, 73], the Nordic countries [51, 74], and Italy [75]. Shoe and leather work involves a wide variety of different work procedures and exposure to numerous toxic substances; in the IARC monograph published in 1981, "shoe and leather work" was considered as carcinogenic to humans [69]. 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 the causal agent (Group 1) by the IARC [4, 15] for the nasal cavity and paranasal sinuses, with sufficient evidence in humans.

The association is stronger for adenocarcinomas, but some results suggest that other histological types could also be involved. More case-control studies and cohort studies revealed leather dust to be related to sinonasal cancer in a dose-dependent manner [69]. Merler and coworkers [34] 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).

Results from numerous cohort and case-control studies were included in a meta-analysis [65]; the results showed a strong increased risk of adenocarcinoma (MetaRR = 35.3; 95% CI 20.6–60.3) and a significant increased risk of squamous cell carcinomas (MetaRR = 2.1; 95% CI 1.1–3.9).

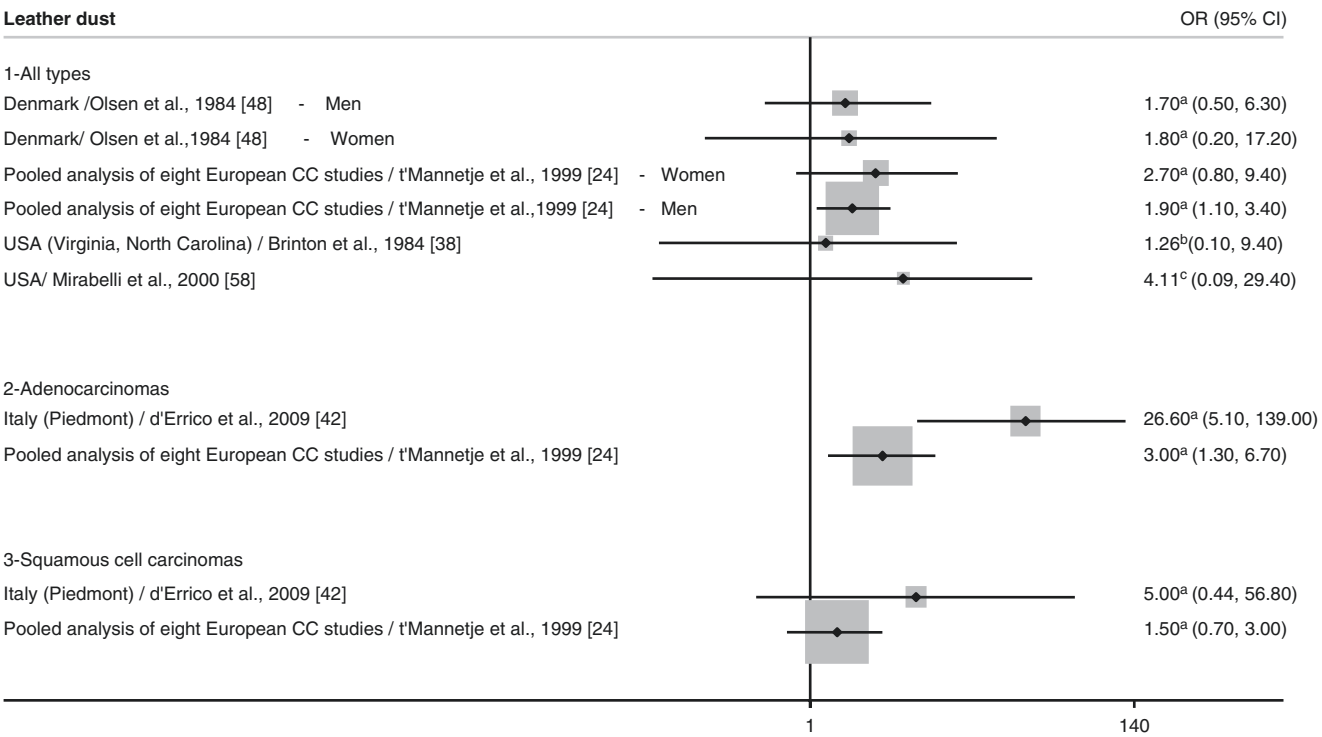
There is no exposure-response data available to identify a possible safe level for shoe and leather work and sinonasal cancer (Fig. 7.3 and Table 7.3).

Nickel and Chromium Compounds

The association between 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, 15, 20].

Nickel compounds and nickel metal are used in many industries and have been in widespread commercial use for more than 100 years. High exposure to airborne nickel occurs in nickel refining, nickel alloy production, welding in stainless steel, electroplating, grinding, and cutting operations [4, 20].

Excess cases of sinonasal cancer were found among workers in the nickel refining industry and employees in



• 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

hydrometallurgy and electrolysis plants, whereas no consistent relation has been seen in other occupations, e.g., in welders [20]. Furthermore, IARC's evaluation is based on exposure to inorganic nickel compounds like nickel sulfate and the combination of nickel sulfides and oxides [4, 20]. 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, 76]. The past concentration levels of individual nickel compounds are not known.

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 [46] 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 [38] observed a nonsignificantly increased risk of sinonasal cancer in 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 [28, 42], 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 [28].

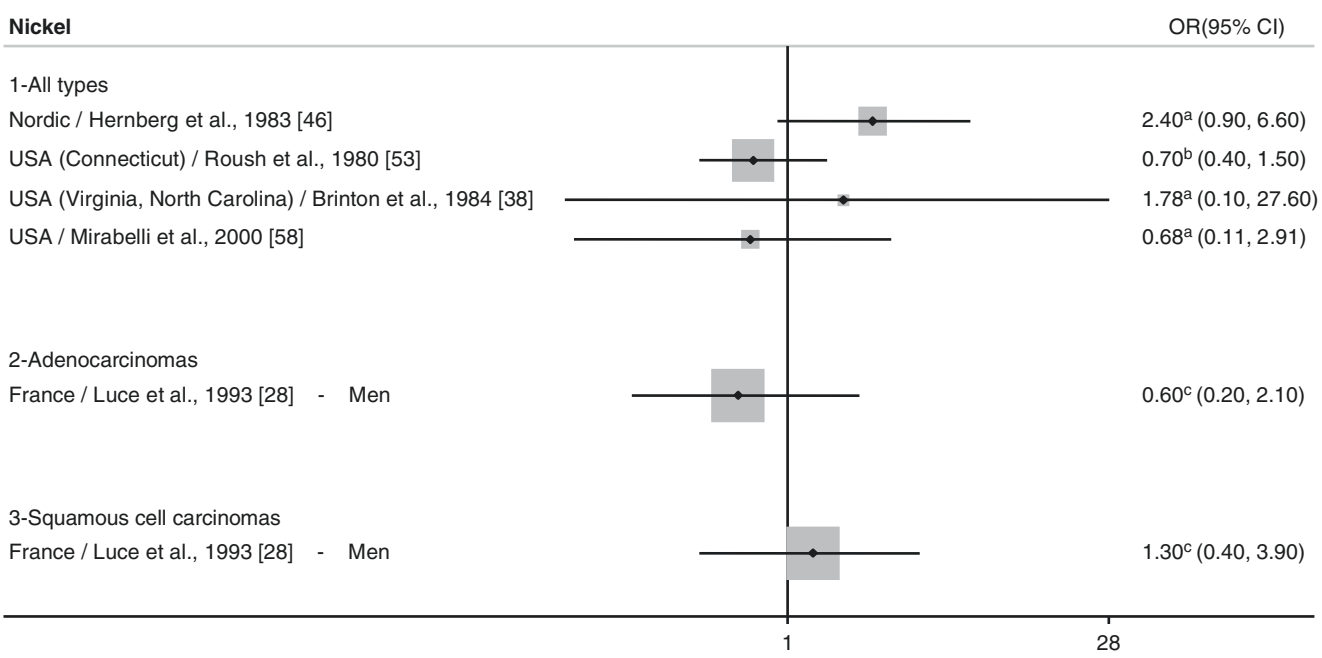
In a meta-analysis, Binazzi and coworkers [65] observed a significant meta-RR for nickel and chromium compound exposures associated with all histological sinonasal cancers (MetaRR = 18.0; 95% CI 14.6–22.3).

A range of epidemiological studies on nickel and/or hexavalent chromium and sinonasal cancer included exposure–response analysis, but no clear exposure-response relationships were revealed (Figs. 7.4, 7.5, and Table 7.3).

Formaldehyde

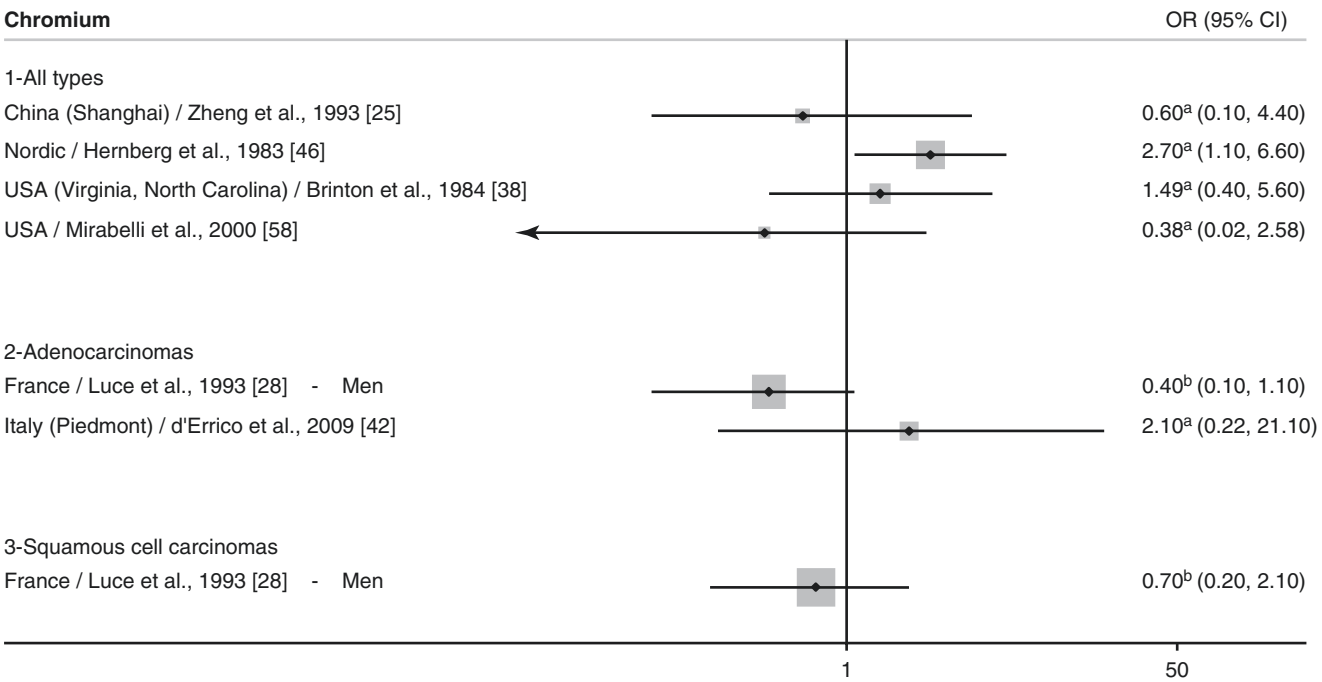
Formaldehyde is a probable cause of sinonasal cancer based on sufficient evidence from excess of squamous cell carcinomas in rodents and limited evidence in humans [14, 77].

Following the reporting of nasal squamous cell carcinogenicity in rats exposed to high doses of formaldehyde in the early 1980s [78], several epidemiological studies have been published [2, 77]. Several studies, including five cohort studies and one study of proportionate morbidity based on industrial formalde-



• 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



• 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]: Ever exposed 'Probable or definite'

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

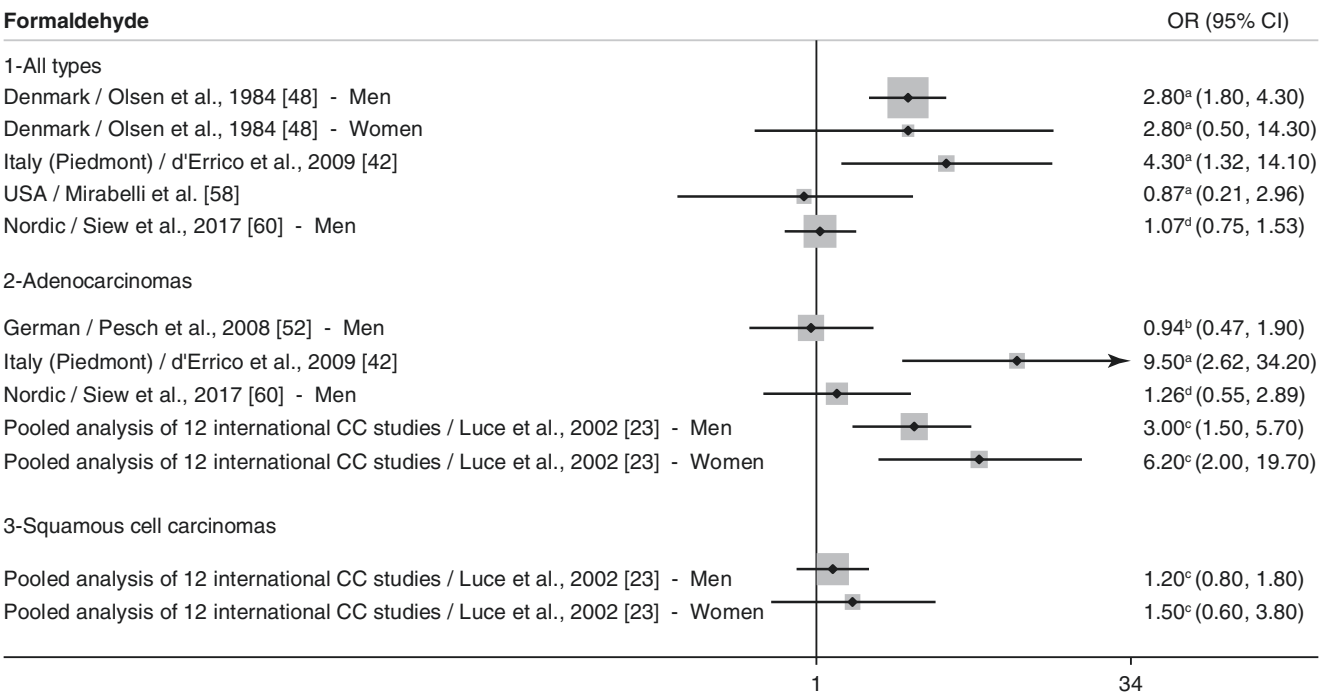


Fig. 7.6 Exposure to formaldehyde. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95% CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR* odds ratio, *95% CI* 95% confidence interval. 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]Ever exposed after 1985, [c]Level of cumulative exposure: high, [d]Level of cumulative exposure : >0.85 ppm-years

hyde exposure [79–87], and five studies based on exposures among pathologists and embalmers [88–92] 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 and the small numbers of observed and expected numbers in each study, the interpretation of risk is 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) [83, 84].

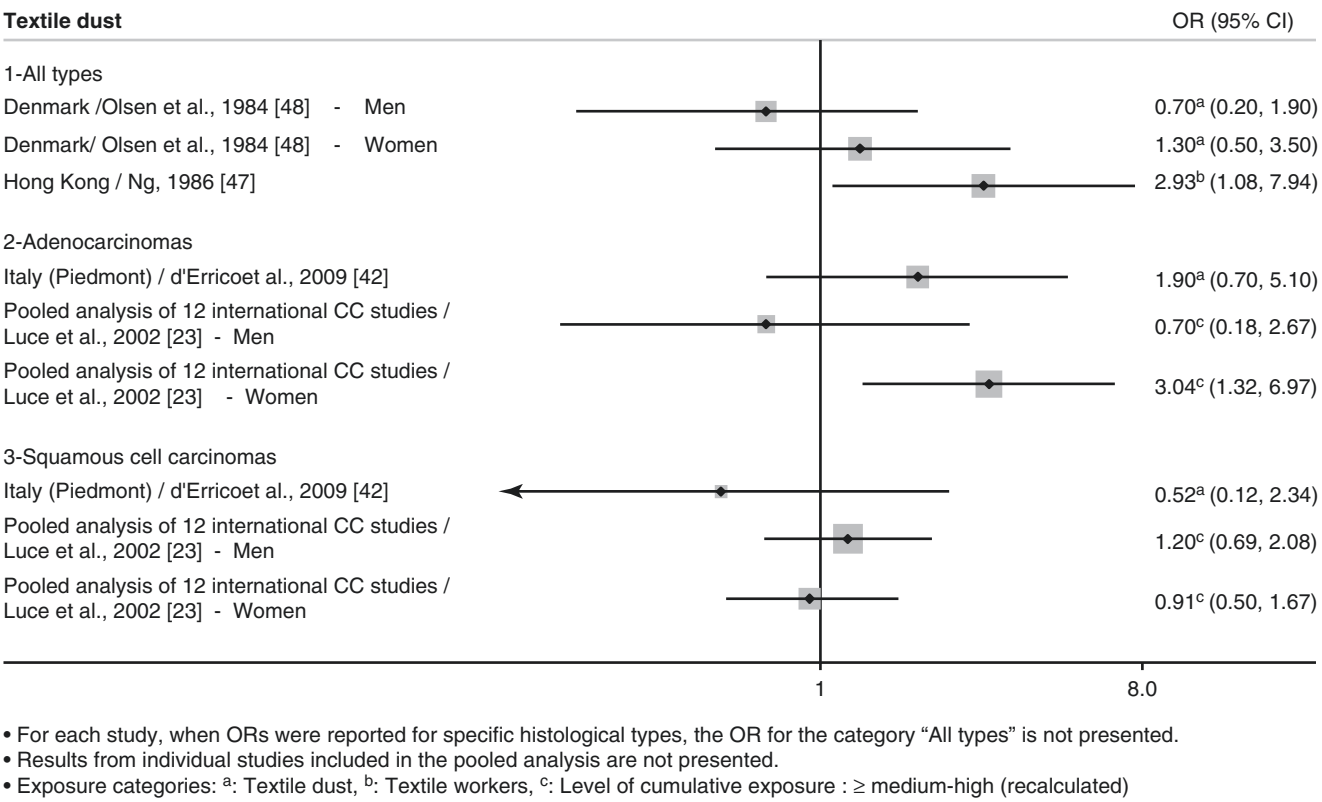
The pooled data of 12 case-control studies were analyzed with respect to formaldehyde exposure [23] (Fig. 7.6). Significantly elevated relative risks for adenocarcinoma appeared in the groups with the highest cumulative exposure in both men (OR 3.0; 95% CI 1.5–5.7) and women (OR 6.2; 95% CI 2.0–19.7), whereas relative risks for squamous cell carcinoma 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 carcinoma 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 five 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 three of them.

A meta-analysis [65] showed increased risks of both adenocarcinoma (MetaRR = 3.8; 95% CI 1.4–10.4) and squamous cell carcinoma (MetaRR = 2.4; 95% CI 1.7–3.3) associated with formaldehyde exposure.

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 [22]. 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 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 [23]. 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 associations with the cumulative level, probability, or duration of exposure to textile dust were found among men for either histological type 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



• 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

with elevated risks of sinonasal cancer in several other case-control studies (Fig. 7.7).

In the meta-analysis conducted by Binazzi and coworkers [65], textile industry was associated with a significant meta-RR for sinonasal adenocarcinoma (MetaRR = 3.5; 95% CI 1.9–6.5) but no association was found for squamous cell carcinoma (MetaRR = 0.9; 95% CI 0.4–1.8).

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 [23]. 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. [39], 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 [23].

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 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 [77].

Other occupational exposures have been associated with the risk of sinonasal cancer, such as paints [46], adhesives [28], cutting oils [53, 54], and chlorophenols [37, 58, 59]. In the pooled analysis [23], 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 [25, 46], 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 [42] 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 [22]. 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 [93], construction [27, 31, 47], or metalworking [32, 51, 93] were not confirmed in the pooled analysis. However, two new associations emerged with respect to sinonasal squamous cell carcinoma: 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). Recently, an increased risk for sinonasal cancer was seen in a Danish styrene exposed cohort, SIR 1.62 (95% CI: 1.16, 2.21), with an indication of an increasing trend with duration; this was, however, without adjustments for potential confounders [94].

Nonoccupational Risk Factors

There is a causal relationship between tobacco smoking and the risk of cancer of the nasal cavity and the paranasal sinuses [71, 95]. Smoking is still very prevalent worldwide and has been a common lifestyle-related exposure for at least subgroups of individuals for several decades [70, 71, 95].

Table 7.3 provides exposure characteristics for smoking and sinonasal cancer. 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 carcinoma than for adenocarcinoma [96]. 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 the estimated relative risk is in the order of 15–30 [96].

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. In general, the associations to cancer of the nose and paranasal sinuses were considerably lower than for wood dust exposure [4, 70].

IARC has also evaluated the effect of involuntary smoking, the type of tobacco smoke exposure related, e.g., to exposure at work, on the development of sinonasal cancer, and the evaluation concluded that the literature was sparse and with conflicting results [4, 70].

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, and to a lesser extent with lymphoepithelial carcinomas, no relation was reported with other histological types. 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 [97–100].

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 and leather dust are predominantly associated with adenocarcinoma, whereas increased risks for tobacco smoking were mainly found in squamous cell carcinoma. 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.

Pathology

General

The WHO Classification of Head and Neck Tumors [6, 101] lists 42 primary tumors occurring in the nasal cavity and paranasal sinuses or its vicinity, excluding tumors of bone and cartilage. Ten of these tumors are malignant epithelial carcinomas (Table 7.4). The other tumor categories are teratocarcinosarcoma, sinonasal papillomas, respiratory epithelial lesions, salivary gland tumors, malignant soft tissue tumors, borderline/low-grade malignant tumors, benign soft tissue tumors, hematolymphoid tumors, and neuroectodermal/melanocytic tumors. In addition to a linkage to occupational exposure, some sinonasal carcinomas are associated with viruses [6, 101]. The lymphoepithelial carcinoma is

Table 7.4 Carcinomas of the nasal cavity and paranasal sinuses[a]

Histological type	ICD-O
Keratinizing squamous cell carcinoma	8071/3
Nonkeratizing squamous cell carcinoma	8072/3
Spindle cell squamous cell carcinoma	8074/3
Lymphoepithelial carcinoma	8082/3
Sinonasal undifferentiated carcinoma	8020/3
NUT carcinoma	8023/3
Neuroendocrine carcinomas	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Adenocarcinomas	
Intestinal-type adenocarcinoma	8144/3
Non-intestinal-type adenocarcinoma	8140/3

[a]Adapted from WHO Classification of Tumors [101]

associated with EBV, and HPV has been identified in cases of squamous cell carcinomas [6, 101].

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 [102, 103] (Fig. 7.1). A staging (T) classification for maxillary and ethmoid carcinomas has been adopted [104]. Occupational exposure is predominantly associated with squamous cell carcinoma and adenocarcinoma (Fig. 7.8), with these two tumor types having somewhat different etiologies as indicated by epidemiological studies [2, 4, 6, 101] (see Section "Epidemiology and Occupational Risk Factors").

In several studies, squamous cell carcinomas have constituted approximately 35–70% of the malignancies in the sinonasal region [101, 103, 105] (see Section "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. Adenocarcinoma accounts for a variable proportion of sinonasal cancers, varying from 10 to 50%, depending on the country [6, 101] (see Section "Epidemiology and Occupational Risk Factors").

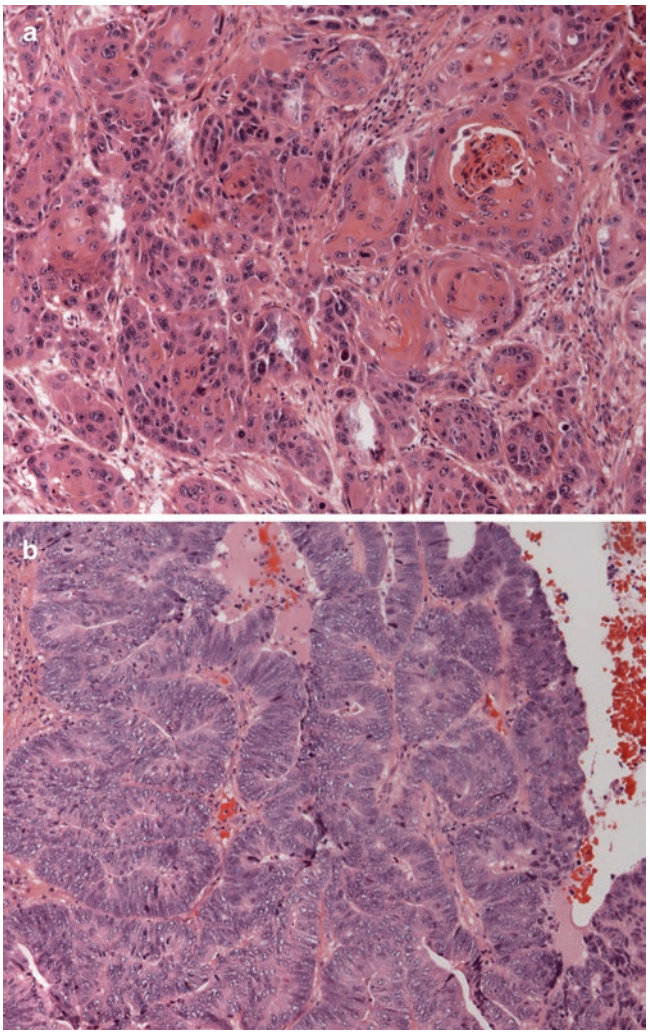


Fig. 7.8 Two main histological types of sinonasal cancer. Squamous cell carcinoma (**a**) and adenocarcinoma (intestinal type) (**b**) are illustrated hematoxylin-eosin staining; 20× objective used

Squamous Cell Carcinoma

Squamous cell carcinomas can be subdivided into distinctive forms including keratinizing, nonkeratinizing, and spindle cell types (Table 7.4) [101]. An example of a keratinizing squamous cell carcinoma is shown in Fig. 7.8a. The precursor lesions for 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]. Etiological risk factors for keratinizing and nonkeratinizing squamous cell carcinoma include cigarette smoking, wood and leather dust and other industrial exposures. For lymphoepithelial carcinomas EBV positivity is common (see Section "Epidemiology and Occupational Risk Factors").

Intestinal-Type Adenocarcinoma

Sinonasal adenocarcinomas are divided into two groups by WHO: namely, the intestinal-type adenocarcinomas (ITACs) (Figs 7.8b and 7.9) and the non-intestinal-type of adenocarcinomas (non-ITACs) [101]. 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% [106, 107]. 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 [101].

Two classifications for ITACs are in use (Table 7.5) [107, 108]. 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 [107]. 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 adenocarcinomas, while cytokeratin 7 is positive in adenocarcinomas 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

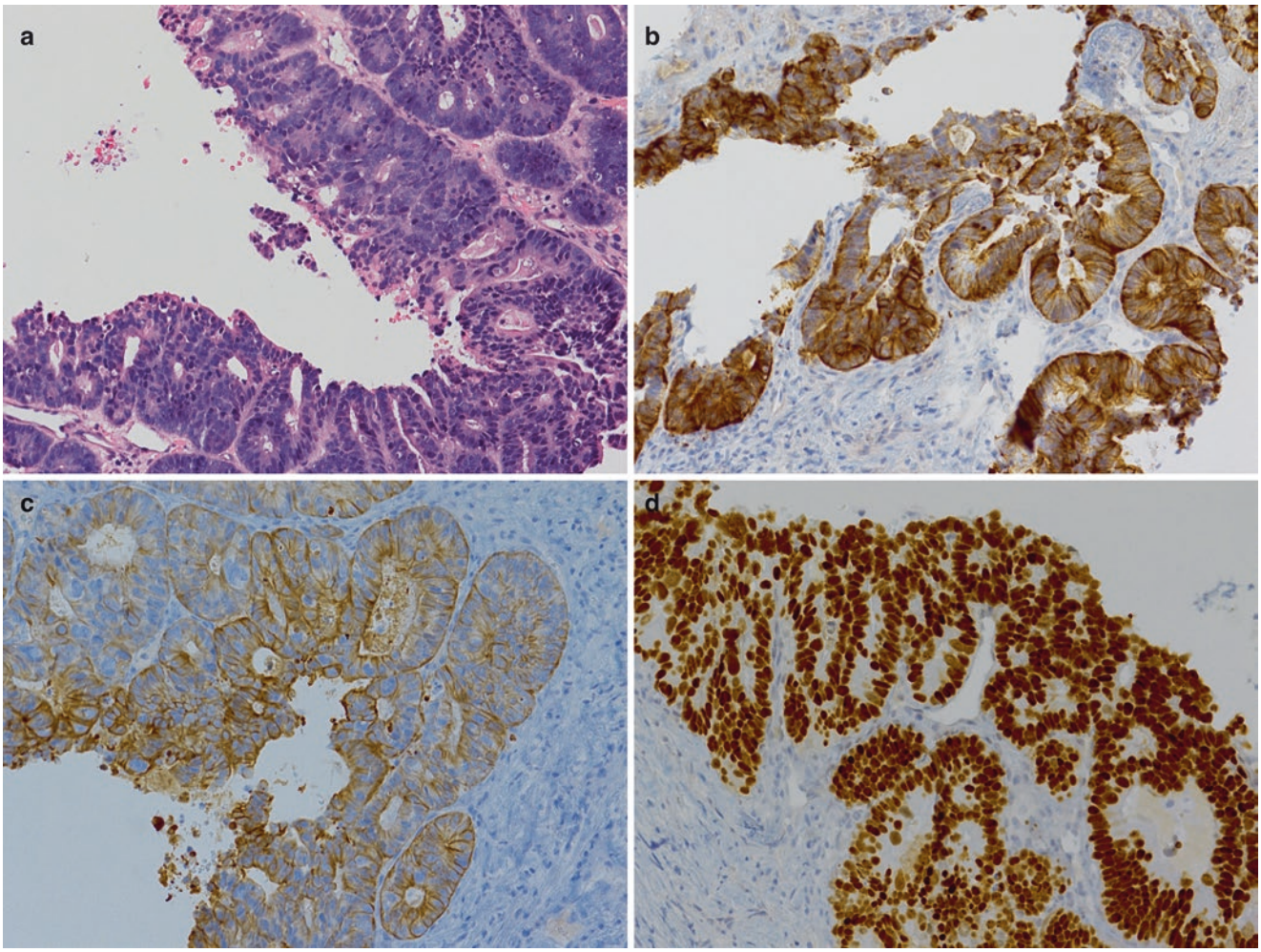


Fig. 7.9 Sinonasal intestinal-type adenocarcinoma (*ITAC*) of colonic type (**a**) hematoxylin-eosin staining, with immunochemistry (**b–d**). Immunohistochemically ITACs are positive for various epithelial markers: positivity for CK20 (**b**), CK7 (**c**), and CDX-2 (**d**) is shown (20× objective used).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

Barnes and WHO Classification of Tumors [107]	Kleinsasser and Schroeder [108]	3-year cumulative survival [108] (%)
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

Three-year survival rates from Kleinsasser and Schroeder are also indicated

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

gene plays a crucial role in the differentiation of the intestine. CDX-2 is commonly expressed in ITACs (Fig. 7.9d) [109–111]. However, in a recent study [112], it was shown that CDX-2 is expressed in some other types of SNCs than ITACs (undifferentiated carcinomas, squamous cell carcinomas, salivary gland carcinomas, and small cell carcinomas).

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 [113–115] to some extent. In a cytological study, cuboidal cell metaplasia and goblet cell hyperplasia were observed in wood dust-exposed workers [114]. Histological metaplastic changes have also been associated with wood dust exposure [115]. In a third study examining mucosal lesions adjacent to ITACs, metaplastic and mild dysplastic lesions were found adjacent to the tumors [113]. However, the changes were present in both wood dust exposed and non-exposed patients. Interestingly, in the two later studies, wood dust was associated with increased expression of p53 tumor suppressor protein in epithelial nonmalignant cells [113, 115].

Non-intestinal-Type Adenocarcinoma

The first description on sinonasal non-intestinal adenocarcinomas emerged in a study published in early 1980s [116]. In that study, high-grade tumors were included, and the article 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 [116]. 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, 101].

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 [101]. The differential diagnosis between the high-grade non-ITACs and other high-grade adenocarcinomas is challenging [117]. It has been proposed that they form a heterogeneous group of tumors of multiple unknown entities or variants of known entities [117]. A subset of ITACs are considered to be true seromucinous adenocarcinomas [118]. 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 [109] 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 [117].

As mentioned above, the epidemiological studies do not differentiate between sinonasal adenocarcinoma subtypes; thus, they are not informative about the possible association of adenocarcinoma subtypes with wood dust exposure, or about the relative frequencies of adenocarcinoma subtypes. In the pathology literature, non-ITACs are not considered to be associated with wood dust exposure; in addition, non-ITACs are regarded rarer than ITACs [6, 101], although there are apparently no studies specifically reporting on the relative frequencies of ITACs and non-ITACs or their association with wood dust exposure. In a recent study, the relative frequencies of ITACs and non-ITACs in France and Finland were studied using immunohistochemistry for the differential diagnosis [119]. The results indicated that among cases from France, where exposure to hardwood dust is common, ITACs were by far the most frequent subtype. On the other hand, in Finland, where exposure to softwood is common and the occurrence of sinonasal adenocarcinomas generally lower, non-ITACs were slightly more frequent than ITACs. Both sinonasal adenocarcinoma subtypes occurred in cases who had been exposed to wood dust. Wood dust exposure was, however, more common with ITACs than non-ITACs [119].

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. 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.

There is a strong epidemiological association between wood dust exposure and adenocarcinomas. In the pathology literature, ITACs are often considered as being associated with occupational exposure to wood dust. In a recent study, both ITAC and non-ITAC tumors appeared to occur in cases with occupational exposure to wood dust. Wood dust exposure was, however, more common with ITACs than non-ITACs.

Mechanisms of Carcinogenesis

Relatively little is known about the pathomechanisms involved in the development of the cancer of the nose and nasal cavities in humans. From the known or suspected risk factors of sinonasal cancer, current knowledge about cancer mechanisms is largely limited to exposure to wood dust, the best documented etiological factor (See Section "Epidemiology and Occupational Risk Factors"), whereas mechanistic data on other factors, such as exposure to leather dust or textile dust, are minimal. On the other hand, there are studies on exposure to nickel and chromium compounds or formaldehyde, as well as a massive body of literature for tobacco smoke; all with evidence for genotoxicity and with at least some other data on possible mechanisms [2, 4, 70, 71, 77, 120].

Information about the likely mechanisms of cancer involved in development of sinonasal cancer in association with wood dust exposure originate to a large extent from experimental studies as well as from studies using a biomarker approach to

examine occupationally exposed workers. In addition, there are series of studies that have investigated molecular alterations in tumor tissue from sinonasal cancer; some of these studies have been focused on cases with or without exposure to wood dust, as reviewed [2, 4].

This section reviews studies, such as those on toxicity, carcinogenicity, DNA damage, and genotoxicity as well as irritation- and inflammation-related effects, considered relevant in this context for illustrating various cellular processes and mechanisms functional in various tissues in association with exposure to wood dust. In particular, experimental studies and studies on workers occupationally exposed to wood dust are described. In addition, a few examples of molecular genetic alterations, as detected in sinonasal cancer tissue from cases with past exposure to wood dust, are briefly mentioned (see Section "Molecular Markers" for more detail).

Toxicological Features of Wood and Wood Dust

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 produced; 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 (often machine-operated), 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. Compounds in wood also 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; they however primarily appear to be present in wood treated with preservatives or stains [2, 4].

A number of biologically active substances has been identified in both hardwood and softwood species. 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) [2, 4]. 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 [121]. 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 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 [122].

An essential characteristic of wood dust, in common with many other exposures with a known or suspected capacity to increase risk of sinonasal cancer (e.g., leather dust, tobacco smoking, textile dust, welding fumes containing nickel or chromium; see Section "Epidemiology and Occupational Risk Factors"), is that, in addition to a multitude of various chemical substances, it also contains particulate matter [2]. In wood dust, the 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., currently mostly using machines) [2, 4].

Related to its complex nature, exposure to wood dust 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, 123, 124]. 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, 123–125]. 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].

In conclusion, biologically active and toxic compounds have been documented as natural components in many hardwood and softwood species. In addition, toxic effects of wood dusts much relate to their predominant feature as particle exposure. 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 shortcomings in design and reporting [2, 4]. In addition to testing wood dusts as such in the animal studies, the mutagenic fraction of beech dust solvent extracts has been studied for skin cancer (exposure by skin application) in mice. Similar to the carcinogenicity studies using wood dust as the exposing agent, the results reported for solvent extracts of beech dust were somewhat variable [2, 4].

After these, a 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 [126].

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.

In conclusion, carcinogenicity studies in rodents on wood dust extracts or wood dust are few and have mostly generated negative or inconclusive results.

DNA Damage and Other Genotoxicity Induced by Wood Dust in Experimental Settings

DNA damage following exposure to wood dust has been investigated in a few genotoxicity studies *in vitro*, 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 dusts (also particle board dust) [2]. Consistent mutagenicity in the *Salmonella* assay was observed for beech wood dust extracts (reviewed in detail in [2]). Wood dust extracts have also been studied in some other experimental systems (hepatocytes and human embryonic lung cell line; nasal epithelial cells from rats exposed *in vivo* for their ability to damage DNA or induce other forms of genotoxicity (micronuclei and DNA adducts), with positive findings [2, 4, 127].

Apart from wood dust extracts, also dusts as such 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) [128]. 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 [128], pointing to primary genotoxicity.

In conclusion, mutagenic, DNA damaging and other genotoxic capacity of wood dusts or wood dust extracts from hardwood and softwood species have been documented in experimental settings.

Inflammatory Response to Wood Dusts Exposure in Experimental Studies

Recent studies have indicated that exposure to wood dusts, both hardwood and softwood dusts, have 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 [129], in a mouse macrophage cell line [130, 131], and in a human lung cell line [128]. In these in vitro experiments, hardwood and softwood dusts have induced the expression of several cytokines (e.g., TNF-α, IL-6, and IL-8) and chemokines [128–131], with some quantitative differences being observed between some of the species [130, 131]. It is likely that the induction of an inflammatory response by wood dusts involves at least in part mechanisms mediated by ROS; also reactive nitrogen species are known to be generated in the inflammatory process [128, 129, 132]. As mentioned above, the timing of DNA damage induction in human A549 lung cells by hardwood and softwood dusts indicates that inflammatory response is, nevertheless, not necessary for genotoxicity of wood dust [128].

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 [133]. 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 [133]. 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 asthmatic response) [134].

In conclusion, evidence from a number of *in vitro* and *in vivo* studies utilizing experimental systems has indicated the capacity of wood dust from multiple hardwood and softwood species to elicit and modulate inflammatory response, with likely involvement of ROS-mediated damage mechanisms.

DNA Damage and Other Genotoxic Effects in Workers Exposed to Wood Dust

Genomic damage in workers exposed to wood dust at work has been studied in multiple studies. In a wooden furniture plant in Poland, workers, most of whom had been working in wooden furniture manufacture for more than 10 years, and controls were investigated for the level of DNA damage (DNA single-strand breaks) in peripheral blood lymphocytes. The level of DNA damage was significantly increased (about twice as high) among the wooden furniture workers who were smokers, when compared to nonexposed smoking controls, while the difference in DNA damage was not significant between the exposed and control nonsmokers [135]. Further, the study also observed significant induction of DNA repair activity, thought to represent DNA damage undergoing repair, in the exposed workers, both smokers and nonsmokers, as compared to the respective activity seen in controls [135]. Another study by the same group assessed DNA damage in white blood cells from another group of workers from the same wooden furniture manufacturing plant. Significantly increased levels of DNA damage in the Comet assay were detected in furniture workers, as compared to controls; the effect was seen in both smokers and nonsmokers [136]. These two studies interpreted the results as indicating that the elevated DNA damage was likely to reflect the genotoxic effects of wood dust exposure. However, the possibility that the effects may have been at least partially related to other exposures present in the work environment of furniture making, such as the use of varnishes, lacquers, and polishes (as was the case for some of the workers in these studies), could not be totally ruled out [135, 136].

Another study investigated micronuclei and other nuclear changes in exfoliated buccal epithelial cells (i.e., in cell types assumed to represent tissue encountering the exposures first) in furniture workers exposed to high concentrations of mixed hardwood and softwood dusts in a poorly ventilated workshop [137]. The furniture workers exhibited significantly higher frequencies of micronuclei and other nuclear alterations (e.g., binucleates, karyorhexis, and karyolysis indicative of cytotoxicity) in buccal mucosa cells, as compared to male controls. Smokers showed higher frequencies of micronuclei and other nuclear changes in both groups, with the wood dust-exposed smokers exhibiting the highest frequencies [137].

Two studies were conducted among workers of wooden furniture industry in India examining genotoxic damage using the Comet, micronuclei, sister chromatid exchange (SCE), and chromosome aberration assays [138, 139]. The first one found a significantly elevated frequency of micronuclei in furniture workers. The frequency of SCE was also increased but without statistical significance [138]. The second study included furniture workers, who had worked for five years or more in carpentry shops and at the time of study worked in poorly ventilated carpentry units exposed mainly to dusts from softwood and hardwood (sometimes also to chemicals used in polishing and as adhesives during furniture manufacture). The results showed significantly increased mean DNA damage as well as frequencies of micronuclei and chromosome aberrations in lymphocytes among the wood dust-exposed furniture carpenters as compared to controls. Also micronuclei detected in buccal epithelial cells showed significantly increased frequency. However, it was noted that the confounding factors included (age, smoking and alcohol consumption) also increased DNA damage in lymphocytes as well as micronucleus frequency in lymphocytes and buccal cells. Levels of some antioxidant enzymes measured as part of the biomonitoring scheme were significantly decreased in the exposed subjects [139].

There are three more recent studies carried out in Europe. In Switzerland, workers who had been exposed to wood dust for at least the past five years in construction (as parquet layers, installers or carpenters) or in furniture industry were investigated for genetic damage [140]. Workers had been mainly exposed to dusts from fir, spruce, beech oak, and wooden boards such as MDF and wooden melamine [140]. Micronuclei and other nuclear changes were studied in nasal and buccal epithelial cells. Frequencies of micronuclei were significantly increased in nasal and buccal epithelial cells among the woodworkers as compared to controls. Significant increases were also observed for some of the other nuclear alterations studied but not for all [140].

A second study by Bruschweiler and the research group [141] examined with the Comet assay DNA damage in peripheral blood cells in the same study population as in the study described above [140]. A significant increase in DNA damage was observed in nonsmoking woodworkers who processed composite wood as compared to the nonexposed controls or those who processed natural wood. However, no difference in DNA damage was seen between the latter group and the controls. There was no effect of the duration of exposure on DNA damage [141].

Another European study focused on low-level exposure and investigated micronuclei and other nuclear changes in nasal and buccal epithelial cells in two groups of wood dust-exposed workers in Austria [142]. One group included furniture carpenters processing pressed boards made of spruce, or spruce, oak and beech (all formaldehyde free). The other

comprised veneer factory workers processing both softwood and hardwood, with exposure to volatile organic chemicals released from the cooking process [142]. Frequencies of nasal cells with micronuclei cells were not significantly increased in furniture carpenters or workers from the veneer factory compared to controls. Nevertheless, the frequencies of cells with the other nuclear changes, such as nuclear buds, karyorhexis, and karyolysis, showed significant elevation particularly in the veneer production workers but also in furniture carpenters. In buccal epithelial cells, the results were similar, with somewhat clearer differences found between the exposed and control groups; in addition, the number of micronuclei (but not micronucleated cells) was significantly increased in veneer workers. Of the biochemical biomarkers studied, levels of malonaldehyde, a marker of oxidative stress, were increased in both groups of workers [142].

Finally, as indication of alterations relevant for malignancy although not representing directly genetic damage, reduced nasal mucociliary transport as well as histological changes of the nasal mucosa such as epithelial hyperplasia, metaplasia, and dysplasia have been observed in woodworkers in a series of earlier studies [2]. In several studies, significant differences have been reported between workers exposed to hardwood dust, but also those exposed to softwood dust, and controls. Often association to long duration and/or high levels of exposure were also reported. It is of note that wood dust particulate matter, as well as the chemical constituents present in wood, are believed either to directly participate in such processes or to be able to enhance them [2, 4, 123].

In conclusion, there are several studies on DNA damage or other genotoxic effects of occupational exposure to wood dust. These cover numerous woodworker groups and woodworking factories. These studies predominantly show increased frequencies of some or several forms of genetic damage, with some suggestions for dose–response.

Other Toxic, Irritation, and Inflammation-Related Effects in WoodDust-Exposed Subjects

In addition to experimental findings on induction of inflammatory response, occupational exposure to wood dust has been associated with a multitude of nonmalignant symptoms and diseases in the exposed subjects; many of such effects involve inflammatory mechanisms. The studies have been focused on symptoms and disorders of the eyes, the upper and lower respiratory tract, and skin affections including allergies [2, 68, 143–146].

Multiple studies since the 1970s have reported eye symptoms among workers exposed to wood dust, with exposures including dusts from softwood and hardwood species and from various wooden boards, as extensively reviewed [2, 68, 143–146]. Collectively, studies have reported an array of work-related eye symptoms, such as redness of eyes, itchy, watering eyes and conjunctivitis, to be relatively common in woodworkers and often with clear differences between woodworkers and controls [2, 68, 143–146].

Similar to eye symptoms, a large variety of nasal symptoms have been reported in association with occupational exposure to wood dust. These include rhinitis, nasal irritation, nasal hypersecretion, nasal discharge, sneezing, nasal obstruction, and sinus problems. Nasal symptoms are often work-related and, in general, with significant differences between the wood dust-exposed and control subjects. Increased prevalences of nasal symptoms have been reported for multiple branches of woodworking industry, including furniture factories, floor factories and other woodworking facilities with exposure primarily to dust from dry wood, but also sawmills and other industries processing fresh or green wood [2, 68, 143–146].

Symptoms of the lower respiratory tract associated with exposure to dust from both hardwood and softwood species have been investigated in an abundant number of studies over several decades. Exposure to dust from Western red cedar, a softwood species, has been thoroughly investigated, and plicatic acid has been identified as the chemical wood component specific to Western red cedar causing asthma [2, 68, 143–150]. Asthma and asthma symptoms (including self-reported, physician-diagnosed or clinical asthma) has been among the most studied ones. Asthma symptoms have often been reported as being work-related, and the symptoms include wheezing, chest tightness, shortness of breath, and chronic cough. Many such studies have reported an overall higher risk of asthma or asthma symptoms among subjects with occupational exposure to wood dust; most studies show significant increase in comparison to controls (or exposure at higher level *versus* lower level) but not all. Dose-response relationships between exposure to wood dust or duration of employment and asthma or asthma symptoms have been reported in many studies [2, 68, 143–146, 148–150]. Also chronic bronchitis have been associated with wood dust exposure [144, 145, 150].

Finally, inflammation-related mechanisms have also been postulated to play a role in the development of sinonasal cancer [2, 151]. Increased expression of COX-2, an enzyme involved in prostaglandin synthesis and upregulated by many inflammatory factors, has been described in sinonasal adenocarcinoma [152]. COX-2 expression showed a significant association to occupational wood dust exposure, whereas tobacco smoking was not linked with COX-2 expression [152].

In conclusion, a large number of studies conducted among workers occupationally exposed to dusts from numerous species of hardwood and softwood as well as from wooden boards, have documented wood dust exposure as a risk factor for various irritation-related symptoms and disorders of the

eyes and nose. Similarly, significantly higher risks of pulmonary effects, predominantly asthma and asthma symptoms but also other adverse effects on the airways, have been reported in woodworkers exposed to dusts from a variety of wood species. Many studies on irritation effects and respiratory disorders have found dose-response relationships. In addition, inflammation-related mechanisms have been observed in wood dust-related sinonasal cancer.

Genetic and Other Alterations in Human Sinonasal Cancer

Studies on the molecular mechanisms involved in human sinonasal cancer have demonstrated a variety of genetic and other molecular alterations in sinonasal tumors. From such studies, some have investigated sinonasal cancers from cases with occupational histories available; however, studies on larger series of sinonasal cancers with well documented data on work-related exposures are low in number [2, 4]. In sinonasal cancer, mutations in *KRAS* gene and the tumor suppressor gene *TP53* in particular exhibit increased frequencies. KRAS and TP53 mutations have been associated with occupational exposure to wood dust as well as with cumulative wood dust exposure and duration of employment in woodwork [153–157]. In some of the studies, sinonasal cancers of adenocarcinoma histology (typically intestinal-type adenocarcinomas) from cases occupationally exposed to wood or leather dust have been investigated, with various genetic and other molecular alterations being reported [153, 157–163]. Genetic and other molecular changes observed in sinonasal cancer are described in more detail in the following section (see Section "Molecular Markers").

Summary and Overall Conclusions

Occupational exposure, in particular exposure to wood dust, plays a predominant role in the etiology of the cancer of the nose and nasal cavities. From nonoccupational risk factors, tobacco smoking—mainly related to squamous cell carcinoma histology—is the only one confirmed. With this background, this section primarily discussed studies relevant for understanding mechanisms of carcinogenesis found or suggested to act in wood dust-related sinonasal cancer.

Animal carcinogenicity studies on wood dust extract or wood dust are few and have largely been less informative. Other experimental *in vitro* and *in vivo* studies, on the other hand, have associated a wide variety of adverse biological effects and molecular changes, such as cytotoxicity, oxidative DNA damage, genotoxicity, inflammatory response, and increased cell proliferation, with exposure to various types of wood dusts. In addition, it is believed that particulates in wood dust are among the primary players in processes evoking these harmful effects. It is likely that particulates, chemical substances, and their combinations act in concert in the biological and molecular pathways leading to development of wood dust-related sinonasal cancer.

Several studies have reported DNA damage and other genotoxic effects in wood dust-exposed workers, in line with findings of the DNA damaging capacity of wood dusts as reported in various *in vitro* test systems. In addition, a multitude of studies have demonstrated significant increases in irritation- and inflammation-related symptoms and disorders in workers occupationally exposed to wood dust. These symptoms and disorders include effects on the eyes as well as on the upper and lower respiratory tract, particularly asthma and asthma symptoms, reported for furniture and other woodworkers.

Studies carried out on tumor tissue from sinonasal cancer cases occupationally exposed to wood dust have observed multiple genetic and other molecular alterations. In particular, mutations in the tumor suppressor gene *TP53* frequently occur in wood dust-related sinonasal cancer and show association with cumulative exposure and duration in woodwork.

Collectively, these data support the capacity of wood dust to act via toxic, inflammatory, genotoxic, and carcinogenic mechanisms. There are, however, very little data available on cancer mechanisms associated with occupational exposure to other known human sinonasal carcinogens than wood dust.

Molecular Markers

Literature data on molecular markers in human sinonasal cancer are still rather limited, especially at the genomic, epigenomic, and proteomic level. 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 [159, 164, 165], while the mutation rates reported for individual genes have in general been lower or variable. Furthermore, a few studies have indicated that epigenetic changes play a role in sinonasal cancer as in many other types of human cancer.

TP53 and *KRAS* Gene Mutations

Most of the studies exploring the tumor suppressor gene *TP53* mutations, a hallmark genetic change in human cancer [166, 167] or investigating accumulation of the p53 protein in the cell have focused on sinonasal 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 [168, 169]. The results reported for sinonasal cancer indicate that p53 accumulation is a common feature, with immunopositivity ranging between 20 and 100% and correlation with worse prognosis [113, 152, 158, 170–175].

In the studies analyzing the *TP53* mutations, a variable occurrence has been reported (18–60%) [158, 176–179]. In one large study, where both adenocarcinoma and squamous cell carcinoma type of sinonasal cancers were collected in three European countries (Denmark, Finland, and France; $n = 358$ cases), an overall high frequency of *TP53* mutations (77%) was found among all sinonasal cancers [155]. The risk of *TP53* mutations was higher among the adenocarcinomas as compared to the squamous cell carcinomas. Furthermore, the *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 [155]. 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 [155]. In another series of sinonasal intestinal-type adenocarcinoma from Spain, *TP53* mutations were also commonly detected (41%) and they were exclusively found in cases with occupational wood dust exposure [157]. From smokers, only 20% exhibited *TP53* mutation [157].

These studies showed differences in the *TP53* mutation profiles between the wood dust-exposed and the nonexposed; collectively, the mutation profile of sinonasal cancer also exhibits differences compared to head and neck cancer as a larger group [156, 157, 180] (Fig. 7.10). Based on the mutation profiles observed (i.e., 50% were G to A transitions, mutations almost exclusively detected in nonsmokers, all G to T transversions detected in smokers), it was proposed that reactive nitrogen species generated via chronic inflammatory process contributed to the *TP53* gene mutagenesis in the wood dust-exposed cases [157]. As a potential clinical marker, nonfunctional *TP53* mutations have been associated with significantly worse prognosis in terms of both overall survival and disease-free survival compared with tumors that have retained a functional *TP53* [181].

Initially, also *KRAS* and *HRAS* mutations were reported to be relatively frequent in sinonasal cancer, with implications for histogenetic and prognostic significance [153, 158, 161, 171, 178]. In more recent studies, the frequency of *KRAS* mutations in adenocarcinoma histology has been shown to be less important, suggesting that the role of *KRAS* gene in the development of sinonasal cancer might be limited [154, 162, 179, 182].

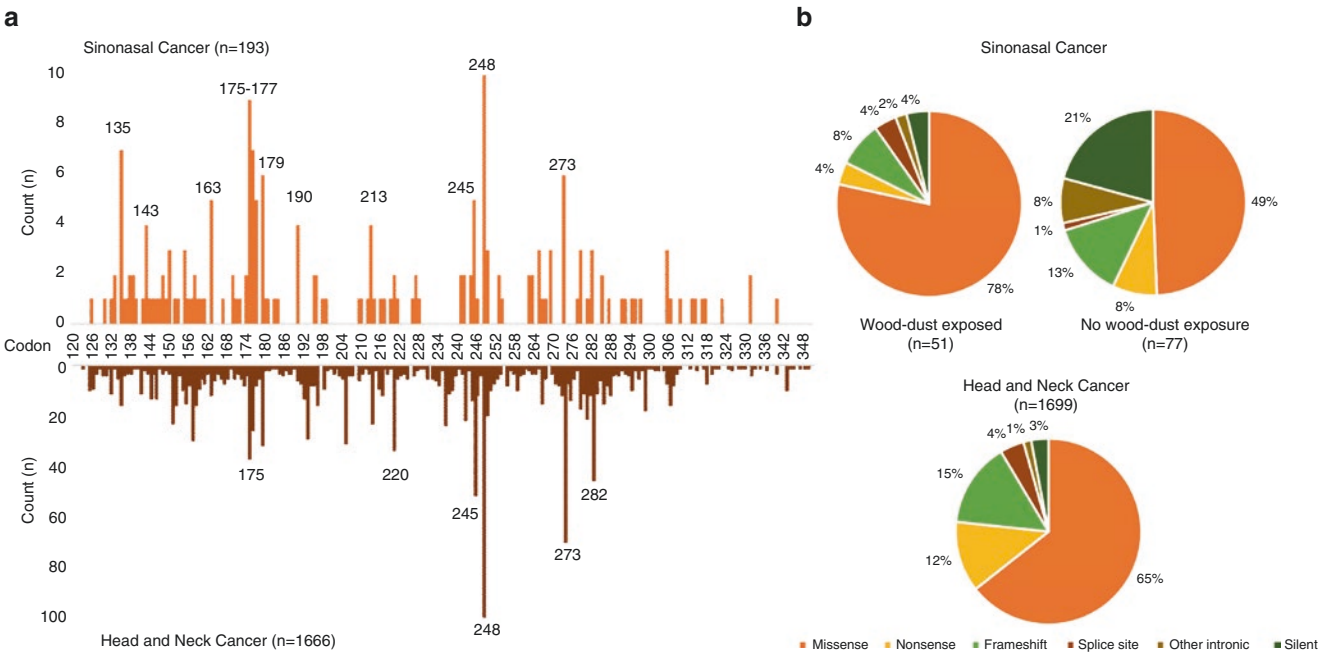


Fig. 7.10 Profile of tumor suppressor gene *TP53* mutations in sinonasal cancer as compared with head and neck cancer as a larger group and according to exposure to wood dust. Data retrieved from the IARC *TP53* Mutation Database, version R18, April 2016 [180]. Mutations are presented (**a**) by location (codon number in *TP53* gene) and (**b**) by type. Numbers of cancer cases included in the database and the frequencies of various classes of mutations by cancer type and wood dust exposure are indicated

Other Molecular 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, 151]). The pattern of chromosomal abnormalities found in sinonasal adenocarcinoma appears to be different from that of the other tumors of the head and neck region, but displays similarities with gastric and colonic adenocarcinomas [160]. 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 [182, 183]. In ITACs, comparative genomic hybridization analysis conducted suggests copy number gains and losses throughout the whole genome [151, 184].

It is well known that even though environmental factors predominantly contribute to the development of most common cancers, heritable factors are also involved [185]. In addition to somatic alterations as reviewed above for sinonasal cancer, genetic susceptibility plays a role in tumorigenesis [186]. 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 [187].

Undifferentiated sinonasal carcinomas (SNUCs) have been shown to harbor *IDH2* (R172) mutations [188, 189]. *IDH2*-targeted therapy is already in clinical trials for the treatment of acute myeloid leukemia, and could potentially be beneficial for treating SNUCs as well [188]. Genome-wide copy number changes have also been studied in SNUCs, and a distinctive copy number profile comprising mainly gains was observed [190].

Epigenetics

Aberrant DNA methylation has been detected in many types of human cancers and global hypomethylation and specific promoter hypermethylation have been linked with genomic instability and inactivation of tumor suppressor genes [191]. Furthermore, a reversal of epigenetic changes represents a potential target of therapeutic strategies [192]. In sinonasal cancer, there are limited studies on epigenetics changes, mainly concentrating on promoter methylation and noncoding RNAs (ncRNAs).

In a small series of sinonasal intestinal-type adenocarcinoma, the promoter methylation of tumor suppressor genes $p14^{ARF}$ and $p16^{INK4a}$ was detected by methylation specific PCR [158]. The $p14^{ARF}$ acts by inhibiting mdm2 and thereby stabilizing the p53; interestingly, in this series, almost all occupationally exposed cancers showed either *TP53* or $p14^{ARF}$ deregulation (15/17 cases, 88%) [158]. Other studies have used methylation specific multiplex ligation-dependent probe amplification (MS-MLPA), which allows simultaneous assessment of aberrant promoter methylation of a set of genes [193, 194]. Methylation in target genes was detected in about half of the sinonasal cancers, including the methylation of *RASSF1, CDH13, ESR1*, *TP73*, *CHFR, APC, CASP8*, *HIC1*, and *TIMP3* genes, with some indication for association with the clinico-pathological features and survival [193, 194].

Another form of epigenetic gene regulation is carried out by the ncRNAs that regulate gene expression at the transcriptional and posttranscriptional level; ncRNAs have also been implicated in various cancer processes. The long noncoding RNAs (lncRNAs) have been analyzed in the sinonasal squamous cell carcinoma, where thousands of significantly differently expressed lncRNAs were identified in tumor tissues compared to adjacent noncancerous tissues, including both upregulation and downregulation [195]. Also, microRNAs (miRNAs) have been studied in the context of sinonasal squamous cell carcinoma and cisplatin resistance [196]. This study found that one of the miRNAs, miR-34a, was associated with acquisition of cisplatin resistance in the cell lines and within clinical samples showed significant association with the prognosis [196].

Gene and Protein Expression

There are not many studies performed on gene expression in sinonasal cancer. In sinonasal squamous cell carcinoma, a gene expression microarray analysis has been used to investigate the differences between radiation-sensitive and radiation-resistant sinonasal squamous cell carcinomas; the study identified 206 differentially expressed genes, e.g., *CCND2*, *COL5A2*, *GADD45B* and *THBS2* [197]. Gene expression profiling was also used to study NOTCH-pathway in sinonasal squamous cell carcinoma, identifying an association of Hes1 with improved survival [198]. In sinonasal adenocarcinoma, gene expression profiling has led to the identification of the two differentially expressed proteins LGALS4 and CLU [199].

The molecular alterations reported for sinonasal cancer have included changes in protein expression. One of the most studied proteins for clinical relevance is EGFR that has been shown to play an important role in the carcinogenesis of head and neck squamous cell carcinoma. Also in sinonasal cancer, the EGFR protein is frequently overexpressed (ranging 7–89% in different studies), but does not show consistent association with clinico-pathological features, such as expo-

sure history or prognosis [163, 174, 179, 182, 200–203]. Similarly MET, a tyrosine kinase receptor which shows synergy with EGFR, has been reported to be overexpressed in 64% of sinonasal intestinal-type adenocarcinoma [204]. Also, c-KIT, another tyrosine kinase receptor, was found to be overexpressed in undifferentiated sinonasal carcinomas [203].

Other overexpressed proteins in sinonasal intestinal-type adenocarcinoma include COX-2, β-catenin, and E-cadherin [152, 174]. In one study, the overexpression of COX-2, an enzyme involved in inflammation, was found to be associated with the adenocarcinoma type of tumors, wood dust exposure, and nonsmoking [152]. However, the association with wood dust was not seen in another study [174]. Both COX-2 and E-cadherin proteins are expressed at a lower level in sinonasal squamous cell carcinoma [152, 205]. In contrast to the loss of E-cadherin, which is an epithelial marker, an increased protein expression of mesenchymal markers fibronectin and SLUG was detected in the squamous cell carcinomas, pointing to epithelial-to-mesenchymal transition (EMT) [204]. Also pRb overexpression appears to be frequent in the sinonasal squamous cell carcinomas [206].

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 tumor tissue in all types of ITACs compared to nonmalignant tissue [207]. 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 [206]. Another protein often found lost in sinonasal intestinal-type adenocarcinoma is OTX1, a member of the OTX homeobox gene family. OTX has an important role in embryonic morphogenesis and likely plays a role in tumorigenesis, as gain or loss of OTX expression can affect the cell growth and differentiation [208]. Loss of tumor suppressor p16 expression has also been reported to be frequent in sinonasal intestinal-type adenocarcinoma [174, 175], whereas undifferentiated sinonasal carcinomas show overexpression of p16 [209].

HPV and EBV

Human papillomavirus (HPV) infection in the sinonasal tract is estimated to be present in around 30% of sinonasal squamous cell carcinomas [210, 211]. The HPV DNA has been shown to have a negative correlation with pRB and p53 expressions [206, 212], whereas p16 has been reported as being both associated [179, 212] and unassociated with HPV DNA [205]. Also Epstain–Barr virus (EBV) has been detected in sinonasal squamous cell carcinomas in 47.7% (21/44) of cases and as associated with metastasis [179].

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 and protein expressions, 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 wood dust, one of the main occupational risk factors. *KRAS* mutations also occur but are clearly less frequent compared to *TP53* mutations. EGFR is often overexpressed in sinonasal carcinomas, but does not show consistent association with exposure history or prognosis. Some molecular characteristics of undifferentiated sinonasal carcinomas as well as sinonasal carcinomas positive for human papillomavirus or Epstein–Barr virus have been reported but the data published so far are sparse. 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.

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Cancers of the Intestine, the Liver, and the Biliary Tract

8

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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.

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Cancer of the Intestine

Cancer of the intestine is the most frequent human neoplasm in non-smokers 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, originate from the glandular cells. Other histological types include carcinoids, 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: they are mainly of diffuse histiocytic type. Patients with acquired immunodeficiency syndrome and celiac sprue are at increased risk of small cell lymphomas. Carcinoid tumors, which originate from the

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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 to 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 non-polyposis colon cancer, 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 two genes involved in DNA 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 non-polyposis 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 pre-neoplastic role of adenomas and non-polypoid 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 other cohort studies, either failed to replicate these findings or detected weak associations, and meta-analyses concluded in favor of a weak association [9]. A 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, and results of more recent studies are consistent with this conclusion [11] 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 are sparse [12]; overall, they do not support the hypothesis of an increased risk from this route of exposure.

Other Occupational Agents

Results on risk of colorectal cancer for occupational agents other than asbestos are sparse. Occupations which may involve exposure to non-occupational risk factors such as excessive alcohol drinking (e.g., brewery workers [13]) 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 [14]. 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) [15].

Oddone and colleagues [16] reviewed the results of studies on risk of colorectal cancer and occupational exposures to several agents and occupations, and suggested associations for laborers employed in industries with a wide use of chemical compounds, such as leather (RR = 1.70, 95% CI: 1.24–2.34), basic metals (RR = 1.32, 95% CI: 1.07–1.65), plastic manufacturing (RR = 1.30, 95% CI: 0.98–1.71) and rubber manufacturing (RR = 1.27, 95% CI: 0.92–1.76), as well as for workers employed in installation and repair machinery entailing potential exposure to asbestos (RR = 1.40, 95% CI: 1.07–1.84). However, consistent associations between colorectal cancer and industrial branches did not emerge from this review.

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, 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, 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, moderately, poorly, and undifferentiated grades [17]. Well-differentiated tumors might be difficult to distinguish from non-malignant neoplastic proliferations such as hepatic adenoma, while undifferentiated tumors show little evidence of hepatocellular differentiation. Most HCCs are moderately differentiated (grades 2 to 3) with more than one histologic 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 [18].

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 as 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 tree-like 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 [19]. 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, South-East Asia, and Africa, while HCV is the predominant virus in Japan and

Southern Europe. The most frequent routes of HCV transmission are parenteral HCC 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% [20].

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, South-East 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 a RR of the order of 1.5 to 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, which is rare in most populations but relatively frequent in infested areas in South-East 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.

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 [21]. Several studies have subsequently been conducted in Europe, North America, and Asia [22], including two large multicenter cohorts [23–25], 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.

An increased risk of HCC has also been reported in cohort studies of workers exposed to vinyl chloride; however, it is important to avoid diagnostic misclassification between HCC and HAS [26]. Furthermore some cohort studies classified all hepatobiliary tumors together [27], and even they reported an increased risk, it is not possible to avoid misclassification and to identify a specific target. A pooled analysis of two multicenter cohort studies of vinyl chloride-exposed workers [23, 24] resulted in a meta-SMR of 1.35 (95% CI: 1.04–4.39) for liver cancer other than HAS [22]. In 2009, an IARC working group [28] concluded in favor of the causal nature of the association between vinyl chloride and HCC, in addition to HAS; based on these two studies [23, 24], an Italian cohort included in one of the multicenter studies [24], in which the incidence of HCC increased significantly increasing high cumulative vinyl chloride exposure [29], and a few additional small and heterogeneous studies, as well as on suggestive evidence that the risk of HCC was higher among workers exposed to vinyl chloride, who were infected with hepatitis B virus [30], or reported high levels of alcoholic beverage consumption [31]. **A** recent update of the US cohort [25] confirmed the elevated liver cancer mortality, with strong associations for both HAS and HCC with cumulative vinyl-chloride exposure, although it remains possible that misdiagnosis between the two types influenced findings.

The epidemiological evidence on the association between trichloroethylene exposure and risk of liver cancer, based on nine cohort studies and one case–control study, is limited and somewhat inconsistent [32], although a study based on individuals undergoing biomonitoring in three Nordic countries reported an association [33]. There is no consistent evidence for a role in liver carcinogenesis of exposure to tetrachloroethylene, which was mainly addressed in studies focused on dry-cleaning and related occupations [34], although a weak association was reported in a study based on Nordic census data [35]. A recent retrospective cohort study examined health outcomes among 34,494 workers employed at a microelectronics and business machine facility (1969–2001), exposed both to trichloroethylene and tetrachloroethylene, and provided no evidence of increased mortality risk for liver or biliary cancer [36].

An increased risk of liver cancer mortality was reported in a cohort study of cellulose fiber production workers exposed to methylene chloride [37], which however was not confirmed by other study (see [38] for review and meta-analysis).

Aflatoxin is known to induce liver cancer, mainly through food contamination. However, workplace exposure to aflatoxin was also suggested to increase the risk of liver cancer in workers in the animal-feed processing industry [39] and other occupations [40, 41].

Based on six deaths, Kumagai et al. observed an increased mortality from cholangiocarcinoma among 62 workers employed between 1991 and 2006 in a small printing plant in Osaka, Japan, where exposure to 1,2-dichloropropane and dichloromethane was reported [42]. Kubo et al. extended the observation including 111 workers employed from 1981 to 2012, and reported 17 cholangiocarcinoma cases [43]. The same authors recently reported an increased risk of cholangiocarcinoma with increasing cumulative exposure to 1,2-dichloropropane among 95 workers of the offset proofprinting section, suggesting that an exposure–response relationship exists [44].

Several studies were conducted to assess whether these results were applicable to other workers in the printing industry. Okamoto et al. compared prevalence of bile duct cancer between workers in the printing industry and age-standardized controls in all other industries using the claims database of the Japan Health Insurance Association: male workers showed a non-significantly elevated risk bile duct cancer in comparison with workers in all other industries [45]. In a linkage analysis between censuses and cancer registries in the Nordic countries, Vlaanderen et al. observed elevated incidence for intrahepatic cholangiocarcinoma—but not extrahepatic cholangiocarcinoma—among printers and lithographers [46]. These authors suggested a possible role of chlorinated solvents. Finally, Ahrens et al. analyzed an European multicentric case–control study of extrahepatic biliary tract cancer to assess the association with employment in the printing industry [47]. Odds ratios were non-significantly increased for both printers and typesetters, but no specific agent was suggested to explain the association. In conclusion, it remains unclear whether the association shown in the initial Japanese study is due to the agents present in that industry, to other exposures, or to extra-occupational factors.

An Italian case–control analysis explored the association between occupational exposure to asbestos and cholangiocarcinoma, and reported an association with both intrahepatic and extrahepatic cholangiocarcinoma, which was statistically significant only for the former [48]. An association between asbestos exposure and intrahepatic (but not extrahepatic) cholangiocarcinoma was also found in an analysis of a record linkage study in the Nordic countries. However, other studies failed to replicate these findings [49, 50].

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 [51]. 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. 8.1).

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 [52] 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 [53]. 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 [54]. Third, HBx can bind and inactivate the tumor suppressor p53 in vitro, thereby increasing cellular proliferation and survival and compromising DNA-damage checkpoints [55, 56]. The carcinogenic potential of HBx has been demonstrated in HBx transgenic mice, 90% of which develop HCC [56, 57]. 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 [58]. 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 [59]. 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.

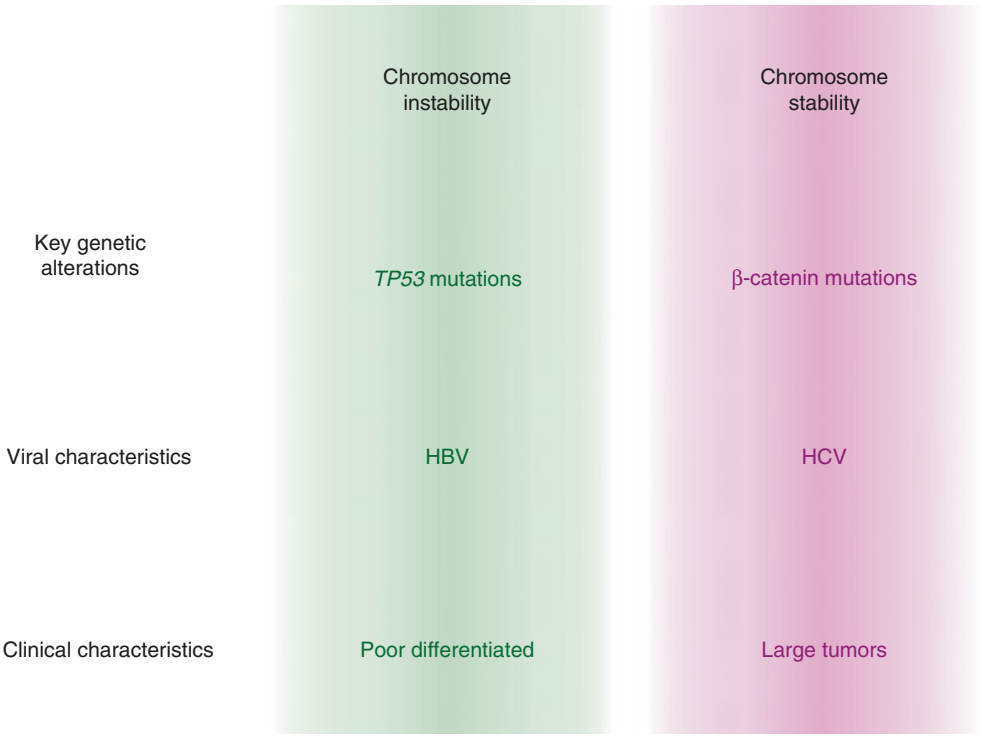

Fig. 8.1 Development of HCC through multiple genetic pathways depending upon the particular combination of risk factors involved

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, South-East 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) [60]. 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 [60, 61]. 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 HCC develop in a context of liver cirrhosis [62]. A model for the cooperation between chronic HBV infection and exposure to AFB_1 (Fig. 8.2) suggests that the *R249S* mutation caused by AFB_1 may down-regulate 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 [63, 64]. 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 [64]. 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 [63].

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. 8.2). In contrast with HBV, HCV is an RNA virus without DNA intermediate form and does not integrate into host genomes [65]. 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 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 [66, 67]. In addition, NS5A has been proposed to interact with and to sequester it to the perinuclear space [68]. 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 co-exist, 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, metabo-

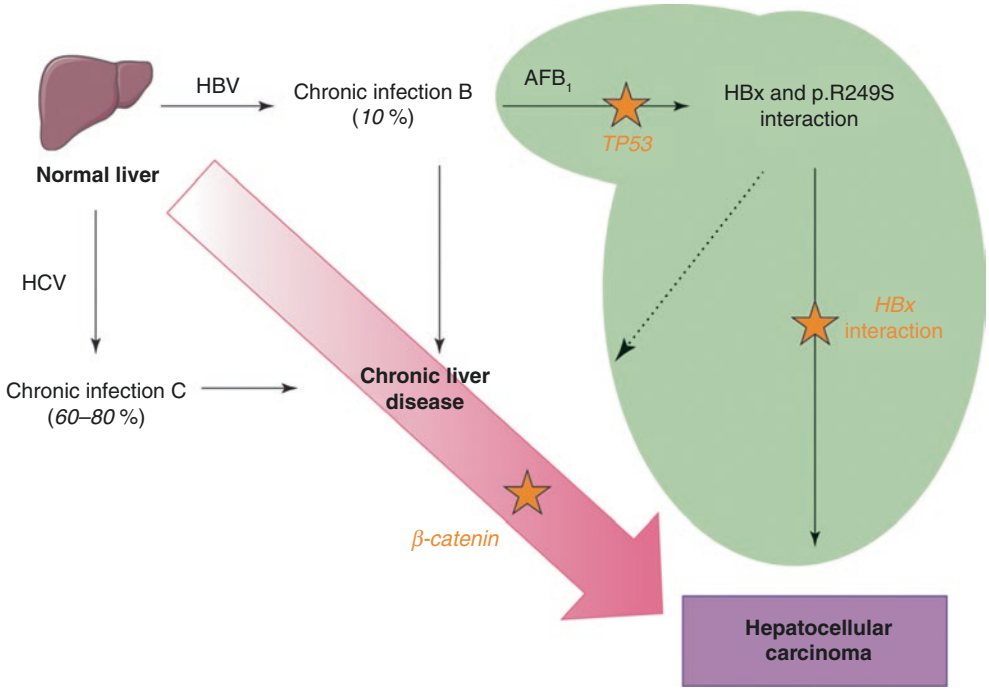

Fig. 8.2 A model of hepatocarcinogenesis driven by different etiologic contexts. The main route to HCC, represented by the large diagonal arrow, generally involves a long phase of precursor, chronic liver disease. Progression from chronic liver disease into HCC involves activation of oncogenic signals (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)

lites 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 pro-inflammatory cytokines with deleterious effects on hepatocyte survival [69, 70]. 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 [71]. 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 [72].

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%) [73]. Established mechanistic events for HBV and HCV in the development of CCA include inflammation, liver cirrhosis, chronic hepatitis, and liver fibrosis [74].

Hepatic Angiosarcoma

HAS associated with exposure to vinyl chloride has been shown to harbor specific mutations in *TP53* (mutations at A:T base pairs) [75]. The same type of mutation has been observed in liver angiosarcomas of rats exposed to vinyl chloride [75, 76]. *KRAS* mutations appear to be common in thorotrast and vinyl chloride associated HAS [77].

Susceptibility to Liver Cancer

Inherited Disorders

Inherited disorders that cause chronic liver inflammation, fibrosis, and cirrhosis may lead to 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) [78]. HH is inherited as autosomal recessive trait. Most HH cases are homozygote carriers of the founder mutation C282Y in *HFE* [78]. 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 [78]. 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 ageing 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 etiological 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 6 SNPs in 5 genes [79]. 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 2 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 [80]).

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) [81, 82]. 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 (K130 M and V131I). These mutations have been proposed as prognostic markers for the development of HCC [83]. 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 [84, 85].

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 [86].

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 [87].

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 [88]: this association was confirmed in a cohort study from Lithuania [89]. A systematic analysis of over 15 million residents from the Nordic countries, including over 8500 cases among men and 19,000 cases among women, did not confirm the increased risk among textile workers [90]. In this study, high-risk groups were cooks and drivers among men and building caretakers among women. Results of studies of workers exposed to asbestos or employed in the printing industry have been reviewed above.

Associations with extrahepatic biliary tract cancer have been sporadically reported for other agents and exposures. A multicenter European case–control study reported associations between occupational exposure to endocrine-disrupting chemicals, in particular polychlorinated biphenyls, and risk of cancer of the extrahepatic biliary tract, particularly of the extrahepatic bile duct and the ampulla of Vater, with no dose–effect relationship for cumulative exposure [91]. A Japanese study examined the association between working rotating shifts and risk of death from biliary tract cancer among men, and reported an increase in risk of biliary tract cancer, which was statistically significant only for extrahepatic bile duct cancer [92]. A significant increased SMR has been reported among meat cutters and meat wrappers in the meat department of supermarkets in a large US cohort study [93]. These suggestive findings require replication.

Conclusions

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.

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Occupational Risk Factors of Laryngeal Cancer

9

Paolo Boffetta and Francesca Donato

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 South-East Asia and Central Africa. The incidence in women is below 1/100,000 in most populations [1]. In the USA, Black 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 among men [2]. 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 [3]. The effect of tobacco, with risks in smokers in the order of 10 relative to non-smokers, 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 [4]. 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 [5].

There are no recognized strong genetic factors in laryngeal carcinogenesis; however, polymorphism for enzymes implicated in the metabolism of alcohol might represent susceptibility factors [6].

Survival from laryngeal cancer is relatively good (five-year survival rates are in the order of 60%) in high-income countries [7]. 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 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.

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Asbestos

Results on incidence or mortality from laryngeal cancer have been reported in more than 30 occupational cohorts and a number of community-based case–control studies.

Table 9.1 reports the design and results of cohort studies of workers exposed to asbestos. In general, these results suggest an increased mortality (or incidence) of laryngeal cancer among workers exposed to asbestos. The magnitude of the excess risk in the most positive studies, however, is rather modest: as shown in Table 9.2, a meta-analysis of the results reported in Table 9.1 results in a summary RR of 1.16 (95% CI 1.01–1.32). The results in Table 9.1 are not adjusted for tobacco smoking and alcohol drinking, the two main risk factors of laryngeal cancer. Based on the formula proposed by Axelson and Steenland [8] for indirect adjustment of confounding, a RR of 1.16 could be explained by a higher prevalence of tobacco smoking or alcohol drinking 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 [9], a RR of 1.16 would be explained by a distribution among exposed of 35% current smokers, 47% former smokers, and 18% never smokers, which does not seem implausible.

In 20/39 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 types" (see Table 9.1 for details). Among the remaining studies, chrysotile was either the only or the predominant type

Table 9.1 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. [57]	Textile product manufacture	P Ch	UK	1933–1974	M	3211	4	1.55	*0.42–3.97*
Gardner et al. [58]	Cement workers	Ch	UK	1941–1983	MF	2090	1	0.91	*0.02–5.06*
Hughes et al. [59]	Cement workers	P Ch	USA	1937–1970	M	5492	3	0.56	*0.11–1.62*
Enterline et al. [60]	Mixed	Mix	USA	1941–1967	M	1074	2	1.14	*0.14–4.13*
Armstrong et al. [61]	Crocidolite miners	Cr	Australia	1943–1966	PM	6505	2	0.68	0.17–2.74
Tola et al. [62]	Shipyard workers	Mix	Finland	1945–1960	M	7775	24[a]	1.20	0.77–1.79
Raffn et al. [63]	Cement workers	Mix	Denmark	1928–1984	M	7996	14[a]	1.66	0.91–2.78
Finkelstein [64]	Automotive part manufacture	Ch	Canada	1950–1980	M	224[b]	8	8.54	*1.76–25.0*
Parnes [65]	Brake lining manufacture	Ch	USA	1937–1980	M	2057	3	4.03	*0.80–11.4*
Selikoff and Seidman [66]	Insulation workers	Mix	USA	1967	M	17,800	18	1.70	*1.01–2.69*
Botta et al. [67]	Cement workers	Mix	Italy	1950–1980	M	2608	5	0.70	0.23–1.64
Sluis-Cremer et al. [68]	Miners	Am, Cr	South Africa	1945–1981	M	7317	5	1.86	0.60–4.34
Giaroli et al. [69]	Cement workers	P Ch	Italy	1952–1987	NA	3341	2	0.82	0.15–2.59
Meurman et al. [70]	Miners	Antho	Finland	1953–1967	M	736	4[a]	1.75	0.48–4.47
Berry [71]	Friction material manufacture	P Ch	UK	1941–1979	M	9104[b]	6	0.64	0.23–1.39
Dement et al. [72]	Textile product manufacture	Ch	USA	1940–1965	MF	1421	4	1.55	0.53–3.55
Tsai et al. [73]	Refinery maintenance workers	NA	USA	1948–1989	M	2504	3	1.06	0.22–3.09
Liddell et al. [74]	Miners	Ch	Canada	1902–1971	M	8923	36	1.11	*0.79–1.55*
Levin et al. [75]	Insulation material manufacture	Am	USA	1954–1972	M	753	1	2.21	0.06–12.3
Germani et al. [76]	Asbestosis patients	Mix	Italy	1979[c]	F	631	1	8.09	0.21–45.1
Karjalainen et al. [77]	Asbestosis patients	Mix	Finland	1964–1995[c]	MF	1376	5[a]	*3.88*	*1.26–9.05*
Battista et al. [78]	Railroad carriage manufacture and repair	Mix	Italy	1945–1969	M	734	5	2.40	0.95–5.05
Berry et al. [79]	Textile, other products; insulators	Mix	UK	1933–1964	M	~3000	3	2.05	*0.42–6.01*
Puntoni et al. [80]	Shipyard workers	NA	Italy	1960–1981	M	3984	32	1.64	1.12–2.32

Table 9.1 (continued)

Reference	Industry	Asbestos type	Country	Period of employment	Sex	No. workers	No. deaths	SMR	95% CI
Szeszenia-Dabrowska et al. [81]	Asbestosis patients	Mix	Poland	1970–1997[c]	M	902	1	0.43	*0.01–2.40*
Sun et al. [82]	Textile workers (spinning)	Ch	China	NA	F	5681	1	1.01	*0.03–5.63*
Smailyte et al. [83]	Cement workers	Ch	Lithuania	1956–1985	M	1285	7[a]	1.4	0.7–2.9
Finkelstein and Verma [84]	Plumbers, pipe- sprinkler-fitters	Mix	Canada	1949–1980	M	14,408	*18*	*1.38*	*0.82–2.18*
Wilczyńska et al. [85]	Textile product manufacture	NA	Poland	1945–1980	M	3027	12	1.41	0.73–2.46
Hein et al. [86]	Textile product manufacture	Ch	USA	1940–1965	MF	3072	6	1.68	0.61–3.66
Musk et al. [87]	Miners millers	Cr	Australia	1943–1966	M	6498	13	2.57	1.37–4.39
Loomis et al. [88]	Textile product manufacture	P Ch	USA	1950–1973	PM	5770	6	1.15	0.42–2.51
Harding et al. [89]	Mixed	Mix	UK	1983–1987[d]	PM	98,117	49	1.48	1.09–1.95
Menegozzo et al. [90]	Cement workers	Mix	Italy	1950–1986	M	1247	5	0.97	0.31–2.26
Wang et al. [91]	Textile product manufacture	Ch	China	1972	M	577	2	4.26	1.17–15.52
van den Borre and Deboosere [43]	Mixed	Mix	Belgium	1991–2009	M	2056	*3*	*4.35*	*0.90–12.71*
Pira et al. [92]	Textile product manufacture	Mix	Italy	1946–1984	MF	1977	8	1.84	0.79–3.62
Pira et al. [93]	Miners	Ch	Italy	1930–1990	M	1056	8	1.58	0.68–3.11
Ferrante et al. [94]	Mixed[e]	Mix	Italy	1907–1990s	PM	51,801	*143*	*0.87*	*0.74–1.03*
Oddone et al. [95]	Cement workers	Mix	Italy	1932–1992	PM	1818	8	0.70	0.30–1.39

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 Peto et al. [57], Botta et al. [67] and Berry et al. [79]. No cases/deaths from laryngeal cancer were observed in these groups of female workers
P Ch predominantly chrysotile, *Ch* chrysotile, *Cr* crocidolite, *Am* amosite, *Mix* mixed exposure, *Tre* tremolite, *Act* actynotile, *Antho* anthophyllite, *M* males, *MF* males and females, *PM* predominantly males, *NA* not available
[a]Incident cases (results are expressed as SIR)
[b]10+ years since first employment
[c]Period of diagnosis
[d]Period of enrolment in the survey
[e]Pooled analysis of 43 cohorts, including [67]

Table 9.2 Meta-analysis of risk of laryngeal cancer in cohort studies of workers exposed to asbestos[a]

	N studies	*N* deaths	RR	95% CI	p het.
All studies	39	476	1.16	1.01–1.32	0.22
Type of fibers					
Pure/predominant chrysotile	14	89	1.03	0.78–1.28	0.83
Amphiboles[b]	5	25	1.60	0.81–2.39	0.45
Mixed, unknown	20	362	1.25	1.02–1.49	0.05
Country					
United Kingdom	5	63	1.17	0.65–1.68	0.22
United States	9	46	1.20	0.79–1.61	0.76
Canada	3	62	1.18	0.85–1.51	0.37
Finland	3	33	1.28	0.77–1.80	0.36
Italy	9	212	1.09	0.78–1.40	0.16

[a]Studies listed in Table 9.1
[b]Pure/predominant amphiboles or mixed chrysotile and amphiboles

of asbestos fiber in 14 studies, while in the remaining 5 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, but not among workers exposed to chrysotile (Table 9.2). Results of studies with mixed/unspecified fiber type might reflect an effect of amphibole exposure. Caution should be applied in interpreting these results, because of the crude classification of exposure, lack of statistical heterogeneity of results, and 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 9.2, the results of the meta-analysis are also stratified by country: the lack of an increased risk 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, is worth noticing.

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 9.3: they are limited by the small number of events in the groups with longer duration or higher exposure, but do not suggest a dose–response relation.

Community-based studies of laryngeal cancer that reported studies on exposure to asbestos are summarized in Table 9.4. Most of these studies reported an association, although in most instances the results were not statistically

Table 9.3 Dose–response analyses of risk of laryngeal cancer in cohort studies of workers exposed to asbestos[a]

Reference	Exposure category	No. deaths	SMR	95% CI
Peto et al. [57]	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. [63]	TSFE 15+ years; duration 1–4 years	2	0.81	0.09–2.94
	5+ years	6	2.27	0.83–4.95
Finkelstein et al. [64]	Duration 1–19 years	0	0	*0–36.3*
	20+ years	3	11.9	*2.46–34.8*
Parnes [65]	Duration 1–4 years	2	6.64	*0.76–22.7*
	5+ years	1	2.24	*0.06–12.4*
Meurman et al. [70]	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. [74]	Cum. exp. <300 mpcf-years	24	1.03	*0.66–1.53*
	300+ mpcf-year	6	1.08	*0.40–2.35*
Berry et al. [79]	Low/moderate exp.	0	0	*0–5.27*
	Severe exp.; duration <2 years	2	4.65	*0.56–16.8*
	>2 years[b]	1	3.03	*0.08–26.4*
Puntoni et al. [80]	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. [83]	Duration <1 year	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. [96][b]	Duration <1 year	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*
Pira et al. [93]	Cum. exposure <100 fb-year	1	0.65	0.02–3.61
	100–400 fb-year	2	1.20	0.16–4.70
	>400 fb-year	5	2.51	0.81–5.85
Ferrante et al. [94][c]	Duration <10 year	56	0.97	0.73–1.25
	10–19 years	29	0.74	0.49–1.06
	20–29 years	48	1.11	0.82–1.47
	30+ years	8	0.36	0.16–0.71

When multiple reports have been published for the same cohort, only the most recent one is summarized in the table
TSFE time since first exposure, *exp* expected deaths
Results in italics were calculated based on raw data
[a]See Table 9.1 for details of the cohort studies
[b]Replaced in Table 9.1 by Pira et al. [92]
[c]Only men

Table 9.4 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 [97]	UK	100/NA	Hospital	M	NA	31	*14.5*	*4.3–49.4*	
Shettigara and Morgan [98]	Canada	43/43	Hospital	M	Self reports	10	∞	NA	0 exposed controls; *p = 0.001*
Hinds et al. [99]	USA	47/NA	Residential	M	Self report	25	1.75	NA	*p* = 0.2
Burch et al. [100]	Canada	204/204	Residential	M	Self report Job titles	36 14	1.6 2.3	NA NA	*p* = 0.07 *p* = 0.05
Olsen and Sabroe [101]	Denmark	276/971	Residential	M	Self report	17	1.8	1.0–3.4	
Zagraniski et al. [50]	USA	92/181	Hospital	M	Job titles	11	1.1	0.4–2.9	
Brown et al. [34]	USA	183/250	Residential	M	Job titles classified by IH	88	1.5	1.0–2.2	No dose–response
Ahrens et al. [36]	Germany	100/100	Hospital	M	Self report	NA	1.1	0.5–2.4	Prevalent cases
Muscat and Wynder [102]	USA	194/184	Hospital	M	Self report	66	1.1	0.7–1.9	
Wortley et al. [30]	USA	235/547	RDD	MW	JEM	90	*1.2*	*0.9–1.7*	Weak dose–response
Zheng et al. [103]	China	177/269	Residential	M	Self report	26	2.0	1.0–4.3	
Gustavsson et al. [45]	Sweden	157/641	Residential	M	Occ. history assessed by IH	62	*1.44*	*1.02–2.05*	Positive dose–response
De Stefani et al. [44]	Uruguay	112/509	Hospital (cancer)	M	Self reported	23	1.8	0.9–3.2	
Marchand et al. [104]	France	296/295	Hospital	M	JEM	216	1.24	0.83–1.90	Positive dose–response
Elci et al. [105]	Turkey	940/1519	Hospital (cancer)	M	JEM	150	1.0	0.8–1.3	No dose–response
Berrino et al. [20]	3 European countries	1070/2176	Residential	M	JEM	< 55–215 55+ – 347	1.5 1.0	1.0–2.4 0.8–1.4	Weak dose–response <55; no dose– response 55+
Dietz et al. [106]	Germany	257/769	Residential	PM	Self reported, JEM	59	1.3	0.8–2.1	
Shangina et al. [28]	4 European countries	316/728	Hospital	M	Occ. history assessed by IH	65	0.86	0.51–1.45	
Langevin et al. [38]	USA	118/857	Residential	M	Self reported	35	1.04	0.64–1.67	Weak dose–response
Menvielle et al. [107]	France	448/2686	Residential	M	JEM	328	*1.73*	*1.43–2.09*	No dose–response

Results in italics were calculated based on raw data

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

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, and the opportunity for selection bias, however, it is not surprising that the evidence from community-based studies is less consistent than that from industry-based studies. Data from case–control studies were inadequate to provide risk estimates for different types of fibers.

Overall, the results of cohort studies are relatively consistent, showing a weak association between asbestos exposure and laryngeal cancer, and indicate a relative risk below 1.2 for ever exposure, with a suggestion of a possible higher risk among workers exposed to amphiboles. The small number of events in most studies, the lack of strong evidence of dose–response, and the presence of potential residual confounding are all limitations of the available dataset. While the evidence from community-based case–control studies is somewhat stronger in suggesting an association, these results are more prone to bias than those of cohort studies, and the discrepancy between the two sets of results argues for a cautious interpretation. In addition, there are no strong data showing

accumulation and persistence of asbestos fibers in the larynx; two studies reported either asbestos bodies [10] or fibers [11] in this organ, 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 [12–16].

An excess risk of laryngeal cancer has been reported among taconite mining workers, which may reflect the potential exposure to non-asbestiform amphibole and non-amphibole elongate mineral particles, respirable silica, and cleavage fragments during this process, although differences in smoking can explain these results [17].

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, 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 [18]. Cohort studies were conducted in these industries, which reported results on risk of laryngeal cancer: they are summarized in Table 9.5. 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 9.5), 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

Table 9.5 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. [108]	Isopropyl alcohol manufacture (H)	USA	1928–1950	M	182	Any	1	NA	NA
Hueper [109]	Isopropyl alcohol manufacture (H)	USA	1927–1950	M	779	Any	2	NA	NA
Lynch et al. [110]	Chemical work, isopropyl alcohol jobs (H)	USA	1950–1976	PM	741	Any	7	3.2	*1.5–6.7*
Ahlborg et al. [111]	Stainless steel pickling house (H)	Sweden	1951–1979	M	181	Any	3[a]	50	16–155
Cooper et al. [112]	Battery manufacture (L)	USA	1947–1970	M	4519	Any 20+ years	6 4	1.28 1.41	0.47–2.8 *0.38–3.61*
Forastiere et al. [113]	Soap manufacture (I)	Italy	1964–1972	M	361	Any	5[a]	*6.94*	*2.26–16.2*
Block et al. [114]	Phosphate fertilizer manufacture (I)	USA	1950–1979	M	2610[b]	Any	2	1.91	*0.23–6.90*
Steenland and Beaumont [115]	Steelworkers in pickling jobs (H)	USA	1940–1965	PM	1165	Any SA daily	14 10	2.19 2.5	1.2–3.7 1.7–4.7
Teta et al. [116]	Isopropyl/ethyl alcohol manufacture (H)[c]	USA	1928–1968	M	538	Any	1	*1.43*	0–8.0
Teta et al. [116]	Isopropyl/ethyl alcohol manufacture (H)	USA	1941–1992	M	493	Any	1	*3.3*	0.1–19
Coggon et al. [117]	Battery manufacture and steel works with acid mist exp.(L)	UK	1950–1990	M	2678	Any	1	0.48	0.01–2.7
Moulin et al. [118]	Stainless steel, metal alloy manufacture (I)	France	1968–1991	M	4288	Any	17	1.47	0.9–2.4
Sorahan and Esmen [119]	Ni-Cd battery manufacture (L)	UK	1947–1975	M	926	Any	2	1.95	0.24–7.06
Pesatori et al. [120]	Sulfuric acid manufacture (H)	Italy	1962–1997	M	1372	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

related exposure were conducted in Canada, the USA, Uruguay, and various European countries. Relevant results are summarized in Table 9.6: they are less consistent than those of cohort studies in showing an increased risk: this can reflect a lower specificity (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 cancer 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 [19]).

Other Occupational Agents

Risk of laryngeal cancer was examined in several cohorts and case–control of workers occupationally exposed to formaldehyde: an association was not consistently suggested by these results [20–30].

An association between PAH exposure and laryngeal cancer risk was suggested in previous reviews [31, 32]. A meta-analysis identified 16 high-quality studies and calculated a pooled RR of 1.45 (95% CI 1.30–1.62) for incidence and 1.34 (95% CI 1.18–1.53) for mortality from PAH exposure [33]. A dose–response relationship was suggested by the few studies providing such results. Although an association between PAH exposure and laryngeal cancer is biologically plausible and appears to be supported by the available studies, confounding by tobacco smoking and alcohol drinking, and publication bias and heterogeneity of exposure circumstances in the available studies suggest caution in the interpretation of these data.

Other occupational exposures associated with laryngeal cancer in some studies include diesel engine exhaust [34, 35], organic solvents [20, 28], mineral oil [36], and wood dust [37, 38]. Positive associations were found also for metal dust [38]; a large study combining three cohorts of lead-exposed workers with blood lead data observed borderline significant trends for larynx cancer [39], while in a cohort of Canadian nickel mining and refining workers there was only little evidence to suggest an increased laryngeal cancer risk [40].

Recently an association was reported for high cumulative exposure to perchlorethylene, but not to other chlorinated solvents [41], while results for exposure to vinyl chloride are not consistent [42].

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 [37, 43], butchers [37, 44], welders [45], transport workers [46, 47], textile workers [48], bartenders [49, 50], and among offshore oil industry workers [51].

An increased risk of laryngeal cancer has been reported among rubber industry workers [52]; Vlaandereen and colleagues recently reported a non-significant excess of risk for laryngeal cancer among men working in rubber industry, in particular for work areas "preparation of materials," but no cases were detected among women and there was no association with duration of employment [53]. A recent meta-analysis based predominantly on cohort studies confirmed the presence of a small increased risk in rubber manufacturing industry [54]. Associations between ionizing radiation and laryngeal cancer were reported among nuclear workers [55].

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 may address some of these limitations. Pukkala et al. [56] conducted an 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: 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 9.7, results are presented for occupational groups with more than 10 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 in 9 occupational groups. 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.

Table 9.6 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 [101]	Denmark	326/1134	Residential	MW	Self report	AL	43	1.3	0.9–1.9	
Cookfair et al. [121]	USA	352/1050	Hospital	M	Review of job titles	SA < 20 year 20+ year	NA	2.05 2.43	NA	
Zemla et al. [122]	Poland	328/656	Hospital	M	Unclear	AM	11	4.27	NA	
Brown et al. [34]	USA	183/250	Residential	M	Job titles classified by IH	SA	22	0.76	0.42–1.35	
Soskolne et al. [123]	Canada	204/204	Neighborh.	PM	JEM	SA ≤ 10 year >10 year	6 19	3.57 5.57	1.19–10.7 2.0–15.5	"Substantial" exposure
Eisen et al. [124]	USA	108/538	Cohort	PM	Measurements, JEM	AM 1+ year	NA	0.90	0.66–1.22	Nested in cohort of auto workers
De Stefani et al. [44]	Uruguay	112/509	Hospital (cancer)	M	Self reported	SA any ≥20 year 20+ year	46 12 34	1.6 1.2 1.8	0.9–2.6 0.6–2.5 1.1–3.1	
Shangina et al. [28]	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

Table 9.7 Standardized incidence ratio of laryngeal cancer in selected occupations

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	1052	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	1226	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	1356	1.12	1.06–1.18
Plumbers	149	1.04	0.89–1.22
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	1322	1.42	1.35–1.50

Results of NOCCA study [56]
Results in italics were calculated based on raw data
N number of cases, *SIR* standardized incidence ratio, *CI* confidence interval

Conclusions

The fact that the laryngeal mucosa is directly exposed to inhaled agents makes this organ a target for respiratory carcinogens. Indeed, there is some evidence of an association 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 weak and inconsistent. 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 the likelihood of reporting bias complicate the identification of additional occupational laryngeal carcinogens.

Control of tobacco smoking and excessive alcohol drinking and the main actions 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 selected occupational groups. Available results contribute to identify avenues of research aimed at clarifying the role of suspected carcinogens.

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Lung Cancer: Clinical Findings, Pathology, and Exposure Assessment

10

Elizabeth N. Pavlisko and Victor L. Roggli

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 2015 WHO classification of carcinoma of the lung includes 6 major histomorphologic patterns: adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma, large cell carcinoma, adenosquamous carcinoma, and sarcomatoid carcinoma. Some major patterns are divided into types due to differences in prognosis/progression/survival. Table 10.1 outlines the major patterns and their "subtypes."

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 patterns include carcinoma in situ, mucinous, acinar, papillary, micropapillary, and solid (Fig. 10.1). 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.

Table 10.1 Histologic classification of lung cancer

Adenocarcinoma
Patterns of invasive adenocarcinoma
Acinar adenocarcinoma
Papillary adenocarcinoma
Solid adenocarcinoma
Micropapillary adenocarcinoma
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma
Colloid adenocarcinoma
Fetal adenocarcinoma
Enteric adenocarcinoma
Minimally invasive adenocarcinoma (defined as ≤3 cm lepidic predominant tumor with ≤5 mm invasive component)
Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ (lepidic)
Squamous cell carcinoma
Variants of squamous cell carcinoma
Keratinizing squamous cell carcinoma
Non-keratinizing squamous cell carcinoma
Basaloid squamous cell carcinoma
Preinvasive lesion
Squamous cell carcinoma in situ
Neuroendocrine tumors
Variants of neuroendocrine tumors
Small cell carcinoma
Large cell neuroendocrine carcinoma
Carcinoid tumor
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
Large cell carcinoma
Adenosquamous carcinoma
Sarcomatoid carcinoma
Variants of sarcomatoid carcinoma
Pleomorphic, spindle cell, and giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma

Data from Travis et al. [2]

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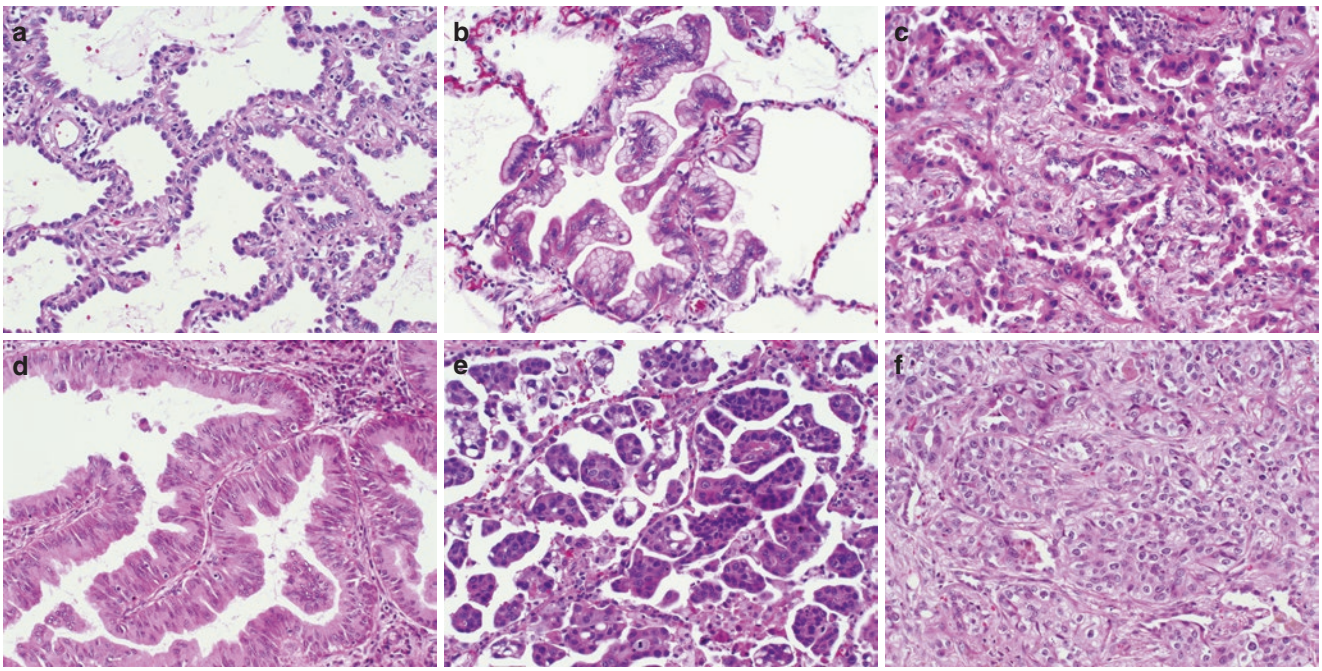

Fig. 10.1 Morphologic variants of adenocarcinoma: (**a**) adenocarcinoma in situ, (**b**) mucinous, (**c**) acinar, (**d**) papillary, (**e**) micropapillary, and (**f**) solid [hematoxylin and eosin (H&E), original magnification ×200]

While the current WHO classification does not consist of grading, in 2011 the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) report aggregated data supporting histologic variants as the basis for a grading system. Their terminology is favorable (non-mucinous lepidic/adenocarcinoma in situ), intermediate (papillary and acinar), and poor (solid and micropapillary) [3]. These can be extrapolated to well-differentiated (grade 1), moderately differentiated (grade 2) or poorly differentiated (grade 3) as histologic variants generally align with degree of differentiation and prognosis, as seen in Table 10.2 [3–5]. 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 lung and follows the 2017 AJCC TNM system (Table 10.3) [6].

The 2015 edition of the WHO's classification of tumors of the lung reflects a burst of growth specifically regarding adenocarcinoma of the lung. The non-mucinous or mucinous bronchioloalveolar cell carcinoma (BAC) terminology has been replaced by adenocarcinoma in situ for only the non-mucinous variant. The reclassification for mucinous BAC is mucinous adenocarcinoma as virtually all have an invasive component [2, 3].

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 10.4 [7].

Table 10.2 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)

Summarized from Travis et al. [3], Yoshizawa et al. [4], and Tsuta et al. [5]

Squamous Cell Carcinoma

Squamous cell carcinoma is a malignant epithelial tumor composed of cells forming keratin or intercellular bridges (Fig. 10.2). Histologic variants of squamous cell carcinoma include: keratinizing, non-keratinizing, basaloid squamous cell carcinoma and the preinvasive squamous cell carcinoma in situ [2]. Immunohistochemical stains helpful in determining squamous differentiation include p63, CK903 (34βE12), and CK5/6 (Table 10.4). The small cell variant may express chromogranin, synaptophysin, and/or CD56.

Table 10.3 AJCC eighth edition 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, surrounded by lung, without involvement more proximal than the lobar bronchus
T1mi	≤3 cm in greatest dimension, predominantly lepidic (in situ) pattern, and ≤5 mm invasion
T1a	≤1 cm
T1b	>1 cm but ≤2 cm
T1c	>2 cm but ≤3 cm
T2	>3 cm but ≤5 cm with any of the following: Involves main bronchus, invades visceral pleura, and/or associated with atelectasis or obstructive pneumonitis extending to the hilar region (involving all or part of the lung)
T2a	>3 cm but ≤4 cm
T2b	>4 cm but ≤5 cm
T3	>5 cm but ≤7 cm or directly invades any of the following: Parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, pericardium, or separate nodule within the same lobe
T4	Tumor >7 cm or invades 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 metastasis 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/pericardial tumor nodules, or malignant effusion
M1b	Single extrathoracic metastasis in a single organ. Includes involvement of a single non-regional lymph node
M1c	Multiple extrathoracic in a single organ or in multiple organs

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Table 10.4 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*	*Breast carcinoma*
Cytokeratin 7	+	+
TTF-1 (nuclear)	+	−
Napsin-A	+	−
Mammaglobin	−	+
BRST-2 (GCDFP)	−	+
GATA3	+/−	+
Panel for lung adenocarcinoma versus metastatic colorectal cancer		
Immunohistochemical stain/antibody	*Primary lung adenocarcinoma*	*Colorectal carcinoma*
Cytokeratin 7	+	+/−
TTF-1 (nuclear)	+	−
Napsin-A	+	−
Cytokeratin 20	−	+
CDX-2	−	+
Panel for lung adenocarcinoma versus mesothelioma		
Immunohistochemical stain/antibody	*Primary lung adenocarcinoma*	*Mesothelioma*
TTF-1 (nuclear)	+	−
Carcinoembryonic antigen (CEA) polyclonal	+	−
B72.3	+	−
MOC-31	+	−
Ber-EP4	+	−
Claudin 4	+	−
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

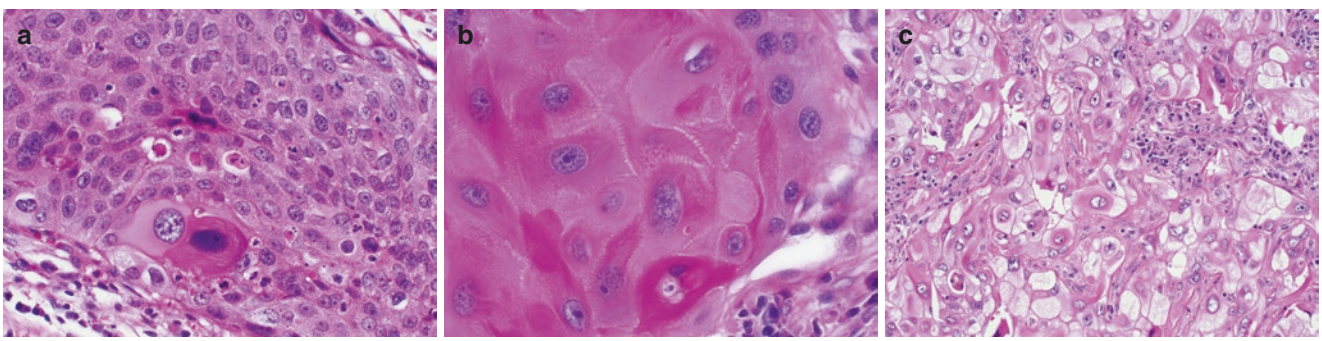

Fig. 10.2 Squamous cell carcinoma: (**a**) H&E stain demonstrates a large keratinizing squamous cell carcinoma [original magnification ×400], (**b**) intercellular bridges can be seen between cells [original magnification ×600], (**c**) clear cell histology in a squamous cell carcinoma [original magnification ×200]

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. Staging is the same TNM system used 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. 10.3). 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. 10.3).

Like squamous cell carcinoma, small cell carcinomas are usually located centrally as a hilar or perihilar mass with hilar/mediastinal lymphadenopathy. Clinical symptoms can

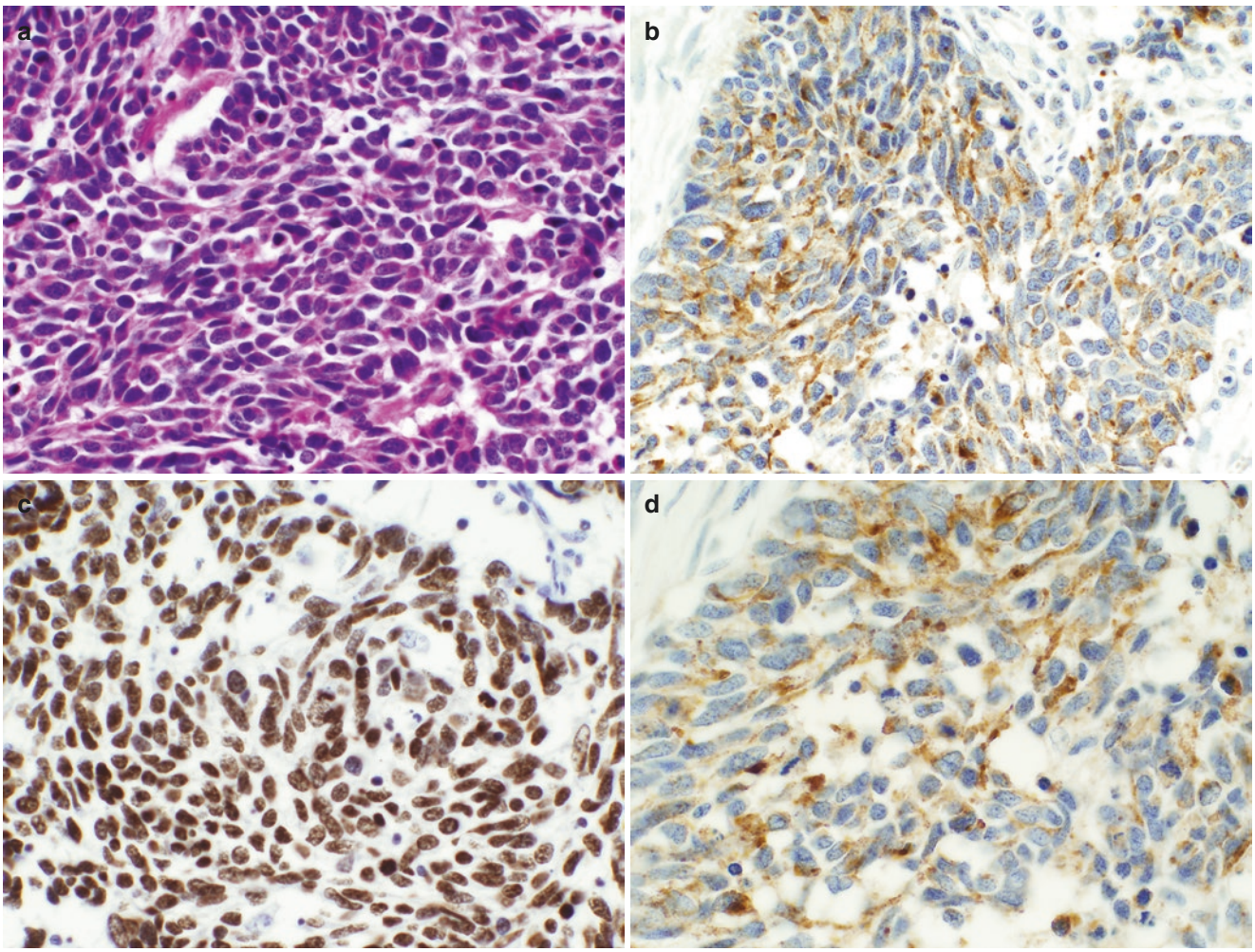

Fig. 10.3 Small cell carcinoma: (**a**) H&E stain demonstrates cells with scant cytoplasm surrounding a nucleus with finely dispersed chromatin, (**b**) cytokeratin immunohistochemical stain with positive cytoplasmic staining, (**c**) TTF-1 immunohistochemical stain with positive nuclear staining, (**d**) chromogranin immunohistochemical stain with positive cytoplasmic staining [original magnification ×400]

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 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 9% of all lung cancers and are poorly differentiated, falling in the non-small cell category and lacking squamous or glandular differentiation (Fig. 10.4). Histologic variants include large cell neuroendocrine, combined large cell neuroendocrine, basaloid, lymphoepithelioma-like, clear cell, and large cell carcinoma 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, combined large cell neuroendocrine, and large cell carcinoma 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. 10.5) 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), vascular compression with edema, superior vena cava (SVC) syndrome (compression/obstruction of the SVC causing congestion/swelling of the upper

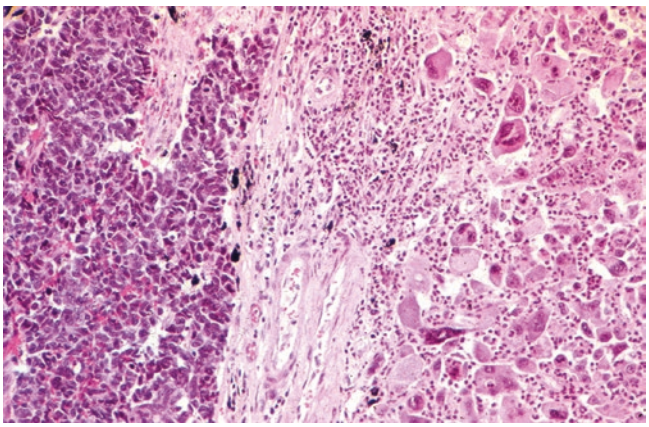

Fig. 10.5 Giant cell carcinoma (*right*) with concurrent small cell carcinoma (*left*) histology [H&E stain, original magnification ×200]

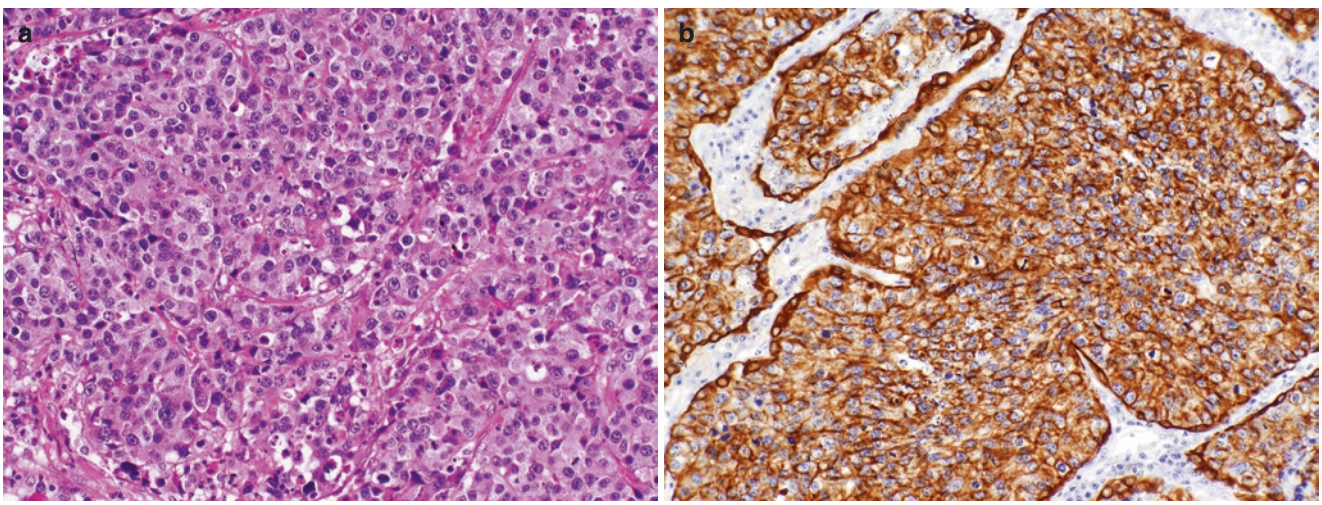

Fig. 10.4 Large cell carcinoma: (**a**) H&E stain showing pleomorphic tumor cells with no histologic evidence of glandular or squamous differentiation, (**b**) cytokeratin 7 (CK7) immunohistochemical stain with positive cytoplasmic staining [original magnification ×200]

Table 10.5 Paraneoplastic syndromes

Clinical symptom	Mechanism	Common carcinoma type
Endocrine		
Hypercalcemia	Parathyroid hormone-related protein (PTHRP) and TGF-a	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
Osseous, articular, and soft tissue changes		
Hypertrophic osteoarthropathy and finger clubbing	Unknown	Bronchogenic carcinoma
Cardiovascular		
Nonbacterial thrombotic endocarditis	Hypercoagulable state/unknown mechanism	Adenocarcinoma

Modified from *Neoplasia*. Kumar et al. [8]. Copyright Elsevier 2018

extremities and head, headache, dyspnea, etc.), hoarseness from involvement of the left recurrent laryngeal nerve, or an elevated hemidiaphragm from phrenic nerve involvement. Paraneoplastic syndromes occur secondary to elaboration of hormones by the tumor and may produce a variety of metabolic derangements (Table 10.5) [8, 9].

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. Plane 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 [3]. Centrally located lung cancer can obstruct 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 plane film and CT imaging studies. Contrast enhanced chest CT and magnetic resonance imaging (MRI) can be useful in distinguishing neoplastic from non-neoplastic 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 [10].

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 fail 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 cytologic 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 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 a potential carcinogen's propensity for lung cancer causation. 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 [11]); rather, we mentioned for each agent the most significant studies.

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 [12, 13]. 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 [13].

Epidemiological studies, discussed in Chap. 15, 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 [14]. In 1955, Sir Richard Doll concluded, following a combined epidemiologic and pathologic study of lung cancer in asbestos workers, that carcinoma of the lung was a "specific industrial hazard" of asbestos workers [15]. The synergistic effect of cigarette smoking and asbestos exposure in the development of lung cancer was first suggested by

Selikoff in 1968 [16]. 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 [17–20]. 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 [19]. 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 asbestosis must be present for causation/attribution of lung cancer to asbestos exposure and that histologic type of tumor was not helpful [21]. 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 [22]. The authors also cite a study by Hillerdal [23] 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 reviewed 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 pure amphibole exposure [20].

Asbestos Exposure

Exposure to asbestos is commonly occupational but rarely may be environmental or through a household contact [12]. Table 10.6 demonstrates occupations of 468 lung cancer cases with asbestos fiber analysis from the authors'

Table 10.6 Occupational exposure category, pleural plaques, and asbestosis in 468 lung cancer cases with lung fiber burden analysis (authors' series)

Exposure category	No.	Pleural plaques[a]	Asbestosis[a]	AB/gm (med)	AB/gm (rg.)	AF/gm (med.)	AF/gm (rg.)
Shipyard worker[b]	76	42/62	19/76	2260	2–1,400,000	27,300	330–7,530,000
Insulators[c]	48	26/37	29/47	30,000	2–343,000	265,000	740–8,540,000
Pipefitter[d]	35	20/25	2/33	1130	<3.3–109,000	14,800	330–580,000
Construction[e]	32	9/23	4/32	190	2–58,800	8740	460–310,000
U.S. Navy[f]	25	11/19	0/25	81	2–57,200	3280	400–1,430,000
Oil/chemical	21	8/13	2/20	46	<3–3620	7990	<460–77,600
Boiler worker	20	8/17	3/19	900	7.0–33,600	13,800	<760–633,000
Railroad	17	8/13	0/16	14	2–6350	1890	<240–434,000
Electrician	16	7/16	2/16	102	<7–33,200	11,200	<490–625,000
Asbestos mfg.	15	6/6	3/13	460	1–79,000	45,900	<490–1,540,000
Maintenance/mechanic	12	3/8	0/12	12.5	2–2730	1550	<730–42,000
Molten metal[g]	11	5/8	0/11	27	3.3–1620	7430	<640–23,000
Power plant	11	4/8	2/11	590	<3.3–58,800	19,400	<490–218,000
Machinist	10	2/8	0/10	82	5.5–1460	4180	880–59,800
Sheet metal	9	2/4	0/8	165	4–8900	10,500	330–142,000
Automotive	7	1/4	0/7	6	<3–38	1580	<440–43,300
Asbestos worker NOS	4	2/3	2/4	10,900	3.0–75,200	96,500	2400–712,000
Papermill	2	2/2	0/2	47	21–73	4670	<760–8960
Other[h]	50	24/38	2/48	60	<3.3–7100	4040	<490–182,000
HHC	6	2/3	0/6	540	5.0–3670	12,400	650–45,000
ND	125	46/74	18/120	130	2–266,000	5450	<160–3,350,000

AB/gm asbestos bodies per gram of wet lung as determined by light microscopy, *AF/gm* 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]Including 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 aircraft maintenance, asbestos exposure (NOS), building occupant, coal miner, copper wire manufacture, engineer (machine room), General Electric, grain elevator operator, heating/AC, military laundry, motor home installer, neighborhood, pressman, printing industry, public utility worker, radioman, RCF worker, superintendent of schools, textile mill, transit manager/oil field worker

series and notes the presence of pleural plaques and/or asbestosis. Table 10.7 shows the histologic types of lung cancer seen in the 468 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. 15). Table 10.8 shows the relative risk of dying from lung cancer [24]. 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 supraadditive to multiplicative and there has been debate over which model, if any, fits best. Henderson et al. cites Lee [25] who found a multiplicative model to best fit as well as others [26, 27] 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" [20]. There are several hypotheses with regard to the mechanism of lung cancer in asbestos-exposed individuals including: (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, (4) tobacco may assist in translocation of iron across cell membranes resulting in enhanced susceptibility to oxidant stress (see also Chaps. 12 and 13 for further discussion of co-carcinogenesis) [19].

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. 15).

Table 10.7 Lung cancer histologic type in 468 cases with lung fiber burden analysis[a] (Authors' series)

Histologic type	No.	%
Adenocarcinoma[b]	221	47
Squamous cell ca.	115	25
Small cell ca.[c]	48	10
Large cell ca.	29	6
Adenosquamous ca.	11	2
Sarcomatoid ca.[d]	22	5
Bronchogenic ca. (NOS)[e]	22	5

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 (seven cases)

[c]Includes combined small cell carcinoma (three cases)

[d]Includes pleomorphic carcinoma (fourteen cases), sarcomatoid carcinoma (six cases), spindle cell squamous carcinoma (one case), and giant cell carcinoma (one case)

[e]Includes carcinoma of lung NOS (three cases)

Table 10.8 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. [24]

Asbestosis

Asbestosis, defined by the Helsinki criteria in 1997 [28] and reclassified by Roggli et al. in 2010 [29], 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. A new article describes advanced parenchymal fibrosis without the aforementioned initiation from bronchiolar wall. Both patterns of fibrosis require sufficient tissue asbestos fiber burden, described below [29, 30].

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 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 [28, 29].

Radiographic features of lung cancers in asbestos-exposed individuals are essentially the same as for any peripherally or centrally located carcinoma (see above discussion). With asbestosis, radiographic profusion (frequency) of irregular opacities increases with disease pro-

gression. The International Labour Office (ILO) guidelines along with a set of standard chest roentgenograms, for the purpose of comparison with 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 10.9). Opacity size and shape are designated by the letters p (≤1.5 mm), q (>1.5–3 mm), and r (>3–10 mm) for regular 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) [31].

Table 10.9 Revised 2011 International Labour Office scoring system of radiographs

Frequency category	*Frequency subcategory*
0	0/–
	0/0
	0/1
1	1/0
	1/1
	1/2
2	2/1
	2/2
	2/3
3	3/2
	3/3
	3/+
Small round opacities	*Size*
p	≤1.5 mm
q	>1.5–3 mm
r	>3–10 mm
Small irregular opacities	*Size*
s	≤1.5 mm
t	>1.5–3 mm
u	>3–10 mm
Large opacities (>10 mm)	*Size*
A	One opacity ≤50 mm, or several opacities with the sum of their greatest dimensions ≤50 mm
B	One opacity >50 mm but not exceeding the area of the area of the right upper lung zone, or several opacities with the sum of their greatest dimensions >50 mm but not exceeding the area of the right upper lung zone
C	One opacity which exceeds the size (area) of the right upper lung zone, or several opacities with the sum dimension exceeding the size (area) of the right upper lung zone

Data from International Labour Office [31]

The diagnosis of asbestosis is often made without histologic examination of lung tissue based on the presence of the following [29]:

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 pleuro-pulmonary 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. 10.6). 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 [29].

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 [32].

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 [33]. 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 [28, 29]. Asbestosis is graded histologically from 1 to 4 depending on the extent of parenchymal fibrosis (Table 10.10). A recent article by Kawabata et al. describes grade 4 asbestosis lacking coexistent grade 1 asbestosis. They conclude that (1) grade 4 asbestosis does not start in the respiratory bronchiole and (2) parenchymal fibrosis in the presence of the abovementioned fiber burden qualification is sufficient for the diagnosis of asbestosis [30].

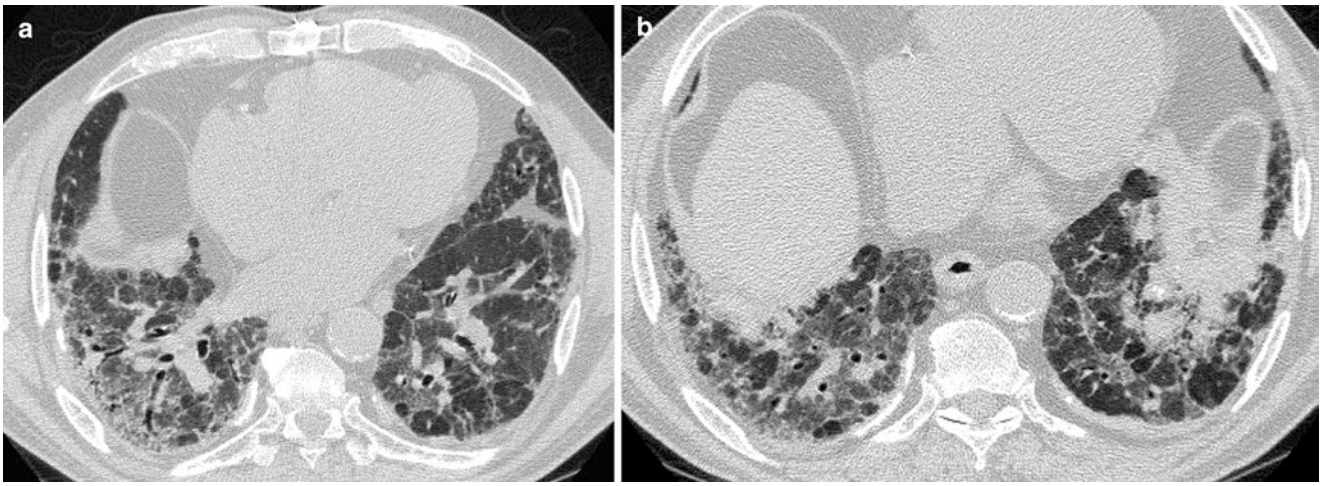

Fig. 10.6 High-resolution computed tomography (*HRCT*) images in a patient with asbestosis, showing lower lung zone reticulonodular opacities consistent with interstitial fibrosis. Calcified pleural plaques are also apparent (**a**, **b**) (Images courtesy of Dr. Page McAdams, Duke University Radiology, Durham, NC)

Table 10.10 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. [29] with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2010. College of American Pathologists

Asbestos Exposure Assessment

Exposure History

Industrial hygienists are sometimes asked to reconstruct exposures based upon simulations of workplace 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 10.13 and another questionnaire is available in the Appendix of this book. 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 [34]. The cumulative asbestos exposure required for the development of asbestosis is estimated to be at least 25 fibers/cc-years [35]. Others have indicated that 25–100 fiber/cc-years are required [36, 37].

Tissue Asbestos Body and Fiber Counting

Histologic assessment of asbestos exposure requires identification of asbestos bodies, defined as iron-coated asbestos fibers with a thin translucent core [38]. Asbestos body (AB) quantitation may be performed on 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 [39]. This is extrapolated from the study by Karjalainen et al. who reported one million asbestos fibers per gram dry lung tissue as significantly associated with lung cancer [40]. This converts to 100,000 fibers per gram of wet lung tissue, and they counted all fibers at least 1 μm in length with 50% of their commercial amphibole fibers being 5 μm or greater in length, thus the derivation of our 50,000 amphibole fiber content criterion. In the presence of histologic asbestosis, a fiber analysis is not required. 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 [41] 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 of asbestos bodies 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 2 asbestos bodies on two perpendicular passes at greatest diameter) and results are reported as asbestos bodies (AB) per gram of wet lung tissue. One asbestos body or fiber per gram of wet lung is approximately equivalent to one fiber per cubic centimeter which is approximately equivalent to 10 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 1000× 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 first 10 asbestos bodies are analyzed by energy dispersive X-ray analysis (EDXA) to determine fiber type [42]. 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 [28].

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 should not be compared to those from another. Furthermore, each laboratory should establish its own reference range to permit interpretation of analytical results [29, 42].

The consensus report from the International Expert Meeting on Asbestos, Asbestosis, and Cancer held in 1997 estimated on the basis of literature that a twofold risk of lung cancer is related to retained amphibole fiber (asbestos fiber types other than chrysotile) levels of approximately two million fibers (>5 μm) per gram of dry lung tissue, as determined by SEM, or five million amphibole fibers (>1 μm) per gram of dry tissue, as determined by TEM [28].

With respect to coated vs. 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 [43]. 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 [44]. 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 [45] in 1991 and Ward et al. [46]. 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 2 oldest beryllium plants in the study [46]. 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 [47]. Several reanalyses of the NIOSH study were performed in subsequent years, including a nested case–control study in one of the plants [48] and an update of the follow-up with additional dose–response analyses [49]. 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 [50]: 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 remains 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 [12].

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, paint pigments, 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 [51]. 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. This classification was revised in 1987 to "limited evidence," and finally, in 1993 there was "sufficient evidence" for a designation of "carcinogenic to humans." Cadmium remains in this designation to date [12, 52–54].

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. Assessment of cadmium levels in whole blood and scalp hair is possible by electrothermal atomic absorption spectrometry [55].

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 [56] 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 [57]. This is 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 [58]. 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 mucosa irritation/ulceration, and skin irritation. Additionally, there is an increased risk of lung and sinonasal cancers with chromium exposure [12, 59].

In the late 1800s, chromium was first linked to cancer of the respiratory tract [60]. 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" [58]. 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 plat-

ing, and to various chromates used during cement production are most important [58]. To date, there has been "inadequate evidence in humans" for the carcinogenicity of metallic chromium and chromium [III] compounds.

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 [59]. 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 was in the setting of short-term high exposure [61]. 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 [62, 63]. 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 [63]. 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. 10.7), and progressive massive fibrosis, a more advanced stage with extensive pulmonary fibrosis most prominent in the upper and posterior lung zones.

There have been several studies examining the relationship between coal mining and lung cancer with different results. 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 (DEE) 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 [64]. 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. Occupations with heavy exposure to DEE include truckers, firefighters, railroad workers, mechanics, miners, and other workers operating diesel powered equipment [65, 66].

DEE was classified as established carcinogen by the IARC in 2012 based on sufficient evidence of carcinogenicity in animal models and in humans [67]. A discussion of the epidemiology can be found in Chap. 15.

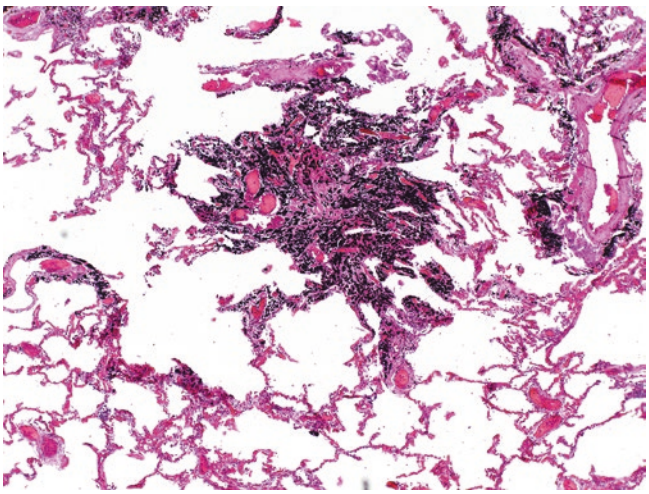

Fig. 10.7 Coal dust macule with perifocal emphysema and incidental adenocarcinoma of the lung [H&E stain, original magnification ×400]

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 in 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 nickel and importation of nickel has been the main source of activity.

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 [68]. 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 propose that it may be useful in determining the nickel burden in lung tissue resulting from occupational exposures [69]. Epidemiological data supports a causal association between exposure to nickel and an increased risk of lung cancer [12]. However, high-risk exposure operations have decreased over the preceding decades; this should be taken into consideration when evaluating the relationship between more recent nickel exposure and lung cancer [70]. See Chap. 15 for a more detailed discussion of the epidemiology.

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 decays 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 [71]. The number of uranium mines has decreased over the past three decades as have the number of uranium mine workers [72, 73].

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 [74].

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 10.11). 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 occupations newly recognized to be at risk include construction workers, surface strip miners, silica flour mixers, and tombstone sandblasters [75, 76]. 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 [62], most often in the form of alpha quartz [77]. 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 [77]. 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 [76].

The 1996 official statement of the American Thoracic Society (ATS) concluded that silicosis produces increased risk for bronchogenic carcinoma, [76] 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 [78]. Despite this statement, controversy remains as to whether silica is truly carcinogenic. Those who believe silica has no role in the development of lung cancer cite studies which poorly controlled for tobacco smoking and radon exposure [79–81].

The causal relationship between silica exposure and carcinoma of the lung in humans remains controversial. See Chap. 15 for a more detailed discussion of the epidemiology.

Table 10.11 Occupations with crystalline silica exposure

Stonecutting
Sandblasting
Quarry work
Refractory brick
Foundry work, molding, and grinding
Mining, drilling, quarrying, and tunneling

Modified from Gibbs [75]

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 [77]. 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 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 [82]. A 2005 study by NIOSH reviewing mortality secondary to tuberculosis among US industries from 1990 to 1999 indicated mortality from tuberculosis continued to be elevated in workers with silica exposure [83]. The increased susceptibility to tuberculosis is secondary to macrophage dysfunction caused by silica leading to impaired resistance [84].

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 [85]. 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 10.9). Eggshell calcification of hilar lymph nodes is classic for silica exposure, yet it 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 [86].

Secondhand Tobacco Smoke

It is well documented that smoking is a potent cause of lung cancer for the smoker, yet they are not the only one exposed to carcinogens when smoking tobacco products. Cigarette smoking contains greater than 50 carcinogens and exists in two forms: mainstream smoke (MSS), generated when a puff of smoke is drawn in 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 ETS was unlikely to be due to chance or bias [87], and in 1992, the EPA declared a causal relationship between SHTS and lung cancer [88]. Finally, in 2004, the IARC determined there was "sufficient evidence" that ETS caused lung cancer in humans [89]. There were 30 supportive epidemiologic studies, of which a majority focused on nonsmoking women who are exposed to a smoker in the home [90–92].

Critique and criticism 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 U.S. 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 ETS [88, 93–97]. 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, the source of energy may be mechanical (forge, friction, vibration, and explosive) and electrical (arc and electron beam), and exposures 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 a chemical pneumonitis. Additionally, chronic rhinitis and bronchitis, wheezing, and dyspnea have also been described, though more common in nonsmokers [98, 99]. Welder's pneumoconiosis will be described below.

In 1990, the IARC determined there was "limited evidence" for carcinogenicity of welding fumes and gases in humans and classified welding fumes as "possibly carcinogenic" [58].

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 [98–100]. See Chap. 15 for a more detailed discussion of the epidemiology.

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 [62, 101].

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 in the above (Table 10.12). 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 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; how-

Table 10.12 Methods of tissue analysis via microprobe techniques

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 [62]

ever, Stettler et al. analyzed particle concentrations of 33 urban lungs [102]. 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 and can be both qualitative and quantitative, detecting most elements with an atomic number (Z) $\geq$ 4. These forms of electron microscopy are collectively termed analytical electron microscopy (AEM). 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 [62, 103].

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 employed 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 varies from five to tenfold and thus adequate sampling of several sites is encouraged [104]. If an ashing method of tissue digestion is to be used, one should know that this procedure may cause fiber breakage and thus false elevation of fiber content [103]. This problem can largely be avoided with low temperature plasma ashing.

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 [103].

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 $Z < 9$ [105]. 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 [103, 105].

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, 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 [105].

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 10.13 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?	Around pipes	*Y/N/DK*	*Hours/week*
	Ovens, boilers		
	Buildings		
	Electrical equipment		
	If other, please specify:		
Q2: Which of the following materials were you in contact with?	Fiberglass	*Y/N/DK*	*Hours/week*
	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?	By injection of foam	*Y/N/DK*	*Hours/week*
	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*	*Y/N/DK*	*Hours/week*
	If yes, hours a week:		
	If yes, was it:		
	By hand		
	With electric-powered machines		
Q6: Did you have to work with cement, concrete?	*Y/N/DK*	*Y/N/DK*	*Hours/week*
	If yes, for which tasks?		
	Making holes in concrete		
	Covering insulation with cement		
	Using a concrete mixer		
	If other, please specify:		
	END SQ14		

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Lung Cancer: Molecular Markers of Occupational Carcinogens

11

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Introduction

Lung cancer is one of the most frequent and most devastating cancers worldwide. Therefore, early detection is a major focus area and could be improved by the use of molecular markers. Specific molecular markers are also crucial for the correct diagnosis (see Chap. 10) and detection of driver mutations for molecular targeted treatments. Furthermore, molecular markers may serve as indicators of favorable or unfavorable disease outcome and thus guide therapeutic options. As regards cancers with suspected occupational etiology, markers of exposure and disease attribution to a specific carcinogen may be developed.

Exposure-related 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 [1].

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 Chaps. 12 and 13 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.

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, sputum, bronchoalveolar lavage fluid, or in exhaled breath condensate (EBC). The use of tissues that can be obtained with noninvasive techniques is important especially in the surveillance and screening of healthy people for cancer prevention or early detection. For example, protein, genetic, and epigenetic biomarkers are detectable in EBC [reviewed in e.g., [2, 3]]. Cancer-associated mutations have been found in EBC by next generation sequencing also from healthy non-smoking individuals, leading investigators to emphasize the importance of knowing the background prevalence of cancer-related alterations in any tissue under study when applying techniques that detect genetic mutations with high sensitivity and low allele frequencies [4].

In the following, we discuss molecular markers in relation to asbestos exposure and touch a few relevant other exposures, such as tobacco smoking. Table 11.1 presents a summary of molecular markers associated with asbestos exposure in lung cancer patients.

Occupational Exposures and Tobacco Smoking

Lung cancer of never smokers (10–25% of all lung cancers) has molecularly been considered a completely different disease to that of smokers [27]. Some of the molecular

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Table 11.1 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	[5]
LOH at 3p14	*FHIT* exon loss	Lung cancer of asbestos-exposed individuals	[6, 7]
LOH at 3p21	Possible downregulation of tumor suppressors	Lung cancer of asbestos-exposed individuals	[8, 9]
LOH/homozygous deletion at 9p21.3	Loss of *P16*/*CDKN2A*	Lung cancer of asbestos-exposed individuals	[10]
CNA at 9q33.1		Lung cancer of asbestos-exposed individuals	[11]
Break at the centromere of chromosome 9		In vitro	[12]
Monosomy of chromosome 19	Possible downregulation of tumor suppressors	In vitro	[13]
AI and loss at 19p13	Possible downregulation of tumor suppressors	In vitro; lung cancer of asbestos-exposed individuals	[14]
Polyploidy	Aneuploidy and chromosomal instability	In vitro; lung cancer of asbestos-exposed individuals	[11, 15]
Accumulation of p53 protein	Decreased or abnormal tumor suppressor activity possibly due to mutations	In vitro; lung cancer of asbestos-exposed individuals	Reviewed in [16, 17]
G to T transversion mutations of *TP53*	Possibly caused by co-exposure with tobacco smoking	In vitro; lung cancer of asbestos-exposed individuals	[18, 19]
Serum Ras (p21)	Upregulation due to mutations	Lung cancer of asbestos-exposed individuals	[20] and reviewed in [21]
KRAS	Specific mutations possibly caused by co-exposure with tobacco smoking	Lung cancer of asbestos-exposed individuals	[22]
Specific miRNA profiles	Regulation of target gene translation	Lung cancer and serum from asbestos-exposed individuals	[23, 24, 85]
Specific differentially methylated regions and differentially methylated CpGs in genes; hypomethylation of differentially methylated CpCs	Alteration in gene expression	In vitro; lung cancer of asbestos-exposed individuals	[25, 26]

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 [28]), which confounds the analysis on specific molecular alterations related to exposures other than tobacco carcinogens.

Some of the typical alterations that are more common in never smokers' than smokers' lung cancer include the *EML4-ALK* fusion gene caused by an inversion in chromosome 2, hypermethylation of *MGMT*, mutations of *EGFR*, specific mutations in *TP53* (G:C to A:T at non-CpG sites) [27, 29], and allelic loss of *FHIT* [27, 30]. Furthermore, the *EFGR* mutations have been different between current or former smokers and never smokers: never smokers have less frequent L858R mutation and more frequent exon 20 mutations and exon 19 deletion than smokers [31–33].

There are only limited data on molecular alterations in lung tumors from never-smoking occupationally or environmentally exposed patients. Paris et al. [34] studied *EGFR*, *KRAS*, *HER2*, *BRAF* and *PIK3* mutations, and *ALK* rearrangements in a cohort of 313 never smoker lung cancer patients categorized into groups exposed and unexposed to polycyclic aromatic hydrocarbons (PAH), asbestos, silica, diesel exhaust fumes, chrome, and paints. Asbestos-exposed patients had less *EGRF* mutations than unexposed (20% vs. 44%); no other significant associations were observed [34]. Ruano-Ravina et al. [35] studied *EFGR* mutations and *ALK* alterations in never-smoking lung cancer patients from a radon-prone area in Spain. They compared median residential radon values between patients with *EGFR* mutations or *ALK* rearrangements versus those without them, and found twofold radon levels in *ALK*-positive patients compared with

ALK-negative patients but observed no differences in radon levels according to *EGFR* mutation status.

Inamura et al. [36] studied loss of heterozygosity (LOH) for all autosomal chromosomes and *TP53* mutations in never smoker and smoker, asbestos-exposed and unexposed lung cancer patients. Fractional allelic loss (FAL) value (number of chromosome arms with LOH/number of informative arms) increased significantly with the increasing exposures to asbestos and tobacco smoking combined but not with either exposure separately. Asbestos exposure increased non-specific *TP53* transition mutations in never smokers [36]. In this study, asbestos exposure was lower in never smokers than smokers and never smokers were almost exclusively women, suggesting exposures other than asbestos in never smokers.

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 [37].

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 possible 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 [38]). In this case, it may be difficult to separate the effects of the two carcinogens on molecular tumor profiles, and both exposures may have 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. 18 for a detailed discussion on the molecular markers in malignant mesothelioma. Chapter 18 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. [8] 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 [8]. 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 [9]. 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. 11.1) [9, 39].

Interestingly, loss of 3p21.3 and promoter hypermethylation of the gene *RASSF1A*, located in this region, have also shown to be frequent in malignant mesothelioma [40, 41]. Another tumor suppressor gene, *BAP1*, is located at 3p21.1. Germline mutations of *BAP1* are known to cause a familial cancer syndrome predisposing to malignant mesothelioma, malignant melanoma, and a few other cancer types [42]. Somatic *BAP1* mutations are frequent in malignant mesothelioma and result in a complete loss of protein expression [43, 44]. Recent research has led investigators to propose that germline *BAP1* mutations may sensitize mutation carriers to asbestos-induced mesothelial carcinogenesis [45]. Loss of BAP1 protein expression is very rare in lung cancer [46].

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 in lung cancer [7]. However, Pylkkänen et al. detected reduced *FHIT* expression in both asbestos-exposed and non-exposed patients' lung tumors [6]. The region contains a fragile site, FRA3, and it has been reported that asbestos-related CNA may be associated with fragile sites [9], 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' than among unexposed patients' lung tumors, which, in contrast, show more frequent methylation of the gene [10]. The frequencies of

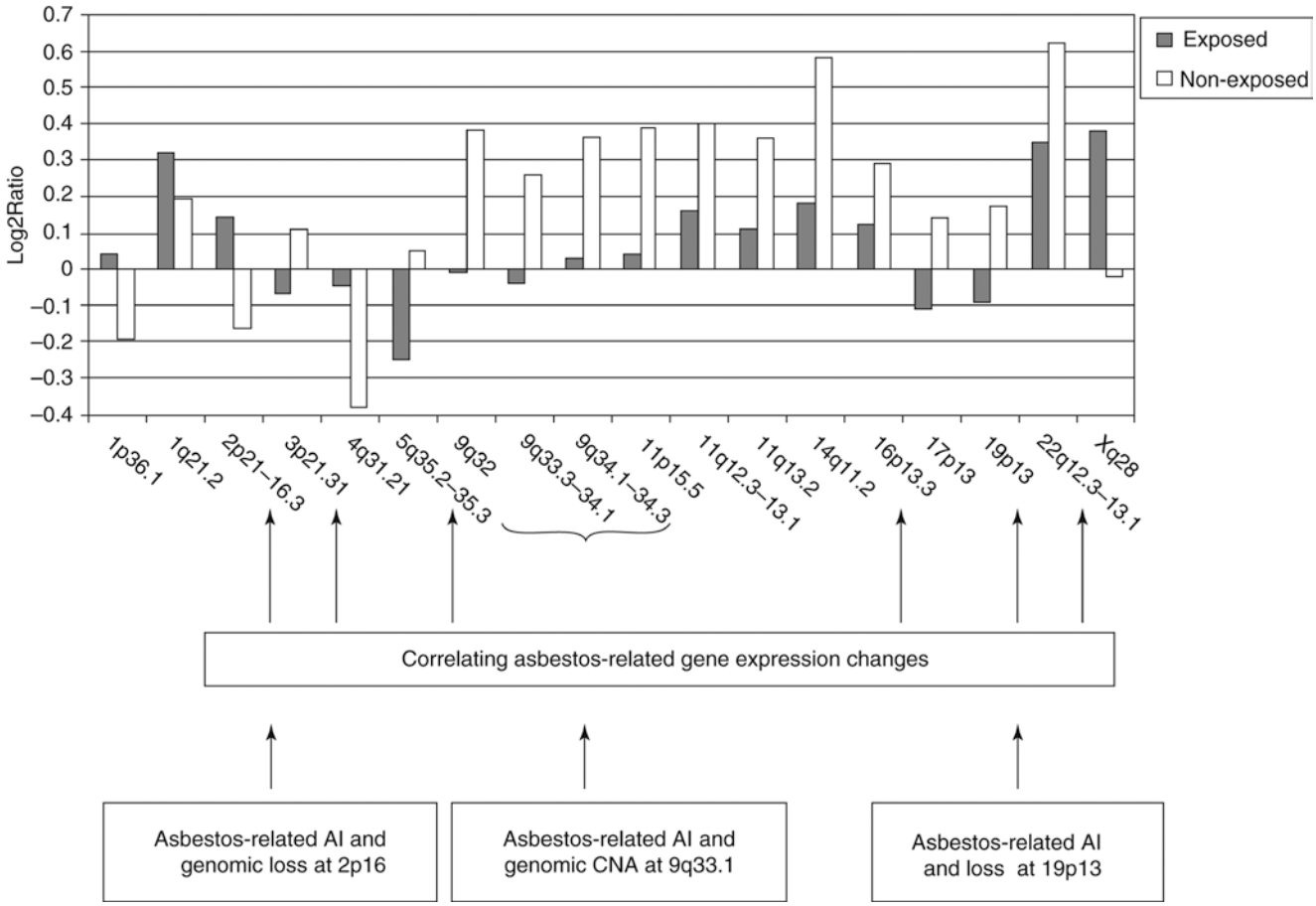

Fig. 11.1 Regions showing different copy numbers between asbestos-related (*gray*) and non-related (*white*) lung cancer using array comparative genomic hybridization (*CGH*). The *Y*-axis represents the average $\log_2$ ratios of all array probes in all samples in each chromosomal region (*X*-axis) (Modified from [9])

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. 18 and [47–49]), while non-asbestos-related lung cancer showed opposite frequencies (24 and 49%, respectively) [10]. Others have, however, reported that both mechanisms of inactivation correlate with asbestos exposure in non-small cell lung cancer [50, 51] and, in general, also epigenetic changes, such as methylation, are thought to contribute significantly to the development of asbestos-related lung cancer [52].

The chromosomal region 9q33.1 is affected by both AI and CNA more frequently in asbestos-related than in non-related non-small cell lung cancer [11] (Fig. 11.2a). Furthermore, CNA in this region increased in frequency with the intensity of exposure, showing a dose–response relationship with the pulmonary asbestos fiber count [11]. The most significant dose dependence was seen among adenocarcinoma patients. Interestingly, losses initiating at 9q33.1 have also been identified in malignant mesothelioma [40]. In vitro, chromosome 9 has been shown to be affected by breaks at the centromere in human amniotic fluid cells exposed to asbestos [12].

Asbestos-related losses and allelic imbalance (AI) in human lung cancer have also been observed in the 19p13.3 region [14, 39]. AI at 19p13.3 appeared to be common in lung adenocarcinoma regardless of the patients' asbestos exposure, whereas in the other major histological types, AI in this region was associated with asbestos exposure [14]. In contrast, loss at 19p13 in adenocarcinoma, detected by FISH, increased in frequency with the intensity of exposure, i.e., showed a dose-dependent response to increasing pulmonary fiber count. Such a trend was not seen with all histological types combined (Fig. 11.2b), although subsequent results from the same laboratory using an increased number of samples indicated a similar dose dependence for 19p13.3 loss among all histological types [53]. Interestingly, monosomy of chromosome 19 has been detected in vitro in asbestos-transformed human bronchial epithelial cell lines [13]. In addition, other in vitro experiments showed that 19p fragments were lost through micronuclei (MN) induced by exposure to crocidolite asbestos in the immortalized human

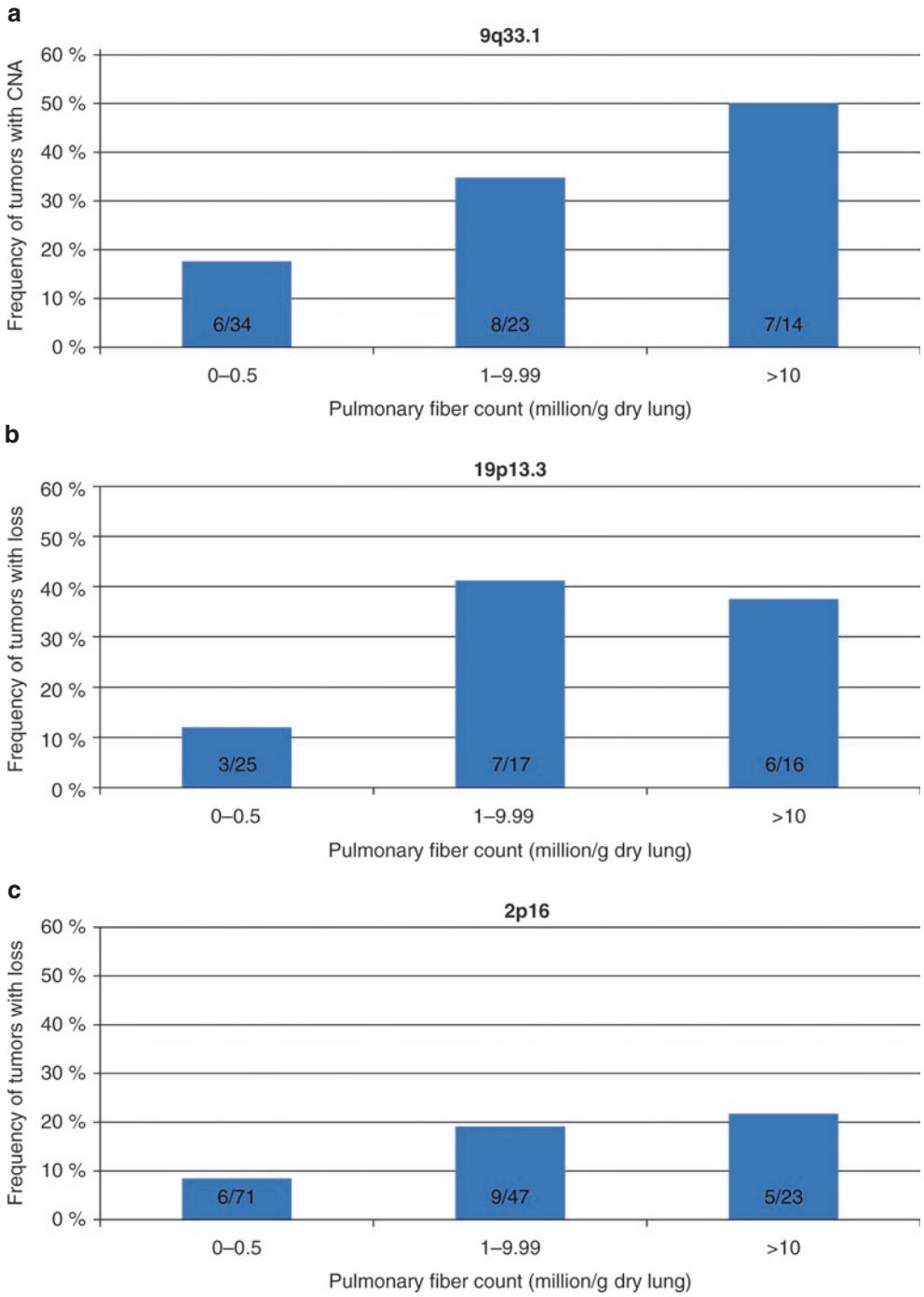

Fig. 11.2 Frequency and dose–response of asbestos-related copy number alterations (CNA) in non-small cell lung cancer. (**a**) CNA at 9q33.1, (**b**) loss at 19p13, and (**c**) loss at 2p16 in tumor tissue from asbestos-exposed (≥10 and 1–9.9 million fibers/g dry lung) and non-exposed (0–0.5 million fibers/g) surgical lung cancer patients. The number of samples with CNA/number of all samples is shown at the bottom of each column (**a** Reprinted from [11])

bronchial epithelial cell line [14]. 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. Ivanov et al. [54] have reported the loss of chromosome 19 as the second most frequent numerical change in malignant mesothelioma [54]. In addition, in the same study, a minimal common area deleted in malignant mesothelioma cases was localized close to region 19p13 [54].

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 [5] (Fig. 11.2c), and the losses showed a dose–response relationship with increasing exposure, similarly to 9q33.1 and 19p13 (Fig. 11.2c). Furthermore, an in vitro study found gene expression changes to be enriched at 2p in asbestos-exposed cell lines compared to untreated cells [55]. Interestingly, the region contains a fragile site, similarly to the 3p region, as mentioned above.

Another region worth mentioning is 14q11.2, which was 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) [9]. The region lies within an area (14q11.2-q21) that has been specifically associated with asbestos exposure in mesothelioma ([56, 57]; see Chap. 18).

Finally, polyploidy has been shown to be more frequent in asbestos-related compared to non-related lung cancer [11]. Indeed, in vitro, asbestos has shown to induce polyploidy by sterically blocking cytokinesis [15] (see Chap. 19 for a more detailed discussion).

Allelic imbalance in the asbestos-associated chromosomal regions 2p16, 9q33.1, and 19p13 has been studied also in the histologically normal bronchial and bronchiolar epithelium microdissected from the tumor resection specimens [53]. In most cases, tumor and normal epithelium expressed concordant AI results, indicating that AI in these chromosomal regions arises early in the carcinogenic process.

In cell line experiments, asbestos induces a number of different chromosomal abnormalities, most typically deletions, breaks, and fragments. Experimentally, asbestos also increases homologous recombination DNA repair, which is the mechanism used for DNA double strand break repair [reviewed in [38]]. Interestingly, germline mutations in DNA repair genes were suggested to predispose asbestos-exposed patients to malignant pleural mesothelioma [58]. Betti et al. [58] identified ten pathogenic truncating variants in genes (*PALB2*, *BRCA1*, *FANC1*, *ATM*, *SLX4*, *BRCA2*, *FANCC*, *FANCF*, *PMS1,* and *XPC*) involved in DNA repair pathways, mostly in homologous recombination repair. Mesothelioma patients who carried truncating variants had lower asbestos exposure than the other patients [58].

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. p53 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 [59–62]. *TP53* mutations are known to be associated with abnormal accumulation of p53 protein, and indeed, many [63–65] but not all studies [66] 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 [67]. Some studies on human lung tumors have linked specific mutations, i.e., predominantly in exons 9–11, to asbestos exposure [68, 69], 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 co-exposure with amosite asbestos in the rat lung [70]. Indeed, in a study of [36] *TP53* mutation frequency in lung adenocarcinoma increased with increasing pack-years of smoking and asbestos exposure but never-smoking asbestos exposed mainly had nonspecific transition mutations. In contrary, Andujar et al. [18] found a significant enhancement of *TP53* G:C to T:A transversion mutations in asbestos-exposed as compared to unexposed non-small cell lung cancer patients matched for smoking habits. The finding may, nevertheless, be induced by the combined exposures as only 13% of the patients were never smokers. The group also detected similar intronic *TP53* polymorphisms in asbestos-related lung cancer and pleural mesothelioma patients [18].

Asbestos exposure causes oxidative stress, which induces 8-OHG adducts (see Chap. 12). These adducts are mutagenic and may cause G:C to T:A transversions. 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 adenocarcinoma, in some studies [e.g. [22]], but not in all [66]. 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 [71]. *KRAS* mutations are significantly more common in smokers' than never smokers' lung tumors [29]. This is in agreement with the study of [18] who found no association between asbestos exposure and *KRAS* or *EGFR* mutations in non-small cell lung cancer.

Gene Expression, Protein, and Immunological 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 identified, 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 [21, 72]. In addition, oncoprotein Ras (p21) has been detected in the serum of asbestosis patients prior to cancer development [20, 21]. Similarly, an 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 [73]. p53 antibodies have specifically been associated with detectable mutations in *TP53* in lung tumors [74].

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 adenocarcinoma [75], and interestingly the gene has been predicted to be regulated by a microRNA (miR-429), which has shown to be downregulated in mesothelioma [76, 77]. It has also been found that the *AnxA2* gene is overexpressed in the lung cancer and normal tissue of asbestos-exposed patients [75, 78].

Plasma proteome may provide means of distinguishing asbestos-exposed from unexposed lung cancer patients in the future. Rostila et al. [79] performed an initial discovery phase by applying two-dimensional gel electrophoresis combined with protein identification by tandem mass spectrometry (LC-MS/MS) on four separate groups: asbestos-exposed lung cancer patients, unexposed lung cancer patients, asbestos-exposed without lung cancer, and healthy tobacco smokers. We observed 28 differentially expressed proteins, 9 of which were validated in over 200 additional plasma samples. In this study, high plasma levels of tropomyosin 4 and antioxidant enzymes peroxiredoxin 1 and 2 correlated with asbestos exposure and asbestosis [79]. The study population did not contain many lung cancer cases attributed to asbestos and it was not possible to detect markers specific to asbestos-related lung cancer.

Asbestos-associated immunological effects have been suggested as biomarkers for screening asbestos-exposed populations. Asbestos exposure exerts influence on various different T-cell populations and impairs antitumor immunity through regulatory T-cells, reduction of CXCR3 chemokine receptor in CD4+ T lymphocytes, and through CD8+ cytotoxic T lymphocytes and NK cells [80]. These effects have been observed in peripheral blood, bronchoalveolar lavage and effusion fluid from asbestos-exposed individuals and in patients with malignant mesothelioma [e.g. [81–83]].

Epigenetic Markers

MicroRNAs

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 [84]. To our knowledge, two studies so far have described asbestos-related miRNA expression signatures in non-small cell lung cancer (NSCLC) [23, 85]. A study using tumor and normal lung tissue samples from 13 asbestos-exposed and 13 unexposed patients identified 13 differentially expressed asbestos-related miRNAs by integrating DNA copy number, gene expression (mRNA), and miRNA expression data from the same patients. Asbestos-related lung cancers, primarily those with adenocarcinoma 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) [23]. 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 [23].

Santarelli et al. [85] performed the initial discovery phase on 4 asbestos-exposed and 4 unexposed NSCLC, and 4 malignant pleural mesotheliomas, and obtained three miRNAs (miR-520 g, miR-504, and miR34a) that were differentially expressed in asbestos-related NSCLC. Further validation with a larger number of tumors confirmed two miRNAs (miR-222 and miR520g) to be representative of asbestos-related NSCLC. The group developed a four-miRNA panel (miR-126, miR-205, miR-222, and miR-520 g), which, as detected in serum samples, was connected with asbestos-related malignant mesothelioma and lung cancer [85]. In another study by [24], serum samples from malignant mesothelioma patients and from asbestos-exposed and unexposed healthy subjects were screened by microarray and RT-qPCR technologies for potential miRNA markers [24]. This group found three miRNAs (miR-197-3p, miR-1281, and miR-32-3) to be upregulated in malignant mesothelioma patients compared to unexposed healthy subjects, two miRNAs (miR-197-3p and miR-32-3p) upregulated in asbestos-exposed compared to unexposed healthy subjects, and one miRNA (miR-1281) upregulated in both malignant mesothelioma patients and asbestos-exposed compared to unexposed healthy subjects [24].

It is remarkable that the three studies described above suggested completely different miRNA panels for identification of asbestos-related malignancies. These results call for further investigations with verification in large study populations as well as complementary data on the role of specific miRNAs in asbestos carcinogenesis.

DNA Methylation Changes

DNA methylation is one of the epigenetic mechanisms of the regulation of gene expression (see Chaps. 2 and 3). It is well known that environmental and lifestyle factors can cause permanent and inheritable changes in DNA methylation. Kettunen et al. [25] were the first to study the influence of asbestos exposure on the DNA methylome in lung cancer. They revealed genome-wide differentially methylated regions and differentially methylated CpGs between 14 asbestos-related and 14 non-related NSCLC and normal lung from the same patients, and further validated the results in an independent series of 91 NSCLC and paired normal lung. Hypomethylation was characteristic to differentially methylated CpGs in tumor and normal lung tissue from asbestos-exposed patients (Fig. 11.3a, b). The group discovered and validated significantly asbestos-associated differentially methylated regions in genes such as *RARB*, *GPR135,* and *TPO;* and differentially methylated CpGs in *NPTN*, *NRG2*, *GLT25D2,* and *TRPC3* in NSCLC [25]. When differentially methylated CpGs related to asbestos or smoking were analyzed, 96% of the elements were unique to either of the exposures. It is worthy of noting that in this study almost all subjects were current or former smokers and smoking was categorized into two groups according to pack-years of smoking. Previously, Christensen et al. [86] have reported that methylation profiles of malignant pleural mesothelioma can predict lung asbestos burden and clinical outcome. These findings are consistent with the concept that methylation changes in tumors may be specific to risk factors [25].

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. Theoretically, for example with a twofold risk, 50% of cancers are caused by asbestos but in reality different carcinogen exposures (e.g., tobacco smoking and asbestos) and individual susceptibility factors have all contributed with varying significance. 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 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 to 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 [53]. 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% [53]. The sensitivity value was based on the assumption that all lung cancers among asbestos-exposed are related to asbestos, which is not the case (see discussion above). 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. 13, 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 (discussed in Chap. 13). Although many of the alterations found in lung cancers related to these exposures

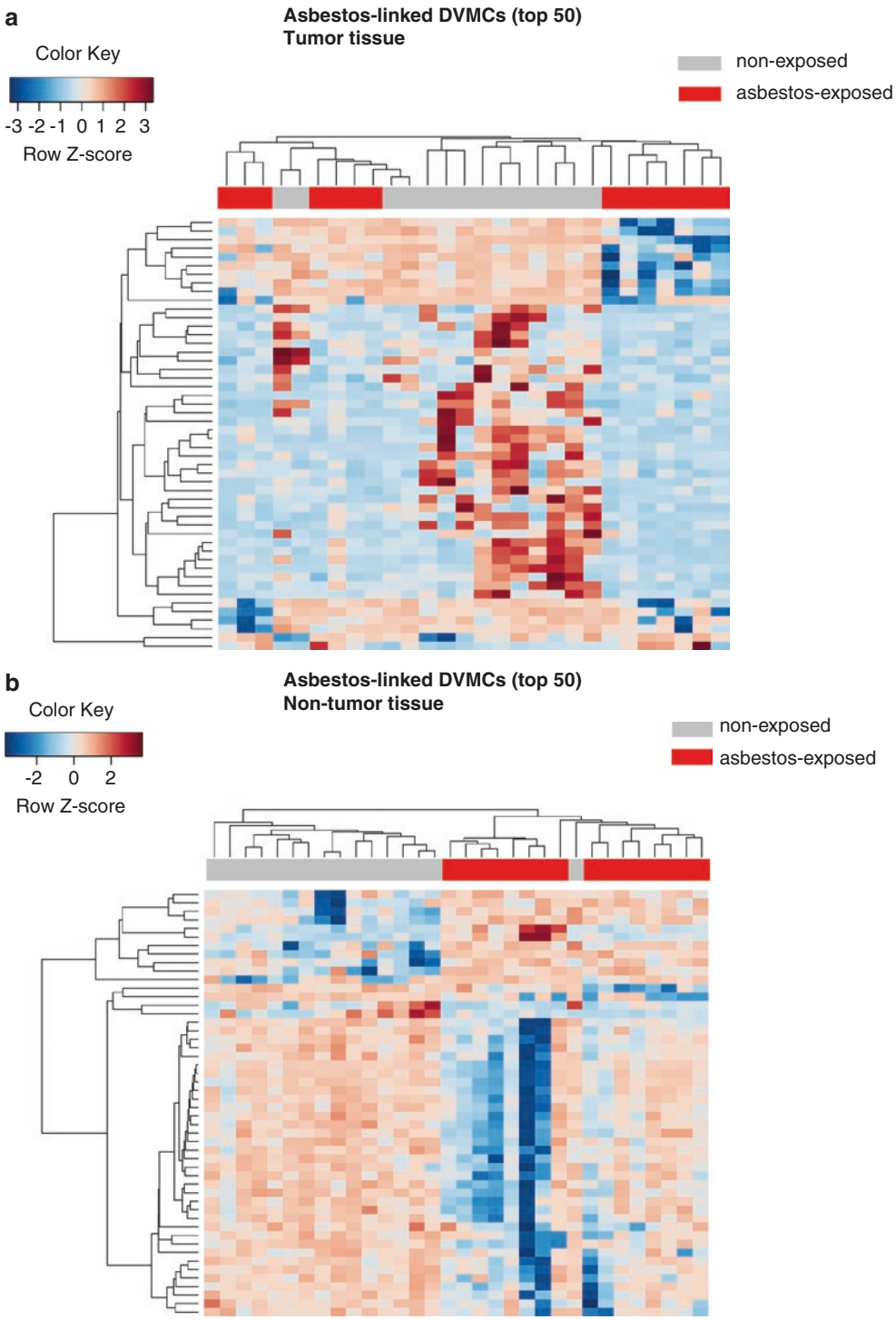

Fig. 11.3 (**a**, **b**) Heat maps for the top 50 asbestos linked differentially methylated CpGs (DVMCs) in lung tumor tissue (**a**) and normal lung tissue from cancer and non-cancer patients (**b**). Exposed cases show more hypomethylation. Samples in heat maps are in columns and CpGs are in rows. The cases were grouped into asbestos-exposed and unexposed according to pulmonary asbestos fiber count (exposed, over five million; unexposed, 0.5 million or less per gram of dry-weight tissue). Different histological types were distributed in all groups. The color key indicates the methylation level of each site (red, higher; blue, lower) (Reprinted with permission from [25])

may be associated to the common carcinogenic pathways, a few changes may be more specific, consequent to unique carcinogenic mechanisms. Examples of these alterations include the typical gene copy number changes in the lung cancer of arsenic-exposed populations [87] and epigenetic alteration profiles in the lung cancer of chromate workers [88, 89].

Conclusions

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.

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Lung Cancer: Mechanisms of Carcinogenesis by Asbestos

12

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Introduction

It has been known for decades that occupational exposures to asbestos lead to an increased risk of lung cancers, especially in smokers. The complex nature of cigarette smoke, which contains hundreds of carcinogens and other toxins, has been the subject of many experimental studies over the past several decades (reviewed in [1]). Despite advances in understanding the etiology, biology, and evolution of lung cancers, tumors of the respiratory system continue to be the leading cause of cancer deaths worldwide [2]. Historically, asbestos fibers have been studied most frequently in the genesis of mesothelioma, a more infrequent tumor unrelated to cigarette smoke, and an understanding of the molecular mechanisms of mesothelioma, despite some progress, remains enigmatic [3].

Unraveling the roles of asbestos fibers in the induction and/or development of lung tumors and how these complex minerals interact with components of cigarette smoke have been daunting due to the lack of experimental inhalation models that allow one to map the development of lung cancers in rodents over time [4]. A confounding factor preventing the study of lung cancers in rodents is the more rapid development of asbestosis or pulmonary fibrosis which causes early death after co-exposures [4]. However, our present knowledge of the mechanisms of lung cancer development by asbestos has been spear-headed by short-term rodent studies as well as differentiated lung epithelial cells and tracheobronchial explants (organ cultures). These models permit identification of critical cell: cell interactions and the development of hyperplastic and metaplastic lesions, early events in the carcinogenic process. Most recently, human lung tissues and bronchial epithelial cells have been used to demonstrate epigenetic signatures of lung tumor development and the importance of a favorable tumor environment consisting of chronic inflammation and cell proliferation.

The objective of this chapter is to describe studies providing insight into the interactions between components of cigarette smoke and asbestos that are important in their accumulation in lung. We then focus on the roles of these agents in lung carcinogenesis with an emphasis on recent studies exploring genetic and epigenetic changes by asbestos in human lung cancers and epithelial cells of the respiratory tract. There are many properties of mineral fibers that have been linked to carcinogenic events by asbestos, and a quantitative model to predict lung cancer risk is presented.

Basic Concepts of Asbestos Mineralogy

Definitions of Asbestos

Asbestos is a broad term used to identify a few silicate minerals that can be found in nature as thin and flexible fibers when crushed. Some of these minerals were of industrial and economic importance and have been used widely in the past [5]. To date, a plethora of different and sometimes contradictory definitions of the term "asbestos" exists, depending upon its usage in commercial, mineralogical, regulatory, and other settings. Unfortunately, the inadequate and incomplete definition of "asbestos" results in the lack of standardized operating definitions for these mineral fibers. Ambiguity in the definition of asbestos minerals also leads to widespread confusion in social, health, and legal contexts [6].

In this chapter, we will refer to the mineralogical term coined in 1982 which applies to six minerals exploited commercially for their desirable physical properties, mostly due to their fibrous-asbestiform habit. The six minerals are the serpentine phase chrysotile and the amphibole minerals amosite, crocidolite, anthophyllite asbestos, tremolite asbestos, and actinolite asbestos [7, 8]. This definition is in line with regula-

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tory and health agencies indicating the six minerals described above as carcinogenic to humans (Group 1) [9, 10].

Serpentine Asbestos

Chrysotile is a layer silicate which belongs to the serpentine group together with the other polymorphs lizardite and antigorite. Serpentine minerals are composed of Si-centered T sheets in a pseudo-hexagonal network joined to Mg-centered O sheets in units with a 1:1 (TO) ratio. The ideal chemical formula of serpentine minerals is $Mg_3(OH)_4Si_2O_5$. In chrysotile, substitutions may occur in both T and O sheets but are limited. Fe^{2+} and Fe^{3+} may substitute for Mg^{2+} in the O sheet while replacement for Si^{+4} in the T sheet is less frequent, with a preference for Al^{3+} [11, 12]. As a result of the misfit between the T and O sheets [13] and because of the polarity of the TO unit, a differential strain occurs between the two sides of the layer. In chrysotile, the strain is released by rolling the TO layer around the fibril axis to end up with a cylindrical lattice responsible for the fibrous crystal habit.

Amphibole Asbestos

The family of amphibole asbestos includes actinolite asbestos $Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$, amosite (fibrous variety of grunerite) $(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$, anthophyllite asbestos $(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$, crocidolite (fibrous variety of riebeckite) $Na_2(Fe^{2+},Mg)_3Fe_2^{3+}Si_8O_{22}(OH)_2$, and tremolite asbestos $Ca_2Mg_5Si_8O_{22}(OH)_2$. Amphiboles are chain silicates with an ideal Si:O ratio of 4:11 whose structures consist of alternating tetrahedral (T) chains and octahedral band sheets that are parallel to the (100) plane. Tetrahedra form infinite double chains running parallel to the **c** axis. In amphiboles, the oxygen atoms of the chains coordinate not only with Si(Al) but a variety of other cations, leading to the general formula [14]: $A_{0-1}B_2C_5T_8O_{22}W_2$. In the most common *C*2/*m* monoclinic amphiboles, A (in the (12)-fold cavity with a complex nomenclature used to describe the positional disorder of the cations) may host vacancies, Na^+, K^+, Ca^{2+}, Li^+; B is the (8)-fold coordinated *M*(4) site with Na^+, Ca^{2+}, Mn^{2+}, Fe^{2+}, Mg^{2+}; C are the octahedrally coordinated sites *M*(1), *M*(2), *M*(3) with Mg^{2+}, Fe^{2+}, Mn^{2+}, Al^{3+}, Fe^{3+}, Mn^{3+}, Ti^{4+}, Li; T are the tetrahedrally coordinated sites within the silicate chain with Si^{4+}, Al^{3+}; and W = OH^-, F^-,Cl^-, O^{2-} [14]. Due to the presence of strong bonds, amphibole crystals normally grow along the **c** axis and may display a fibrous habit due to the mono-dimensional character of their structural units (chains).

According to the IARC [10], there is *sufficient evidence* in humans for the carcinogenicity of all forms of asbestos; hence they all have been classified as *carcinogenic to humans* (*Group 1*).

Physical-Chemical and Crystallographic Characteristics of Minerals Important in Lung Cancers

This section discusses the multiple parameters of mineral fibers (morphometric, chemical, biodurability-related, and surface activity) considered to prompt the cellular processes related to lung carcinogenesis. More than 20 years ago, George D. Guthrie stated that "*Extensive research has focused on the biological mechanisms responsible for asbestos-induced diseases, but much less attention has been paid to the mineralogical properties that might influence a mineral's biological activity. Several important mineralogical characteristics are likely to determine its biological reactivity and play important roles in determining the toxicity and carcinogenicity of a particle*." [15]. In addition to the traditionally considered variables of particle size and shape that exert a major control on deposition, translocation, and clearance, other mineralogical properties with roles in determining the toxicity and carcinogenicity of a particle are:

- Surface reactivity and sample history. For example, differences between generation of oxidants from freshly fractured materials and aged materials exist [16].
- Sorption and ion exchange. Ion exchange occurs when a sorbed species on the mineral exchanges with a similarly charged species in fluids. Some minerals like zeolites have great capacities for cation exchange because the ions can diffuse rapidly from the surface of the mineral to its interior, thereby enabling the entire particle to provide a buffering capacity [15]. Cation exchange could play an important role in cellular responses through a number of mechanisms, including the buffering of Ca^{2+} activity at the surface of a cell. It was observed that cation-exchanged erionites (Na, K, Ca, and Fe^{3+}) can have an effect on cytotoxicity, gene response, and apoptosis in pleural mesothelial cells.
- Catalytic properties of mineral particles that can function in a manner similar to that of traditional enzymes.
- Surface oxidation/reduction with electron transfer that has the potential to produce a sustained or chronic redox condition to drive formation of $HO^{\bullet}$ in the fluid. For example, iron release to the fluid may drive Fenton-type reactions to maintain charge balance.
- Dissolution/leaching, a major component of particle clearance mechanisms that causes the release of ions (e.g., iron and other metals, see below) to the lung fluid.
- Surface reactivity.

Surface Properties

At first glance, the surface properties of native mineral fibers may be overlooked as they may be modified in lung fluids or

by cells. In cells, a complex protein corona surrounds some engulfed particles. As observed for nanoparticles (NPs), the formation of the protein corona is an unstable and reversible mechanism for which a hetero-aggregation model is applied [17]. In fact, the protein corona that surrounds a fiber is porous, and the properties and processes active at the surface such as dissolution, exchange, and surface activity may only be partly inhibited. The protein corona is porous because it is formed, for example, by globular proteins such as albumin with a diameter of about 8 nm that stick to the surface of the fiber (it is possible to align 1250 albumin proteins along a 10 μm long asbestos fiber). The globular proteins adapt their structure to the surface but will never be able to entirely cover it, forming a porous layer around the fiber that does not inhibit, for example, ion exchange.

Fiber Dimensions

Among the morphometric parameters of a fiber, length and diameter play a major role in the kinetics of inhalation and lung response. According to the "Stanton hypothesis" [18], the ideal morphology of fibers for inducing intrapleural tumors in rats consists of a diameter $D \leq 0.25$ μm and a length $L > 8$ μm. Elongated particles with $L > 8$ μm ("Stanton fibers") are not eliminated by phagocytic cells like alveolar macrophages [19] leading to "frustrated phagocytosis" which in turn prompts chronic inflammation and adverse effects. The curvature of the fibers plays a role as well because it affects protein binding and biological responses, as observed for NPs [20]. As a matter of fact, protein adsorption on curved surfaces like that of chrysotile asbestos can be suppressed up to the point when it no longer occurs.

Crystal Structure and Adsorptive Properties

The fiber crystal habit also influences its toxic and pathogenic potential as curled vs. needle-like fibers have different deposition patterns. Compared to needle-like fibers, curled chrysotile fibers tend to deposit in the upper airways where they are more efficiently cleared [21]. The density of a fiber is used for the calculation of its aerodynamic diameter [22] and influences the deposition depth of inhaled particles in the airways [23].

The hydrophilicity/hydrophobicity of fibers affects their adsorption of biopolymers and interaction with human phagocytic cells. Hydrophobic surfaces adsorb biopolymers more strongly than hydrophilic surfaces and are more prone to cell uptake [24]. The surface area of a fiber is a factor that affects not only its biodurability and dissolution rate but also its availability for interaction with cells.

Iron and Trace Metals

Concerning the different chemical parameters of fibers, iron and especially active Fe^{2+} sites available at the surface of asbestos minerals promote the formation of hydroxyl radicals ($HO^{\bullet}$) and have been associated with cytotoxic and genotoxic effects [25]. The surface availability of iron favors the production of $HO^{\bullet}$ through the Haber–Weiss cycle, whenever H_2O_2, the radical species superoxide (O_2^-) and free oxygen are released in vivo by macrophages during the inflammatory burst, following frustrated phagocytosis [26]. The activity of surface iron is also dependent upon its nuclearity at the catalytic site, the number of iron atoms joined in a single coordination entity by bridging ligands. Cluster nuclearity is indicated by monomeric (single iron atom, no other iron atoms in the second shell coordination), dinuclear or dimeric (a cluster of two iron atoms, connected by a bridging oxygen atom), trinuclear or trimeric (a cluster of three iron atoms, connected by bridging oxygen atoms), and so on [22]. The sites with isolated $(FeO)^{2+}$ structures are the preferred candidate active sites $((H_2O)_5FeO)^{2+}$ as they have a low iron nuclearity [27].

The rate of fiber dissolution controls the amount of bulk iron that becomes available for the production of HO• at the surface of the fibers [22]. Despite the huge difference in iron content between iron-poor chrysotile and the iron-rich amphiboles, crocidolite and amosite, the much faster dissolution rate of chrysotile compared to amphiboles prompts comparable amounts of available active surface iron within a short time frame [22].

The content and association of asbestos fibers with trace metals are important as these elements are capable of inducing lung cancer [28]. Asbestos fibers can act as carriers of trace elements [29] as well as PAH as described later in this chapter. Because chrysotile undergoes faster dissolution in comparison to amphibole asbestos, it may release its metal cargo in the lung environment, mimicking the phenomenon that explains the toxicity of nanoparticles. Hence, a non-biodurable fiber (e.g., chrysotile) should be undeniably considered less hazardous than a biodurable fiber (e.g., crocidolite: [30, 31]) but its rapid dissolution may prompt acute release of toxic metals in the intracellular/extracellular medium.

Biodurability

As introduced in the previous paragraph, a basic property of mineral fibers is their biodurability (see above), one of the two components of biopersistence [32, 33] which play a key role in the fibers' toxicity paradigm [34]: a fiber rapidly dissolving in lung fluids has a low biopersistence and is considered less harmful. It is long known that the

biodurability of chrysotile is much lower than that of amphibole asbestos [35, 36]. For long fibers that cannot be fully phagocytosed, biopersistence is a key determinant of potential toxicity over time. If long fibers are biosoluble in lung fluids, they can either dissolve or break apart into shorter fibers and be cleared. Long fibers which are not biosoluble will persist in the lung and initiate inflammatory and carcinogenic responses.

The amount of silica-rich reactive relicts produced during the dissolution of mineral fibers is another critical parameter that should be taken into account in assessing the toxicity/pathogenicity potential of a mineral fiber. In chrysotile, the first step of dissolution produces a "pseudomorphic" Si-rich amorphous phase [37] characterized by silanol groups (Si–OH) and ionized silanol groups ($Si–O^-$) that may prompt the production of HO• [38]. If this proviso is correct, when rating the toxicity/pathogenicity of a mineral fiber, one should consider the rate of production of reactive silica-rich relicts during the dissolution process [22]. The rate of release of metals must also be carefully evaluated as they display a catalytic activity with production of $HO^{\bullet}$ and other reactive species when they are available at the surface of the particles.

A re-evaluation of the content of metals in mineral fibers and their possible adverse effects in vivo considers the so-called "Trojan horse-type effect" observed for NPs [39]. In NPs, intracellular ion release elicited by the acidic conditions of the lysosomal cellular compartment is responsible for the sequence of events associated with their intracellular toxicity [40]. For a wide class of NPs, the acidic environment of the lysosomes triggers the release of relatively toxic ions in the cell and these ions can be the true mediators responsible for the observed intracellular toxicity profiles [40].

Surface Charge

Concerning the surface activity of mineral fibers, the ξ potential, a measure of the surface charge of particles, may correlate with a number of phenomena responsible for adverse effects [22]. A negative ξ potential may prompt the formation of $HO^{\bullet}$ in contact with peroxide and may favor the binding of collagen and redox-activated Fe-rich proteins. It may also affect crosstalk phenomena and apoptosis [41]. The ξ potential of mineral fibers also affects their agglomeration. This is a critical point as conditions having the highest degree of agglomeration induce highest biological responses [42]. Hence, fibers with low absolute values of ξ potential (i.e., tendency to agglomerate) are virtually more prone to cause adverse effects such as frustrated phagocytosis compared to fibers with high absolute values of ξ potential (i.e., stable) [22].

Interactions Between Cigarette Smoke and Asbestos Fibers Affecting Deposition in the Lung

Inhalation is the primary route of entry of asbestos fibers and components of cigarette smoke into the lung. The normal human lung is equipped with a battery of effective clearance mechanisms including a mucociliary escalator comprised of ciliated and mucin-secreting cells, alveolar and interstitial macrophages, and a lymphatic system allowing transfer of particles to distal sites and elimination from the body. Inhaled fibers first encounter a variety of inflammatory cell types and are also taken up by epithelial cells lining the airways and alveoli (Fig. 12.1). These are the cell types developing into bronchogenic and peripheral lung carcinomas.

Recent reviews point to the importance of asbestos fiber type, geometry, length, and high aspect (length to diameter) ratio as important determinants of cancer risk [43–46]. One reason is because long (>15–20 μm), thin amphibole fibers exceeding the cell diameters of human and rodent alveolar macrophages are cleared less effectively and remain in the lung. In contrast, both macrophages and lung epithelial cells engulf shorter fibers and transport them intra- or intercellularly to distal sites including the lung interstitium [47, 48].

Effects on Clearance Mechanisms

Several studies show that toxic components of cigarette smoke impair clearance of asbestos and other particles from the upper airways [49–52]. For example, smoking hinders the removal of amosite asbestos fibers after their intratracheal injection into rats [50, 51]. This is accompanied by toxicity to lung epithelial cells and increased penetration of fibers into airway walls. A comparison between asbestos fiber burdens in cigarette smokers versus never smokers, both groups with heavy occupational asbestos exposures, showed that cigarette smoking caused enhanced accumulation of both amosite and chrysotile asbestos in the airway mucosa [52]. Cigarette smoke or amosite exposures produced increased bromodeoxyuridine (BrdU) labeling, a marker of unscheduled DNA synthesis, in small airway walls, epithelial cells, and pulmonary artery cells, and a brief synergistic increase in cell labeling in the small airways was noted with both agents [53]. Tracheal organ cultures showed that amosite fiber binding to epithelial cells was a rapid process that was enhanced in the presence of cigarette smoke [54]. These authors concluded that iron on the surface of fibers was important in cellular adhesion of fibers to epithelial cells.

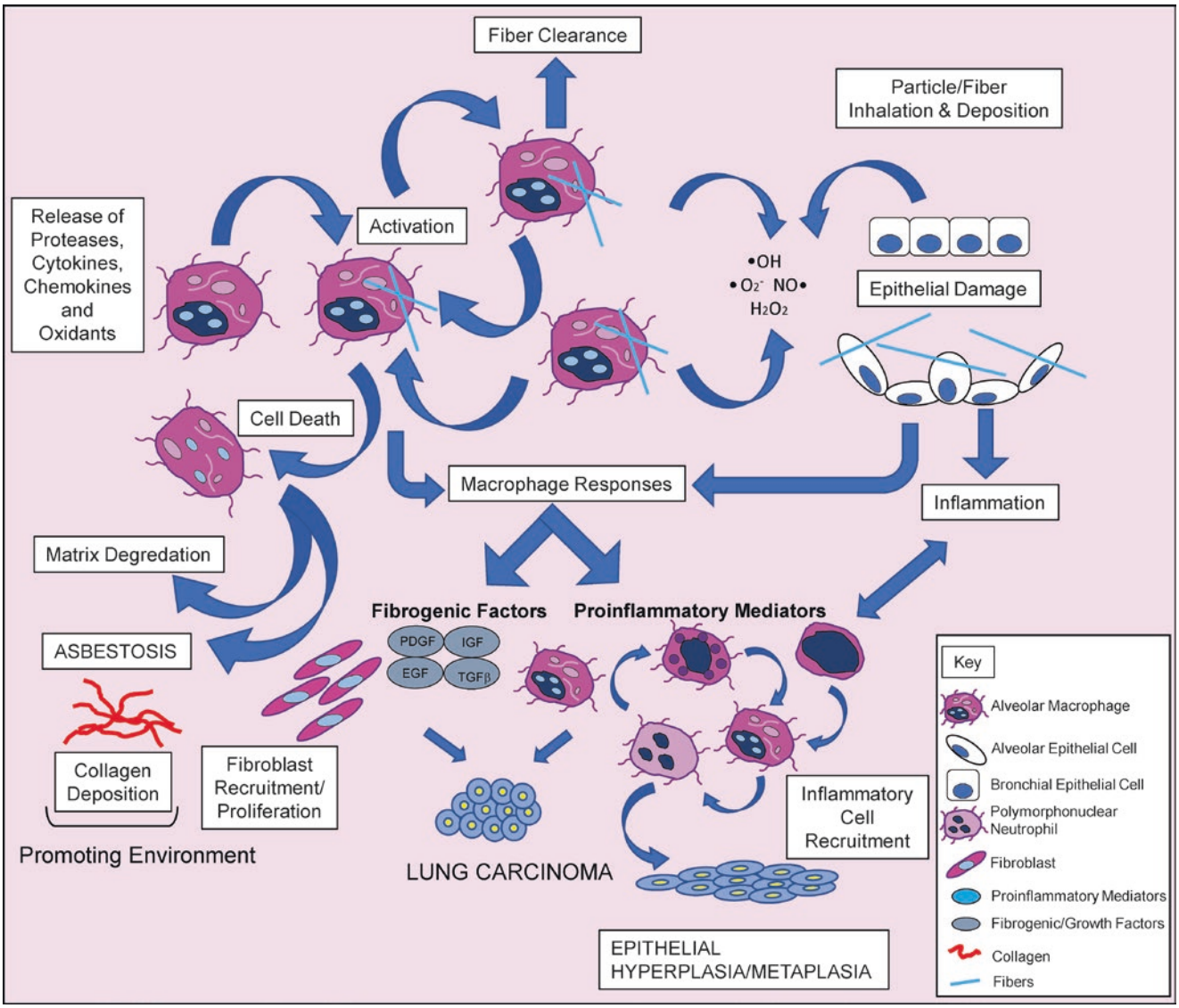

Fig. 12.1 A diagram illustrating the complex cellular responses in the lung after inhalation of asbestos fibers. The development of chronic inflammation and fibrosis (asbestosis) creates a lung microenvironment favoring lung carcinomas

Metabolism of Chemical Carcinogens

Asbestos fibers cause increases in uptake and metabolism of polycyclic aromatic hydrocarbons (PAH) by lung epithelial cells. PAH are perhaps the most widely studied chemical carcinogens of the many mutagenic and carcinogenic substances found in the particulate or vapor phases of cigarette smoke. They are known to form adducts with DNA that are linked to their carcinogenicity. PAH adhere to asbestos fibers and other particles in the atmosphere and are eluted from the particle surfaces in the upper airways [55]. In vitro studies have shown that dispersions of PAH alone are not readily taken up by tracheal epithelial cells. However, epithelial cell uptake and retention over time, as evidenced by adduct formation of PAH with DNA, are substantially increased when PAH are pre-adsorbed to chrysotile or crocidolite asbestos before their addition to cell cultures [56, 57].

Crocidolite asbestos and PAH interact synergistically to cause cell proliferation and squamous metaplasia, a preneoplastic lesion, in tracheal organ cultures [58]. Both agents are required for the development of tumors after implantation of explants into syngeneic animals [59, 60]. In assessing a number of particles (crocidolite asbestos, kaolin, carbon, hematite) as carriers of PAH in these studies, no tumors were observed with either particles or PAH alone. However, a direct relationship was observed between numbers of tumors and the amount of PAH adsorbed to particles when explants were exposed to PAH-coated particles.

The studies above suggest that asbestos and other particles act as vehicles for adsorption and delivery of chemical

carcinogens to lung tissues. Thus, doses to epithelial cells, the progenitor cell types of lung cancer, are increased. In addition, PAH and asbestos may cooperatively activate cellular pathways that are important in initiating hyperplasia or cell proliferation as well as squamous metaplasia, critical early lesions in the development of lung carcinomas. (See also Chap. 13: Co-carcinogenesis of PAH and inhaled particulates)

The induction of squamous metaplasia by cigarette smoke was noted in humans by Auerbach [61] and has been widely studied in hamster and human tracheal explants using a variety of particles of different geometries and dimensions [58, 62–66]. In these models, the severity and extent of squamous metaplasia are dose-related when long (>10 μm length) rod-like fibers are added to explants. These fibers serve as matrices for epithelial cell proliferation, whereas short fiber analogs and cleavage fragments do not.

Modern Concepts of Carcinogenesis

The majority of chemical carcinogens tested in bacterial and mammalian cell assays are mutagens that directly interact with DNA or require cell metabolism to do so. Mutations are also caused by replication errors and heredity, giving rise to a hypothesis in which the overwhelming drivers of cancer risk are accumulated mutations [67]. This model has been criticized by some as it does not reflect the importance of tissue microenvironments, evolutionary processes, and epigenetic events in tumor development [68].

In a two-step model of carcinogenesis developed in the 1960s [69], "initiation" of cancers was viewed as an irreversible effect caused by a heritable mutation in DNA, whereas the second stage, "promotion" encompassed a series of events during the period from initiation to the demonstration of frank cancers. This model has evolved into a contemporary multi-step model of tumor progression defined broadly as a stepwise series of events favoring increased genomic instability of cells during which they acquire invasive and metastatic properties. During tumor promotion and progression, premalignant cells are rapidly dividing, and additional errors in DNA replication and repair accrue. Emphasis in cancer research has shifted from studying mutations and genetic changes in DNA to revealing proteins and transcription factors that stimulate cell signaling and mitochondrial pathways necessary for malignant tumor development [70].

The term "epigenetics" has evolved over time to explain traits not involving alterations in the primary structure or sequence of DNA. According to definition, "an epigenetic trait can be a stable inheritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" [71]. Epigenetic events also can be reversible as a result of many repair pathways.

Multiple modes of epigenetic signaling have been recognized including DNA methylation, histone modifications, chromatin remodeling, and effects induced by noncoding RNAs, a class of regulatory molecules that control gene expression by binding to complementary sites on target messenger RNA (mRNA) transcripts. Noncoding RNAs can be long (lncRNAs) or short (miRNAs) and can alter expression of multiple mRNAs. Downregulation of certain miRNAs is observed in a number of human cancers, suggesting their functional similarities to tumor suppressor genes. Other miRNAs can regulate cell differentiation and programmed cell death, i.e., apoptosis. For these reasons, they are under investigation as biomarkers, prognostic factors, and therapeutic targets in lung cancers (see below).

It is important to recognize that there are many different manifestations of toxic injury at the cell and tissue level that are dependent on concentration, type, and other properties of mineral fibers. For example, at high concentrations of agents, cell death frequently occurs, precluding transfer of mutagenic and other heritable alterations to cell progeny. However, at low concentrations, cells may remain intact or exhibit uncontrolled cell proliferation and other heritable, functional and phenotypic changes that may be critical to tumor development. Often the term "genotoxicity," i.e., alterations in the genome of cells resulting in cell death, altered function or division of cells, is used incorrectly and synonymously with "carcinogenicity" in the scientific literature.

Genetic Alterations in Human Lung Cancers by Cigarette Smoke and Asbestos

Certain oncogenes and tumor suppressor genes are the likely targets of somatic alterations resulting from tobacco smoke carcinogens including PAH, nitrosamines, and aromatic amines [reviewed in [1]]. Karyotypic analyses and molecular screening show that lung cancer cells typically demonstrate dozens of genetic lesions including aneuploidy gene copy number alterations, and alterations in proto-oncogenes or their encoded proteins. These changes include mutations in growth factor receptors, tyrosine and serine-threonine protein kinases (both receptor and non-receptor-related), membrane-associated G proteins, and nuclear transcription factors.

Oncogenes

The most common aberrations in lung cancers are overexpression (due to mutations and/or chromosomal rearrangements) of members of the epidermal growth factor receptor (ErbB family) of tyrosine kinases. These include ERBB1 (also known as EGFR) and ERBB2. Chromosomal

rearrangements involving the tyrosine kinase anaplastic lymphoma kinase (ALK), ROS1, and an orphan receptor tyrosine kinase also are noted. Mutations in KRAS correlate with smoking history and occur more frequently in tumors from former or current smokers [72], and mutations in BRAF (a downstream effector of the RAS pathway) are also observed. Amplification and/or mutations in the nuclear transcription factors MYC, MYB, JUN, and FOS also occur in lung tumors although their precise roles in lung carcinogenesis are unknown [1].

Tumor Suppressor Genes

A number of tumor suppressor genes (TSG) also undergo structural abnormalities and loss of function in lung cancers. These include TP53, genes in the RB1/Cyclin D1/CDK4/CDKN2A pathway, candidate chromosomal 3p tumor suppressor genes, and the LKB1/STK11 gene. Involvement of other tumor suppressor genes has been suggested based upon the loss of many corresponding chromosomal regions in lung cancers [1].

Modern technology has enabled genome-wide investigation of somatic mutations as well as gene expression profiling of lung cancers. Most recently, knowledge of gene deregulation caused by cigarette smoking and persisting after smoking cessation has been obtained from a gene expression (mRNA profiling) study that examined human airway epithelial cells isolated from bronchoscopy in smokers and never smokers [73–75]. A gene biomarker panel could distinguish between smokers with and without lung cancers [75].

A recent examination of mutations by exome sequencing in lung adenocarcinomas in Finnish patients with occupational exposures to asbestos suggests that smoking is an overriding confounder in interpretation of results [76]. Only 1 tumor from 26 patient samples was from a never smoker. KRAS mutations occurred in 42% of patients with and without exposures to asbestos, and less frequent BRAF mutations were also observed. Both mutations were associated with smoking, but not asbestos exposures. Moreover, no activating EGFR mutations could be attributed to asbestos exposures.

Another study explored the occurrence of somatic mutations (EGFR, ERBB2, HER2, KRAS, BRAF, PIK3 kinase, and ALK) in lung cancers from never smokers with occupational exposures to asbestos, silica, diesel exhaust fumes, chrome, and paints [77]. Asbestos-exposed patients exhibited a significantly lower rate of EGFR mutations but a higher rate of less frequent HER2 mutations. These investigators concluded that occupational exposures "slightly affect the molecular pattern of lung cancers in never smokers" [77]. The studies summarized above indicate that driving mutations by asbestos in lung cancers are absent or obscured by changes rendered by cigarette smoking.

Epigenetic Effects of Asbestos in Lung Cancers and Human Bronchial Epithelial Cells

Epigenetic markers include: (1) Noncoding RNAs, including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs); (2) Histone modifications, DNA methylation changes, and chromatin remodeling.

Noncoding RNAs

Small single-stranded RNA molecules have been widely studied in lung cancers [reviewed in [78–80]]. Over 30% of exons (protein-coding human genes) are regulated by miRNAs, and an estimated 1000 or more human miRNAs exist [81]. Nucleotide precursors, i.e., pre-miRNAs, are transported from the nucleus into the cytoplasm where they are further processed to generate a mature, double-stranded duplex (miRNA/miRNA) as part of an RNA-induced silencing complex (RISC). RISC and its miRNA complex then bind to a number of target mRNAs to cause cleavage or translational repression. miRNA loss and downregulation have been observed in a number of tumor types including lung cancers [78–80] and mesotheliomas [82]. In contrast to miRNAs, long noncoding RNAs (lncRNAs) have not been studied as intensely but are important in epithelial mesenchymal transition (EMT), tumor progression, and metastases [83]. LncRNAs function as chromatin modulators in that they target histone-modifying enzymes to repress homeobox transcription factor (HOX) genes aberrantly expressed in some tumors [84] as well as genes suppressing metastases [85].

Histone/DNA Modifications

Histone acetylation (addition of $–COCH_3$) and removal, i.e., via deacetylation and methylation, affect nucleosome–DNA interactions and result in altered gene expression. In general, acetylation has been linked to increased accessibility of DNA as euchromatin, whereas methylation causes condensation of chromatin, making it inaccessible for transcription. The most frequently studied epigenetic marker is DNA methylation, a process catalyzed by DNA methyl transferases (DNMT) and resulting in covalent attachment of a methyl group to cytosine. This also occurs at sites of CpG dinucleotides located within the promoter regions of genes.

Aberrant DNA methylation, characterized by hypermethylation of CpG islands, as well as hypomethylation of other regions occurs commonly in several tumor types. These alterations lead to silencing of tumor suppressor gene and/or genomic instability [86]. Overall, human tumors show global hypomethylation or hypermethylation of CpG islands. Methyl-DNA binding domain (MBD) proteins interact with different chromatin-modifying proteins to form compact chromatin with repression of transcription. Different CpG island methylation patterns recruit different sets of MBD proteins that may assume unique functions. These changes may also be important in epithelial cell gene silencing, the development of EMT, and the evolution of tumors [87].

DNA Methylation Changes in Lung Cancers and Mesotheliomas

Although epigenetic signatures have been widely studied in lung cancers in general [reviewed in [1, 78–80, 88, 89]], and less frequently in mesotheliomas [reviewed in [3, 82, 90]], little information is available on epigenetic changes by cigarette smoke or asbestos in lung tumors or human bronchial epithelial cells. Recently, asbestos and smoking associated genome-wide DNA methylation were examined in lung cancer tissues from asbestos-exposed or non-asbestos-exposed patients [91]. Both groups consisted of mostly smokers. Hypomethylation was an overall characteristic of differentially methylated regions (DMR) in lung cancers from asbestos-exposed patients. Moreover, when patterns of methylation in asbestos-related vs. "mostly smoking related" tumors were compared, novel methylation changes appeared to be specific for each of the two risk factors.

Aberrant methylation of the CDKN2A/p16INK4A gene promoter region and other TSGs that have been associated with cell cycle control has been reported in human mesotheliomas [92]. The *CDKN2A* locus encodes the tumor suppressor proteins, p16INK4 and p14ARF known to regulate the Rb and p53 cell cycle regulatory pathways. In these patients, lung content of asbestos (ferruginous) bodies was measured as an indication of exposures to asbestos. These studies are important as they show a direct relationship between numbers of asbestos bodies and increases in methylation changes related to gene silencing, thus providing a causal link between asbestos, methylation of TSGs, and the development of tumors. Loss of CDK2NKB function has also been noted in both lung cancers [reviewed in [1]] and experimental models of mesothelioma, where increased sensitivity to crocidolite asbestos reflected increased numbers of tumors with decreased latency periods in knockdown animals [93].

Methylation status of the CDKN2A gene has also been evaluated in precancerous bronchial lesions from a series of 37 patients at high risk for lung cancer [94]. Aberrant methylation of the CDKN2A promoter was found in 19% of preinvasive lesions. Increases in frequency occurred with the severity of lesions, suggesting its causal relationship to the development of lung cancers.

Asbestosis is a lung disease where increased interstitial accumulation of asbestos fibers occurs in the lung with the development of chronic inflammation and thickening of lung matrix. A recent study evaluated the functional ramifications of loss of CDKN2B function in lung tissues and isolated lung fibroblasts from patients with idiopathic pulmonary fibrosis (IPF), an interstitial disease with many similarities to asbestosis in that proliferation of lung fibroblasts and their differentiation to myofibroblasts occur [95]. In comparison to normal controls, fibroblasts from patients with IPF showed hypermethylation at the CDKN2B gene locus, and decreased protein expression in lungs was localized to regions of myofibroblast and fibroblast accumulation. Targeted overexpression or silencing of CDKN2B caused inhibition of or increased myofibroblast differentiation, respectively, but did not affect cell proliferation *per se*. Cdkn2b knockout mice also developed more fibrosis after exposures to bleomycin when compared to wild-type rodents. Although CDKN2B is traditionally regarded as a cell cycle inhibitor, its roles in proliferation and altered differentiation may be multi-faceted.

DNA Methylation Changes by Asbestos

A very recent study has documented global and gene-specific DNA methylation effects of different types of asbestos fibers on immortalized human bronchial epithelial cells [96]. DNA methylation on CpG sites was evaluated as these are the most common sites of altered DNA methylation in cancers. Global DNA methylation on total cytosine residues was quantified over a range of asbestos concentrations, and subsets of differentially methylated genes at a single concentration of each fiber type (amosite, crocidolite, and chrysotile) were examined. Since asbestos exposures in vitro are typically at high concentrations of fibers that induce chromosomal aberrations, micronuclei formation, and DNA strand breaks in rodent cells, a COMET assay for DNA strand breaks was used to show the correlations between DNA damage and cell viability in human cells. Comparisons here showed that chrysotile asbestos was most damaging to cells at equal weight concentrations when compared to both amphibole types of asbestos. Also noteworthy was the detection of dose-related DNA damage at amounts of dusts not affecting cell viability, suggesting the effectiveness of DNA repair processes at lowest concentrations of asbestos fibers.

Others have shown that chrysotile is more cytotoxic than crocidolite or amosite asbestos on an equal mass or fiber concentration basis in rodent and human lung epithelial and

mesothelial cells [97–99]. Moreover, large-scale deletions incompatible with cell viability have been noted by chrysotile in a hamster-human hybrid cell mutation assay [100]. However, despite the increased cytotoxicity of chrysotile, global DNA methylation was only observed after exposures to crocidolite or amosite asbestos—no changes were observed at the lowest concentrations of amphibole fibers indicating a threshold effect [96]. Exposure to either amphibole type induced global hypo- and hypermethylation at CpG sites, whereas exposure to chrysotile induced differential methylation only in gene promoter regions with a different frequency distribution. Hierarchical clustering of gene-specific DNA methylation patterns also showed differential clustering in chrysotile-exposed cells. Gene functional classification of shared genes methylated after exposure to all types of asbestos revealed five common clusters related to: (1) nuclear (homeobox or HOX) transcription factors that control embryogenesis; (2) ATP binding functions; (3) Rho proteins and serine-threonine and tyrosine protein kinases; (4) Wnt signaling family members; and (5) Ankyrin repeat domains and NF-KB inhibition.

Epigenetic signatures and RNA profiling (described below) are promising as they detect changes specific to smoking or asbestos exposures. In addition, they appear to reveal differences between types of asbestos and inhaled minerals that may reflect their respective pathogenic potentials in lung and pleural diseases. Dose–response experiments suggest a threshold for responses as has been demonstrated for chrysotile exposures in human lung cancers [101]. Lastly, once gene promoter methylation targets, i.e., specific genes, are identified, overexpression and inhibition studies can be performed to determine the functional significance of these events in carcinogenesis.

RNA Profiling Studies and Asbestos-Induced Pulmonary Responses in Animals

Inhalation is the physiological route of exposures to mineral fibers, but long-term inhalation experiments are expensive and time-consuming [reviewed in [99]]. Whereas experiments using intratracheal instillation and injection of particles have many limitations [99, 102], oropharyngeal aspiration provides dissemination of materials throughout the lung without impairment of clearance mechanisms.

Gene expression profiles (mRNA profiling) have been recently examined in mice after a single oropharyngeal aspiration of asbestos fibers (crocidolite, tremolite), erionite (a non-asbestos fiber associated with increased mesotheliomas and lung cancers in humans), and wollastonite (a fiber not associated with adverse health effects) [103]. Inflammatory cell and cytokine changes and tissue responses were evaluated at days 1, 7, and 56 days post exposures, and a high-throughput mRNA microarray analysis was performed at 7 days. To identify pathways and networks perturbed by various fiber preparations, ingenuity pathway analysis was performed on differentially expressed gene expression. The targeted dose of each fiber preparation was calculated as 8.8×10^7 fibers/mouse although it was noted that the total numbers of fibers for erionite or wollastonite were less than asbestos fibers. The crocidolite preparation had the greatest range of fiber lengths and high aspect ratios followed by tremolite, erionite, and wollastonite that consisted almost exclusively of shorter, low aspect ratio fibers. Overall, the severity of both inflammation and fibrosis was greatest with crocidolite, but cytokine responses were different with erionite and wollastonite exposures as compared to the two asbestos types. Analyses of the top 10 significantly upregulated vs. downregulated genes in each of the four treatment groups showed only one common gene (chloride channel accessory 1 or CLCA1) that was upregulated in all mineral groups. The variability in data may reflect the fact that whole lung homogenates consisting of multiple cell types and the small numbers of animals (N = 3/group) were analyzed in gene profiling experiments.

Cell Signaling Pathways

Cell signaling pathways are other routes linked to altered cell proliferation and differentiation that are perturbed by asbestos fibers as they come in contact with lung epithelial cells. Many of these pathways are also stimulated after interaction of fibers with receptors on cells or by active oxygen and nitrogen species (ROS/RNS) that are generated by fibers (see below). Alternatively, crosstalk between macrophages and/or lung fibroblast and epithelial cells stimulates many cell signaling pathways as well as cytokine circuits that may cause epithelial cell proliferation or injury [reviewed in [99]]. As indicated in Fig. 12.1, circuits of activated macrophages and other immune cell types may amplify these responses.

After exposures in vitro to long (>10 μm), thin fibers, epithelial cells exhibit many alterations in mitogenic signaling pathways that are linked to increased survival, proliferation, and disruption of cell cycle control. Activation of receptor tyrosine kinases (RTK), mitogen activated protein kinases (MEK1 or Ras/Extracellular Signal Regulated Kinases (ERK1/2)), and phosphatidyl 3-kinase (PI3)-kinase/AKT pathways are events observed after exposures to asbestos fibers [reviewed in [99, 104–113]]. These signaling pathways and their protein targets can be stimulated by: (1) increased activity of RTKs or their receptors and ligands; (2) phosphorylation or dephosphorylation of specific kinases; (3) increased activation and binding of transcription factor proteins to target genes; and (4) inactivation of negative regulators in these cascades.

Lung epithelial cells express a number of cytokine and chemokine receptors that trigger inflammation and cell proliferation. Cells also respond to a broad array of growth factors that are stimulated by autocrine or paracrine mechanisms, including epidermal growth factor (EGF), keratinocyte growth factor (KGF), hepatocyte growth factor (HGF), tumor necrosis factor α (TNF-α), interleukin 8 (IL-8), fibroblast growth factors (FGFs), transforming growth factor β (TGF-β), and insulin-like growth factor 1 (IGF-1) [reviewed in [99]].

Activation of the MEK1/ERK1/2 cascade results in induction of AP-1, a heterodimeric transcription factor comprised of members of the c-Fos and c-Jun proto-oncogene families. These kinases in turn phosphorylate a number of intracellular substrates and increase gene expression of respective proto-oncogenes as well as other proliferation-related genes such as *cyclin D1*. After inhalation of crocidolite asbestos, cell-specific increases in unphosphorylated and phosphorylated ERK1 and ERK2 are noted in bronchiolar and alveolar type II epithelial cells in areas of epithelial cell hyperplasia [104]. Asbestos-exposed transgenic mice expressing a dominant-negative MEK1 targeted to lung epithelial cells to inhibit this signaling pathway show less cell proliferation in response to asbestos, suggesting a causative role of ERK1/2 signaling in lung epithelial cell proliferation [105]. Related studies have indicated that crocidolite asbestos causes increased c-Jun expression in tracheal epithelial cells [106] and in lung homogenates after inhalation in a dose-related fashion [107]. These changes are not observed after exposures to riebeckite or polystyrene beads in vitro [106, 109].

Crocidolite asbestos fibers also cause dose-dependent proliferation of lung epithelial and pleural mesothelial cells after inhalation that are sustained after cessation of inhalation [reviewed in [99, 107, 108, 110]]. Epithelial cell proliferation at high airborne concentrations of crocidolite is accompanied by inflammatory and fibrotic changes that are known to perpetuate lung cancers.

EGFR Receptors

Mutation or activation of EGFR receptors is linked to stimulation of a number of cell signaling cascades including MEK1/ERK1/2 and the AKT pathway. Long crocidolite asbestos fibers activate the EGFR via direct membrane interactions or by affecting the kinetics of EGFR binding to its ligands [111, 112]. A direct link between the EGFR and expression of Fos and Jun family members has been shown in mutant EGFR mice exhibiting loss of function in pulmonary epithelial cells [113]. After inhalation of crocidolite asbestos, mice with downregulation of EGFR exhibit loss of epithelial cell proliferation and no increases in Fos/Jun expression [113]. As emphasized above, gain of function mutations of the EGFR receptor family and consequent upregulated signaling cascades are a feature of many lung cancers, and blockade of EGFR signaling is an approach used in patient populations demonstrating mutations and other anomalies in this pathway [114].

Uptake of Asbestos Fibers by Lung Epithelial Cells

In tracheal or lung epithelial cells, short asbestos fibers and fragments are incorporated into membrane-bound phagolysosomes without morphologic or quantitative decreases in cell viability [47, 97, 99]. Fibers less than 5 μm in length accumulate in the perinuclear region of lung epithelial cells and are presumably transported away from a forming mitotic spindle [115]. However, long, thin crocidolite fibers may orient parallel to the mitotic spindle and attach to the nuclear envelope, sterically blocking cytokinesis when cells divide. Interactions between lung epithelial cells and crocidolite asbestos fibers were studied using high resolution time lapse video-enhanced microscopy during mitosis [116]. These studies showed that physical interactions between long crocidolite fibers and chromosomes occurred randomly and infrequently with most crocidolite-containing cells completing mitosis normally. Although physical interactions of crocidolite asbestos fibers with DNA have been suggested as a mechanism of aneuploidy, studies with lung fibroblasts show that intracellular asbestos fibers induce aneuploidy by binding to a subset of intracellular proteins that regulate the cell cycle and cytoskeleton [117].

The kinetics of uptake of asbestos fibers by different cell types in the lung and pleura may be different. For example, human mesothelial cells are more sensitive than human bronchial epithelial cells and fibroblasts to the cytotoxic and genetic changes triggered by amosite asbestos, phenomena linked to increased uptake of fibers by human mesothelial cells [98]. Species-specific differences in DNA repair may also be relevant to cell response. For example, in contrast to crocidolite, chrysotile is 100 to 300 times more toxic to human bronchial epithelial cells but does not induce significant numbers of chromosome changes [118]. Micronuclei formation, i.e., small fragments of chromosomes, is observed as a consequence of chrysotile but not of crocidolite exposures. Overall, changes in chromosomal stability are more infrequent than reports in the literature using rodent cells.

The Role of the Lung Microenvironment in Lung Cancer Development

Lung epithelial cells are critical in repair of the lung after exposures to cigarette smoke or asbestos. Epithelial cells interact with macrophages and other cells of the immune

system as well as other cell types to maintain the normal architecture of the lung. However, epithelial cell perturbations and lung cancers occur when the normal defense mechanisms of the lung are overwhelmed.

Chronic Inflammation

The interplay between alveolar macrophages, polymorphonuclear leukocytes (PMNs), and epithelial cells in early injury by asbestos fibers has been studied historically in acute inhalation studies [reviewed in [99, 119, 120]]. Tumor-associated macrophages are also critical to establishing and maintaining lung cancers as well as promotion of metastases [reviewed in [121, 122]].

Early inflammation after exposure to asbestos is characterized by activation of multiple signaling pathways in activated macrophages and epithelial cells that produce a number of cytokines and chemokines affecting cell function and repair [reviewed in [99]]. At concentrations of fibers causing overload of defense mechanisms, more cells may be recruited to sites of fiber injury, leading to chronic inflammation and disease. For example, NADPH oxidases are upregulated and activated in cells after frustrated phagocytosis of long fibers [123] and in epithelial cells forming carcinomas [124]. Oxidants are generated via an NADPH-dependent process, inducing genetic and epigenetic changes [reviewed in [125]].

Inflammatory processes including ROS induce a number of epigenetic events linked to tumorigenesis, and fibrosis [121, 126, 127]. Moreover, chronic inflammation is associated with the development of fibrosis and lung cancers both in animal models [reviewed in [99]] and humans [119, 124]. Rodent inhalation studies by Davis and colleagues emphasize the importance of long fibers in inflammation, asbestosis, and lung cancers [128–130].

Inflammasomes

Inflammasomes play critical roles in the development of chronic inflammation, pulmonary fibrosis, and lung cancers. "Inflammasomes" are cytoplasmic protein complexes activated upon recognition of a number of diverse "danger signals." Their assembly and activation are associated with exposures to pathogenic particles and fibers in a number of cell types [131]. Macrophages have been studied most frequently with regard to the mechanisms of uptake of exogenous crystals such as silica, asbestos, and nanomaterials and consequent activation of the NLRP3 inflammasome [reviewed in [132]]. Priming and activation of the NLRP3 inflammasome are linked causally to early inflammation and cytokine release after inhalation of chrysotile asbestos in rodents [123], and a number of particle characteristics have been linked to inflammasome activation by different pathogenic fibers and particles [reviewed in [131]].

A recent review summarizes the multi-faceted roles of different inflammasomes in lung cancers and other tumors, emphasizing their distinct roles in release of inflammatory cytokines, cell death, and tissue repair [133]. Cigarette smoke causes activation and release of IL-1B and CXCL-8, critical inflammatory cytokines produced after inflammasome activation, from human bronchial epithelial cells [134]. A number of other alterations in immune response and cell proliferation have been linked to inflammasome activation in lung cancers including establishment of a lung microenvironment that permits growth, progression, and metastases of lung tumors [reviewed in [133]].

ROS, including mitochondrial-derived oxidants, are known effectors of inflammasome activation and function [reviewed in [131]]. Mitochondrial DNA damage and apoptosis are noted in alveolar epithelial cells after exposure to amosite asbestos [135] and mitochondrial-derived oxidants contribute to crocidolite asbestos-induced gene expression of NF-κB and MIP-2 [136]. Accumulation of the NLRP3 inflammasome in cytosol is dependent upon its production by NF-κB signaling and removal by autophagy. The priming, assembly, and activation of inflammasomes are threshold-like responses in cells exposed to asbestos fibers as are the stability of cytokine and inflammation networks, and the spread of inflammation [137]. These damage thresholds reflect cooperativity of a number of antioxidant pathways and repair responses at low exposures to asbestos fibers. However, at high occupational exposures, interstitial disease or asbestosis can occur and this may create a lung environment conducive to the development of lung tumors (see Fig. 12.1).

Interstitial Accumulation of Asbestos and Formation of Asbestos Bodies

If both mucociliary clearance of inhaled fibers and phagocytosis of fibers by macrophages fail, the ultimate response to interstitial fibers is isolation of the invading fiber via encapsulation inside the so-called *asbestos body* (AB). The first AB was observed in 1906 in a human lung as pigmented crystal [138], but was at that time called *asbestosis body* [139]. Only later the term was substituted by *asbestos body* when these aggregates were discovered in patients with lung diseases other than asbestosis [140].

When ABs were found to grow also around fibers other than asbestos (e.g., Al-silicates and glass fibers) or around particles of uncertain nature, the term *ferruginous body* was applied [141]. The term *asbestos body* is now generally used to indicate bodies containing asbestos fibers while the term *ferruginous body* or *pseudoasbestos body* is applied to all non-asbestos-containing aggregates [142].

The coating process of the particles is mediated by iron with the ferritin core of ABs composed of ferric oxyhydroxide (FeOOH or $FeOOPO_3H_3$ if phosphate is present [143]). Besides iron and phosphorus, calcium and magnesium may also participate in the coating process (see, for example, [144]). AB formation is extracellular and the various configurations found around the fibers might reflect repeated contact of the same AB with different macrophages [145]. ABs can be formed within 2–3 months of exposure in rats, with a time span of formation in animals similar to humans [146]. A shared mechanism of formation of ABs points to a biological origin via intracellular coating that begins with deposition of a ferritin layer around the fibers. The formation of ABs is certainly a complex and not yet fully understood mechanism that involves many distinct parameters such as the nature of the inhaled fiber, its morphometry, the coating efficiency of the animal host, and the fiber entry process. Differences in accumulation of amphibole asbestos vs. chrysotile fibers within the lungs of different animals following long-term inhalation exposures indicated that the relative retention of amphibole asbestos fibers in the lungs was higher than that of chrysotile [147].

In a recent study aimed at understanding the process of formation of ABs, FEG–SEM (field emission gun-scanning electron microscopy) and μ-Raman were used to investigate the characteristics of both fibers and ABs formed in rats after a single intraperitoneal or intrapleural injection of selected mineral fibers [148]. Regarding the residual fibers found in the tissues of the rats, chrysotile showed a mean fiber length ranging from 14.3 to 15.8 μm with diameters in the range 0.45–0.54 μm. The average size of chrysotile fibers encapsulated in ABs was 29.6 μm in length and 0.5 μm in diameter. Leaching of Mg from chrysotile was also observed in agreement with reports in the literature data [149]. Remarkable variations in size and morphology of ABs formed around chrysotile fibers were noted. Their size ranged from 1.5 to 20 μm in length and from 0.6 to 15 μm in diameter. Uncoated fibers were detected in all samples. The percentage of coated fibers was 3.3%. This relative amount did not change over time, indicating that the number of ABs does not increase with time.

Crocidolite fibers displayed a mean length ranging from 13.7 to 18.6 μm with diameters in the range 0.54–0.71 μm. The mean size of crocidolite fibers producing ABs was 41.0 μm in length and 0.86 μm in diameter. For crocidolite, the size of ABs varied in length from 4 μm to 25 μm, and from 4 μm to 8 μm in diameter. ABs were predominantly formed on long crocidolite fibers and could occur around a single fiber as well as around clusters of particles. Most of the observed fibers were uncoated. The percentage of coated fibers was 6.0% and the relative amount did not change with time.

There were no differences in the characteristics of ABs formed in the pleural and peritoneal cavities. ABs appeared around chrysotile and crocidolite fibers in less than 40 weeks. Such short times of formation are in line with human observations [150]. The large morphological variability of ABs suggests that a high concentration of fibers prompts changes in the shape of ABs and favors the appearance of new forms [151].

Diminished generation of oxidant species and reduced toxicity of coated fibers with respect to uncoated fibers have been reported by many authors [150]. The limited number of coated fibers observed in the tissue of the rats after intrapleural or intraperitoneal injection may be due to both fiber overload and the lack of nutrients, specifically Fe, P, and Ca, to form the asbestos coating. Fibers found in human lungs also display variable degrees of coating and morphologies of ABs. Figure 12.2 portrays examples of naked (a) and coated (b) crocidolite fibers found in the lungs of a patient with occupational exposure to asbestos.

More extensive reviews on ferruginous bodies are provided [150, 152–154].

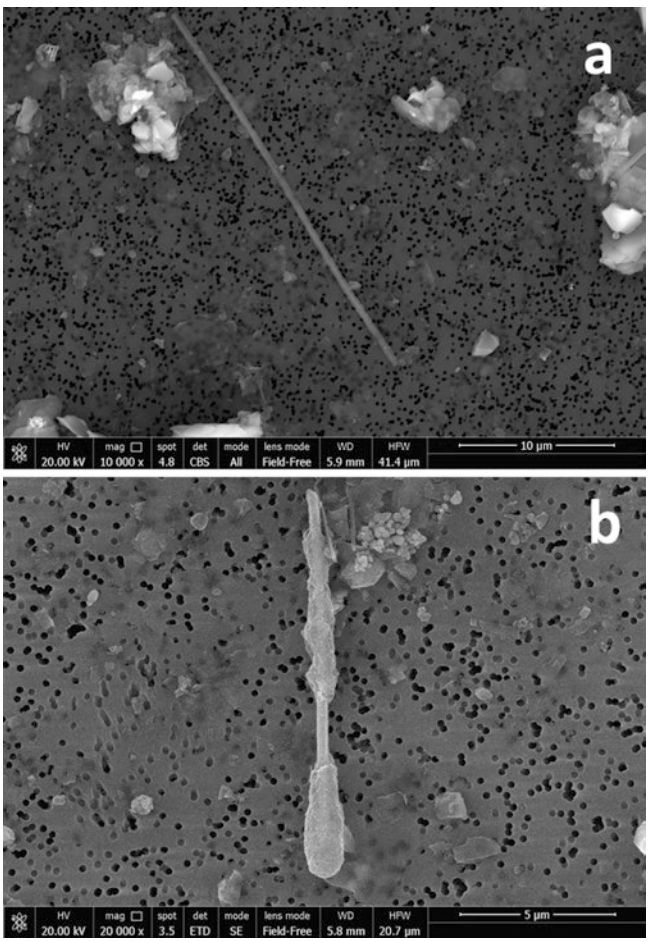

Fig. 12.2 Naked (**a**) and coated (**b**) crocidolite fibers found in the lung lobe of the human lung of a patient developing lung cancer after occupational exposure to asbestos

Towards a Predictive Model of the Potential of Mineral Fibers to Induce Lung Cancer

Recently, a quantitative predictive model for toxicity/pathogenicity of mineral fibers has been developed based upon the physical/chemical and morphological parameters described above [155]. The model derives a Fiber Potential Toxicity Index (FPTI) to predict and rank the toxic and pathogenic potential of asbestos fibers, unregulated/unclassified fibers, and other elongated mineral particles (EMP). The parameters of the model that have been considered are: 1. *Morphometric parameters*: (1,1) mean fiber length, (1,2) mean fiber diameter, (1,3) crystal curvature, (1,4) crystal habit, (1,5) density, (1,6) hydrophobic character, (1,7) specific surface area; 2. *Chemical parameters*: (2,1) iron content, (2,2) content of ferrous iron, (2,3) surface iron and its nuclearity, (2,4) content of metals other than iron; 3. *Biodurability-related parameters*: (3,1) dissolution rate, (3,2) rate of iron dissolution/release, (3,3) rate of silica dissolution/release, (3,4) rate of release of metals from the fiber; 4. *Surface activity-related parameters*: (4,1) ζ potential, (4,2) aggregation state of the fibers in suspension, (4,3) cation exchange capacity (from fibrous zeolite species).

A score is assigned to each parameter depending on its measured value. For example, the mean fiber length L of a fiber species (1,1) takes a score $T_i = 0.1$ if 5 μm < L < 10 μm, $T_i = 0.2$ if 10 μm < L < 20 μm, and $T_i = 0.4$ if L > 20 μm. Because the parameters of the model can be correlated with each other, a hierarchical scheme taking into account cross-correlations was developed. Figure 12.3 [modified after [155]] depicts the scheme of the hierarchical clustering of the FPTI model. A weighing scheme is associated with each parameter of the model according to its step/hierarchy H where $w_1 = 1/H$ with H = 1, 2, or 3. A weight defined as $w_2 = 1/U$ is also applied to each parameter of the model. It accounts for the uncertainty in the determination of a specific parameter (n,m) and is defined by the penalty parameter U (1 = low to null uncertainty, 2 = some degree of uncertainty, 3 = high uncertainty). Having defined the weighing scheme of the parameters, the FPTI_i of each fiber is calculated according to the equation:

$$\mathrm{FPTI}_i = \sum_{i=1}^{n} w_1 \cdot w_2 \cdot T_i$$

with T_i = class value of the parameter i of the model; $w_1 = 1/H$ weight of the parameter according to its hierarchy H; $w_2 = 1/U$ weight of the parameter according to the uncertainty U of its determination. In the example above of the mean fiber length L, both $w_1 = 1/H$ and $w_2 = 1/U$ are = 1 because $H = 1$ and $U = 1$.

The FPTI has been calculated for some mineral fibers of social and economic importance [155], and it was found that all the amphibole asbestos species (amosite UICC standard, South African, NB #4173–111-4; anthophyllite UICC standard asbestos, Finnish NB #4173–111-5; crocidolite UICC standard, South African, NB #4173–111-3; fibrous fluoroedenite from Biancavilla, Sicilia (Italy); and tremolite asbestos from Val d'Ala, Turin, Italy) display FPTI values >2.50, whereas chrysotile asbestos samples (chrysotile from Balangero, Torino, Italy; chrysotile "B" asbestos UICC standard; chrysotile from Valmalenco, Sondrio, Italy) have values in the range 2.00–2.30. FPTI values <2.00 have been derived from nonpathogenic mineral fibers (fibrous sepiolite from Vallecas (Spain) and wollastonite NYAD G [156]).

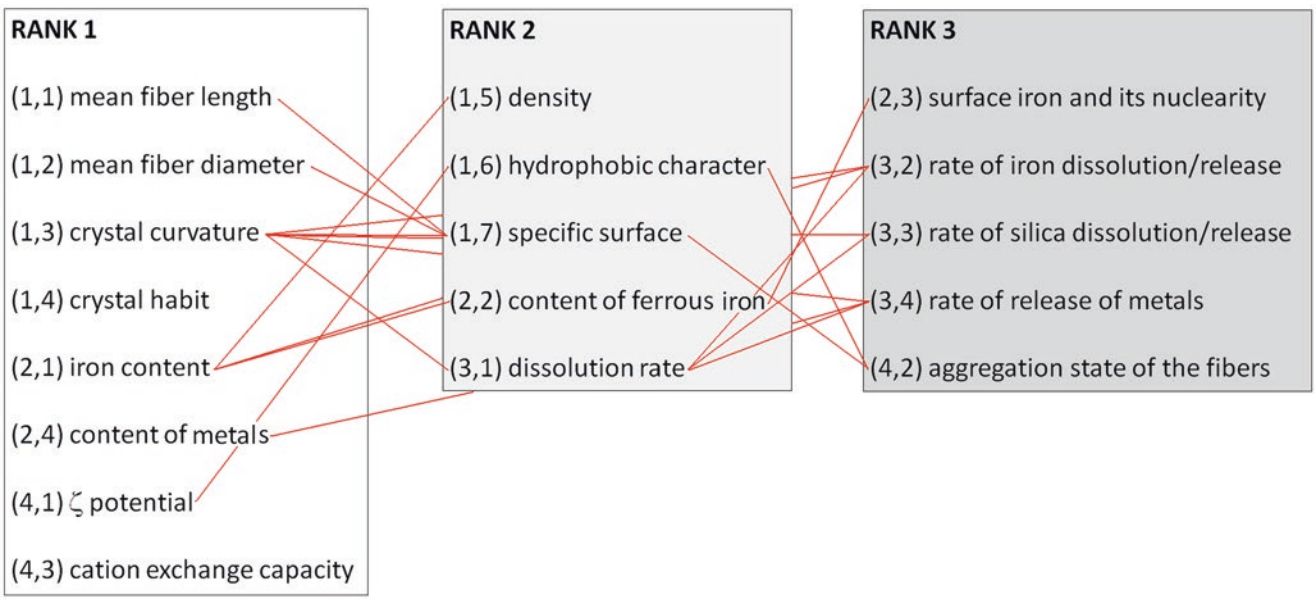

Fig. 12.3 The hierarchy (rank 1, 2, and 3) of various parameters of fibers considered in the Fiber Potential Toxicity Index (FPTI) model

This model quantitatively supports the concept of a different pathogenic potential range for amphibole asbestos as compared to chrysotile asbestos. The difference in biodurability between amphibole asbestos and chrysotile asbestos [157] is the key to explaining why chrysotile is less pathogenic than amphiboles. In fact, the low biopersistence of chrysotile determines its disintegration in the lungs with fibers becoming shorter [157]. Nevertheless, the FPTI indices for both amphibole and chrysotile asbestos are higher than nonpathogenic mineral fibers. Work is in progress to validate the model in collaboration with international organizations, and to deliver a FPTI model-based user-friendly code.

Conclusions

Occupational exposures to asbestos are associated with an increased risk of lung cancers, especially in smokers. The complexity of asbestos fibers, distinct minerals with different chemical, physical, and structural features, coupled with the thousands of chemicals and particles in cigarette smoke, have made study of the interactions between these agents difficult. However, several commonalities between smoking and asbestos exist that can be related to their additive or multiplicative potencies. For example, both impede normal clearance mechanisms of the lung. Both agents also cause chronic inflammation and lung fibrosis that favor the development of lung tumors. Most importantly, both agents can cause proliferation and metaplasia of lung epithelial cells through epigenetic mechanisms including stimulation of cell signaling pathways. Understanding the properties of asbestos minerals and their contributions to the development of lung cancers will facilitate predictive models for prediction of the potential of other mineral types in lung diseases.

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13 Lung Cancer: Mechanisms and Markers—Carcinogens Other Than Asbestos

Sisko Anttila

Introduction

Inhaled carcinogenic chemicals, mineral fibers and particulates, and carcinogenic metals are the most significant occupational and environmental 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. As an example, inhalation of silver nanoparticles of 20 nm in diameter resulted in a greater lung burden and persistence than larger nanoparticles in animal experiments [1]. 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.

The mechanisms and markers of asbestos carcinogenesis are reviewed in Chaps. 11 and 12. The present Chap. 13 handles pulmonary carcinogens other than asbestos. For more detailed information, the reader is referred to several recent comprehensive reviews cited in this chapter.

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Polycyclic Aromatic Hydrocarbons and Complex Mixtures

Occupational Exposure to Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) arise in the incomplete combustion of fossil and carbonaceous materials and also occur in crude oil deposits. The highest occupational exposures are found in petrochemical industry workers, especially in coke-oven workers, and in workers of metal plants and foundries [2]. Sources of indoor PAH exposure include tobacco smoke, meat and fish roasting and frying, and charcoal grilling in poorly ventilated environments [3]. Examples of occupations with PAH exposure are given in Table 13.1. 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 [4–7].

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 aryl hydrocarbon receptor (AHR)-mediated pathway to DNA-reactive intermediates, or detoxified and excreted from the

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Table 13.1 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 breaks in blood lymphocytes (measured by comet assay) • Changes in global and gene-specific promoter methylation • Shorter telomere length

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

body, particulates, fibers and some metals induce the formation of reactive oxygen (ROS) and nitrogen species (RNS), and oxidative DNA damage. The oxidative stress-induced gene expression is regulated by the transcription factor, nuclear factor erythroid 2-related factor 2 (NRF2). Nevertheless, these two pathways co-operate in many ways, and may potentiate each other in the formation of oxidative DNA damage (e.g., [8]).

Involuntary Tobacco Smoking

Environmental tobacco smoke (ETS) is a significant source of PAH and other tobacco carcinogens for non-smokers 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 [6, 9, 10]. ETS consists mainly of sidestream smoke emitted from smoldering cigarettes between puffs and to a lesser extent of mainstream smoke exhaled by tobacco smokers [11]. 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 [12]. 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 [12, 13]. Furthermore, levels of carcinogenic PAH compound benzo[a]pyrene are especially high in sidestream tobacco smoke [12]. Most carcinogenic PAH compounds are present in the particulate phase of tobacco smoke.

The use of electronic cigarettes (e-cigarettes, "vaping") also carries adverse effects on the indoor air quality and exposes the users and non-users to toxic or carcinogenic chemicals. Although the concentrations of many conventional tobacco carcinogens are much lower in e-cigarette aerosols, new harmful chemicals such as formaldehyde and acetaldehyde, are produced from the heating process of glycerol which is one of the main ingredients of e-liquids (see review Zainol Abidin et al. [14]).

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 AH (dioxin) receptor 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 (for example [15, 16]). 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 [15, 17].

In the lung, cytochrome P450 enzymes CYP1A1 and CYP1B1, which are under the regulative control of AHR, 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.

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 [17, 18]. PAH-diols are also metabolized by aldo-keto reductases (AKR) into reactive PAH *o*-quinones, which are able to form stable and depurinated DNA adducts. The metabolic route catalyzed by AKRs leads to amplified production of ROS ([8], see section Co-carcinogenesis of PAH and inhaled particulates). Furthermore, PAHs are catalyzed by peroxidase activities into radical cations that form depurinated adducts [17, 19–21].

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. Dennissenko 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 [22]. 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 [23, 24]. The molecular alterations caused by tobacco-derived PAH and occupational PAH exposures are not separable.

Co-carcinogenesis of PAH 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 co-operation between the transcription factors and signaling pathways that are induced by PAH procarcinogens and oxidative stress offers a plausible view on co-carcinogenesis. 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.

While PAH compounds exert their effects via the AH receptor, which regulates the transcription of a number of xenobiotic-metabolizing enzymes by binding to XRE in the promoters of responsive genes, NRF2 is involved in the regulation of redox homeostasis and controls the antioxidant gene battery via binding to antioxidant responsive elements (ARE) in the regulatory sequences of NRF2-driven genes [25, 26].

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 [27, 28]. 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 [25]. Furthermore, induction of the expression of a group of genes, such as detoxification enzyme NQO1, requires both AHR and NRF2 [26].

Human aldo-keto reductases AKR1C1, AKR1C2, and AKR1C3 that are under the regulative control of NRF2 catalyze the oxidation of non-K-region PAH *trans*-dihydrodiols to the corresponding *o*-quinones with concomitant production of ROS. The ROS produced can lead to further induction of AKRs, and CYPs via AHR, and amplification of the PAH activation, resulting in the formation of DNA adducts, above all formation of the marker adduct of oxidative DNA damage, namely 8-hydroxyguanine (8-hydroxydeoxyguanosine, 8-OH-G) [8]. Similarly, the ROS produced by particle-induced oxidative stress can potentiate NRF2- and AHR-mediated PAH procarcinogen activation and aggravate the formation of oxidative DNA damage (Fig. 13.1).

The Role of NRF2 in Cancer Promotion

The cytoprotective role of NRF2 as activator of the cellular antioxidant response is long known. It has been shown recently that the constant activation of NRF2 may not be beneficial in all stages of carcinogenesis [29]. The 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* (Kelch-like ECH-associated protein 1) [30, 31]. *KEAP1*, which is considered a tumor suppressor, may also be silenced by hypermethylation or the deletion of the chromosomal region 19p [32, 33]. These aberrations, which lead to constant NRF2 activation, may arise as a protective response against reactive electrophiles and oxygen species, or become selected by means of giving a growth advantage and permitting cancer cells to avoid apoptosis [18, 34]. 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

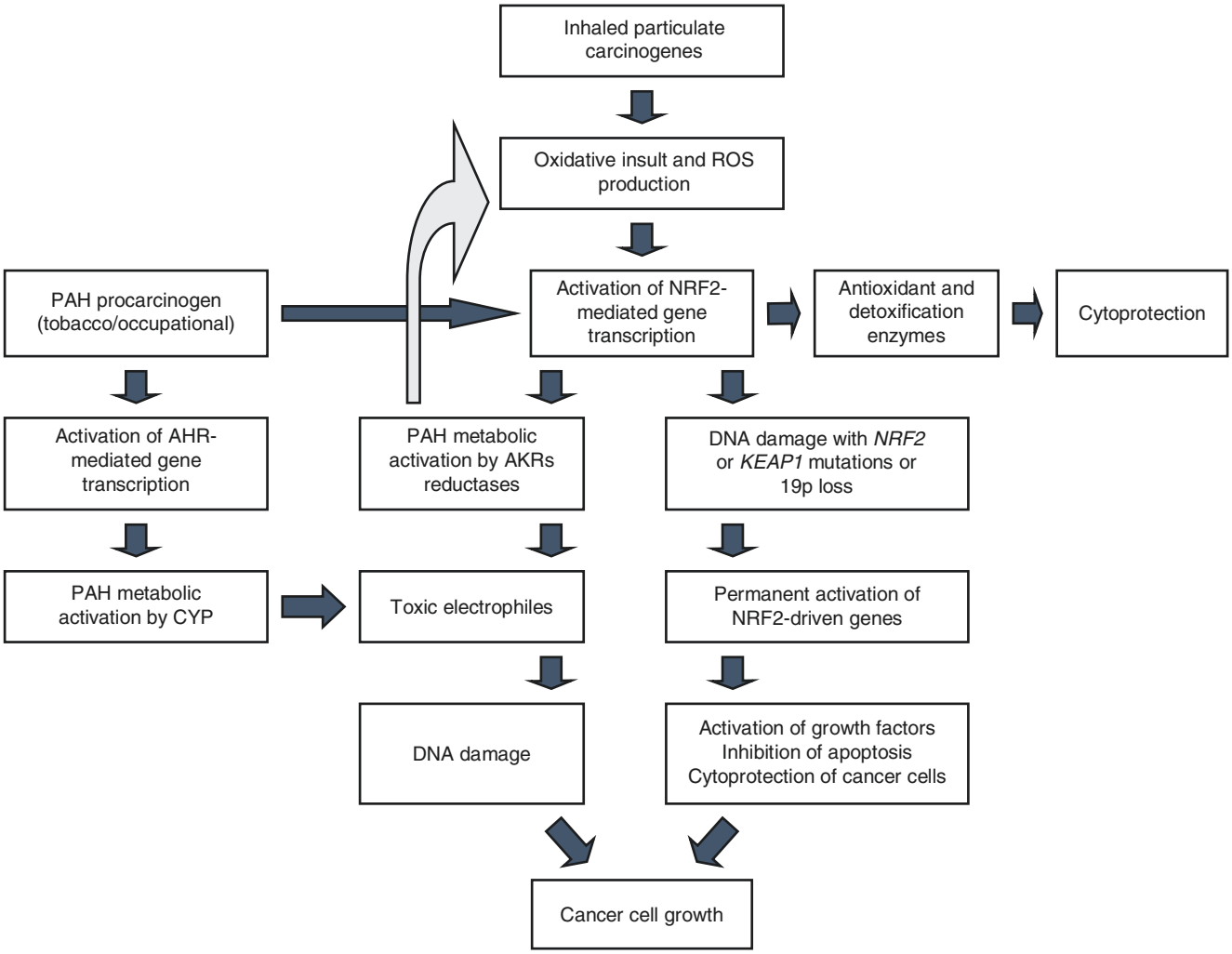

Fig. 13.1 Co-carcinogenesis mechanisms of PAH procarcinogens and oxidative stress damage. *PAH* polycyclic aromatic hydrocarbon, *AKR* aldo-keto reductases

fibroblast growth factor 13, TGF-α, TGF-β1, and -β2, and growth factor receptors [34]. It has been shown that NRF2 activity regulates the sensitivity of death signals and NRF2 overexpression antagonizes apoptosis [35–38]. The antiapoptotic Bcl-2 family proteins are under the regulative control of NFR2, and constant activation of NRF2 leads to overexpression of Bcl-2 and Bcl-xL, decreased apoptosis, and increased survival of cancer cells [37, 38]. 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 [39].

The enhancement of the oxidative stress and consequent apoptotic pressure by combined exposures to tobacco and particulate carcinogens 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 [32, 40]. The postulated mechanisms of co-carcinogenesis of tobacco carcinogens and oxidative stress are shown in Fig. 13.1.

Biomarkers

Biomarkers of PAH Exposure

The biomarkers of PAH exposure most commonly used are urinary PAH metabolites, in particular 1-hydroxypyrene. 1-hydroxypyrene and other urinary noncarcinogenic and carcinogenic PAH metabolites 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 breaks and 8-hydroxyguanine (8-hydroxydeoxyguanosine, 8-oxoGuo, 8-OH-G, 8-OH-dG) 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-OH-G is formed in the reaction of guanine with hydroxyl radical [41]. This mutagenic and carcinogenic DNA product is a good biomarker of oxidative stress, and can be determined in urine or circulating white blood cells [41]. 8-OH-G levels in urine are also influenced by gender, age, body mass index, and lifestyle factors, such as tobacco smoking, hard physical labor, and diet [42, 43].

DNA strand breaks can be studied by comet assay (alkaline single-cell gel electrophoresis assay) in cultured cells or in the circulating blood lymphocytes of exposed individuals [44]. Tarantini et al. [45] studied the relative contribution of DNA strand breaks and DNA adducts to the genotoxicity of B[a]P as a pure compound and in complex mixtures collected from an urban peri-industrial site and a metallurgical plant. Treatment of HepG2-cultured human hepatocytes with pure B[a]P or with a fraction of atmospheric particles containing soluble PAH did not induce oxidative DNA damage as measured by DNA strand breaks in comet assay or the formation of 8-oxoGuo, 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 breaks and the formation of 8-oxoGuo, and less BPDE adducts, suggesting that a component other than PAH, possibly particulate matter in the mixture, modulates the genotoxic properties of complex mixtures [45].

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 13.1.

Metal-Induced Lung Carcinogenesis

Metal-induced carcinogenesis has been covered in detail in several recent reviews cited in this chapter. For more information regarding metal carcinogenesis, readers are referred to these and other literature, and for the basic biological mechanisms of carcinogenesis, Chap. 3 of this book.

Arsenic

Arsenic (As) and its compounds have been identified by IARC as group I human carcinogen, causing cancers of the skin, liver, kidney, bladder, and lung [46]. 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 bladder. Occupational exposure, via inhalation of As compounds such as arsenic trioxide, arsenic trisulfide, and calcium arsenate, increases lung cancer risk in ore smelters, insecticide manufacture, and sheep dip workers [47].

Oxidative DNA Damage

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 [47–50]. As 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 [41, 51]. 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 [41, 52]. As(III) and MMA(III) have been shown to cause NRF2 activation via mechanisms involving autophagy and p62, a substrate adaptor protein with a critical role in autophagy [53]. 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, animal models, and in arsenic-induced lesions of human skin [51, 52, 54, 55].

Genotoxicity and DNA Repair

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 [56–59]. As(III) has been demonstrated by alkaline single-cell gel electrophoresis (comet) assay to induce DNA strand breaks in various human and rodent cells [51, 60–62]. As(III)-induced DNA strand breaks are caused by ROS production, and breaks may lead to chromosomal rearrangements. Wang et al. [63] have shown that As(III)-induced DNA strand breaks largely result from excision of oxidative DNA adducts and DNA-protein cross-links during excision repair. As 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 [51, 64–67]. Exposure to As has been shown to inhibit critical DNA repair enzymes. Morales et al. [68] demonstrated in a culture assay system that exposure to As trioxide shifted double strand break DNA repair towards error prone non-homologous end joining and inhibited homologous recombination. Exposure to As(III) has also been linked to mismatch repair deficiency and concomitant microsatellite instability in human colorectal cancer cells [69].

Arsenic exposure has been related especially with squamous cell histological lung cancer type [70, 71]. Martinez et al. [72] studied gene copy number alterations in squamous cell lung carcinomas from non-smokers exposed to As 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. These findings are in agreement with the ability of As to induce DNA strand breaks and genomic instability. Martinez et al. [73] performed whole-genome sequencing analysis on lung squamous cell carcinoma from a heavily arsenic-exposed non-smoker. They found increased number of copies at 3q26 and overall low number of point mutations, including mutations rarely detected in squamous cell carcinoma of the lung.

Epigenetic Mechanisms

Epigenetic mechanisms, such as methylation, histone modifications and microRNAs are involved in arsenic-induced carcinogenesis. As treatment of rat liver cells and human keratinocytes has resulted in reduced expression and activity of DNA methyltransferases, inducing global DNA hypomethylation [74–76]. As 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 [77], *p16(INK4a)* and *RASSF1A* in murine lung cancer [78], *DEPK* in SV-40-immortalized human urothelial cells and in human urothelial (bladder) carcinomas from the arsenic-contaminated area [79, 80], *TP53* in human lung adenocarcinoma A549 cells [81], and *TP53* and *P16(INK4A)* in whole blood DNA of people exposed to arsenic in drinking water [82]. 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 As(III) changes global histone H3 methylation levels in human lung adenocarcinoma A549 cells [76, 83] and in blood mononuclear cells of individuals exposed to arsenic in drinking water [76, 83, 84].

MicroRNAs are a family of small non-coding RNA molecules that negatively regulate protein-coding gene expression. Aberrant expression of non-coding RNAs and the consequent disruption of signaling pathways have been implicated in As-induced carcinogenesis [85, 86]. As 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 [86]. Downregulation of microRNAs of miR-200 family and upregulation of miR-21 (oncomiR-21) are involved in arsenite-induced malignant transformation of human bronchial epithelial cells [87, 88].

Arsenic as a Co-carcinogen

Arsenic is a powerful co-carcinogen 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 in cell and animal models [65, 66, 89–95]. There is epidemiological evidence of the synergistic effect of ingested As and tobacco smoking on lung cancer risk [96, 97]. A Taiwanese study demonstrated the synergy for the squamous and small cell but not for the adenocarcinoma of the lung [98]. The same group demonstrated that As 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 [101, 102]. CYP enzymes catalyze the initial step (Phase I) in the metabolism of nitrosamine and PAH procarcinogens, including benzo[a]pyrene, which is necessary for the subsequent reactions leading to the formation of DNA-reactive metabolites, as well as detoxification (Fig. 13.1).

Beryllium

Beryllium (Be) and beryllium-containing compounds are classified as human carcinogens or likely human carcinogens, causing lung cancer [46, 103]. 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 [103].

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 [104]. 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 [103, 104].

Mammalian test systems have shown evidence of beryllium-induced mutations, chromosomal aberrations, and cell transformation, whereas bacterial tests have been negative [104].

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 [105].

Cadmium

Cadmium (Cd) is classified as a human lung carcinogen by the International Agency for Research on Cancer [46]. Exposure to Cd is common because the metal is widely used in industry, for example in electroplating, paints and pigments, welding, and in Nickel-Cd batteries. Significant amounts of Cd are also released into the environment by human activities [106]. An emerging source of exposure is cadmium-based quantum dots, which are light-emitting nanoparticles used as fluorescent labels in bioimaging and biodiagnostic applications [107, 108]. 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 [106, 109].

Oxidative DNA Damage

Several mechanisms contribute to the carcinogenicity of Cd [106, 110]. Cd is a weak genotoxic agent and its genotoxicity, i.e., chromosomal aberrations, sister chromatid exchange, DNA strand breaks, and DNA-protein cross-links, is partially mediated by oxygen radical damage [106, 111–113]. 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 [110]. 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 [41, 114]. 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 NRF2, and mitogen-activated protein kinases (MAPKs) signal transduction pathways [110]. MAPKs play an important role in programmed cell death (apoptosis) for the elimination of cells with oxidative DNA damage.

Recent research reports have highlighted the significance of NRF2/p62 pathway in metal-induced carcinogenesis. The p62 is ubiquitin-binding scaffolding protein with a critical role in the cellular processes of autophagy and oxidative stress signaling [116]. It has been shown that Cd induces malignant transformation of human bronchial epithelial cells via ROS production, and that Cd-transformed cells exhibit dysfunction of autophagy resulting in p62 overexpression and accumulation [117, 118]. The p62 interacts with the NFR2-binding site of KEAP1, the repressor protein of NRF2, leading to constitutive NRF2 activation, and consequently, high expression of antioxidant and antiapoptotic proteins, apoptosis resistance, and increased cancer cell survival and proliferation [117].

DNA Repair

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 [106, 119, 120]. The repair mechanisms reported to be inhibited by Cd include nucleotide excision repair, non-homologous end joining, base excision repair, and mismatch repair (Morales et al. [68] and references therein). 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 [106, 121]. Morales et al. [68] demonstrated in a cell culture assay system that low doses of nickel and Cd promote mutagenic non-allelic recombination as a major repair pathway of DNA double strand breaks. Cd has also been shown to increase microsatellite instability concomitantly with ROS production and decreased levels of mismatch repair proteins [69].

Epigenetic Mechanisms

The role of epigenetic mechanisms in Cd carcinogenesis is uncertain [74]. In human prostate cells and in another study using rat liver cells, Cd initially induced global DNA hypomethylation followed by hypermethylation after prolonged exposure [122, 123]. In human prostate cells, promoter hypermethylation and reduced expression of *RASSF1A* and *p16* tumor suppressor genes were observed [122]. It is hypothesized that global DNA hypomethylation is associated with Cd-induced cell proliferation [74, 124]. The possible effect of Cd on histone tail posttranslational modifications is not known [74].

Chromium

Chromium VI [hexavalent chromium, Cr(VI)] compounds have been identified as human lung carcinogens [46]. Cr(VI) is widely used in a variety of industries, for example in paints, metal finishes, stainless steel manufacturing, alloys,

welding, and in wood treatment. In contrast to other oxidation states of Cr, Cr(VI) 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, cysteine, lipoic acid, hydrogen peroxide, fructose, and ribose [125, 126]. It is thought that Cr(III) is unable to cross cell membranes, but recently it has been suggested that certain Cr(V) and Cr(III) forms generated by reduction in the extracellular space have high permeability through cell membranes [41, 127, 128]. Insoluble Cr compounds can enter cells via phagocytosis. Particulate or water-insoluble Cr(VI) compounds are more potent than soluble species in causing DNA damage, possibly because of the fast clearance of soluble Cr(VI), whereas poorly soluble particulates may form a persistent source of carcinogenic Cr species in the lung [129, 130].

Oxidative DNA Damage and Genotoxicity

Intracellular reduction of Cr(VI) is the main source of reactive intermediates and the extensive formation of Cr-DNA adducts and subsequent DNA damage [41, 86, 126]. Cr(V), when formed, can have a Fenton-like reaction with hydrogen peroxide, generating hydroxyl radical. Associated other reactions can produce thiyl and superoxide radicals [41, 126]. In addition to free radical induced DNA damage, the formation of Cr-DNA adducts, above others Cr(III)-mediated DNA cross-links of glutathione, cysteine, histidine, and ascorbate, is responsible for the mutagenicity and genotoxicity of Cr(VI) [41, 131]. 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 [126, 132]. Wakeman et al. [133, 134] have shown that exposure to the unstable intermediates Cr(V) and Cr(IV), generated during the reduction of Cr(VI) to Cr(III), can induce highly genotoxic DNA double strand breaks. While Cr(VI) is not able to directly interact with DNA and exposure to Cr(V) resulted in the initiation of cell cycle checkpoints, exposure to Cr(IV) failed to activate optimal DNA damage response and caused a high frequency of mutations, supporting the role of Cr(IV) as the ultimate mutagenic species [134]. The group also found that a mismatch repair protein MLH1 is required for the activation of the G2/M cell cycle checkpoint in response to Cr exposure.

DNA Repair

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 MLH1 and MLH2 in the lung cancers of chromate-exposed workers [135, 136]. These findings are contradicted by the lung cell experiments by Rodrigues et al. [137], 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. 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 [138, 139]. However, *TP53* mutations were unusual changes of AT base pairs and double missense mutations [139].

Epigenetic Mechanisms

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 been published concerning mechanisms contributing to the co-carcinogenesis 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 [115]. It was shown that Cr cross-links histone deacetylase 1-methyltransferase complexes to the Cyp1a1 promoter and inhibits gene transcription. 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 [140]. 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, *MLH1*, and a decrease of its expression [141]. Furthermore, hypermethylation of the promoter regions of several tumor suppressor genes, particularly *MLH1*, *APC*, and *P16* genes, has been reported in lung carcinomas of patients with over 15 years' occupational exposure to chromates [142, 143].

Cr has also been shown to exert its cell transformation capacity via induction of a stress response protein NUPR1 (nuclear protein 1 or p8). NUPR1 regulates key cellular functions, such as cell cycle, apoptosis, autophagy, chromatin accessibility, and transcription, via interactions with molecular partners [144]. Exposure to Cr(VI) induces NUPR1 overexpression, which decreases the level of histone

H4K16 acetylation leading to the transcriptional downregulation at several genomic loci, thereby contributing malignant transformation [145].

Recent literature has highlighted the role of microRNAs in Cr(VI)-induced malignant transformation. He et al. [146] found that miR-143 was downregulated in Cr(VI)-transformed human bronchial epithelial cells. Pratheeshkumar et al. [147] showed that exposure to Cr(VI) increased (onco) miR-21 levels in human bronchial epithelial cells, resulting in inhibition of the tumor suppressor programmed cell death 4 (PDCD4), and furthermore, knockdown of miR-21 significantly reduced the Cr(VI)-induced cell transformation.

Nickel

All nickel [Ni(II)] compounds are classified into group I human carcinogens, which can cause nasal and lung cancer, and metallic Ni as possibly carcinogenic to humans (Group 2B) [46]. Ni 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, stainless steel welding, Ni-Cd batteries, and in the production of nanoparticles [148]. Ni pollution in the environment originates from the combustion of fossil fuels in vehicles and power plants, industrial sources, waste incinerators, disposal of Ni compounds, and volcanic eruptions. Ni 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 Ni compounds in industry. While both soluble and poorly soluble Ni 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 [149]. 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 [150].

Genotoxicity

Although Ni compounds are not mutagenic in traditional mutation tests, they can induce malignant transformation in human and rodent cells [149, 151–155]. Soluble and insoluble Ni 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 [156].

Compared with Cd and Cr, Ni is a weak inducer of oxidative stress [157, 158]. However, the reactivity of Ni 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 [158]. 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 [159]. Several Ni compounds have been shown to increase oxidative DNA damage and the formation of 8-hydroxydeoxyguanosine (8-OH-dG) adducts in cultured cells and in rat lungs after intratracheal instillation of Ni compounds [160]. Furthermore, high levels of 8-OH-dG adducts and the DNA repair marker 8-hydroxyguanine DNA glycosidase 1 have been detected in blood cells of Ni-smelting workers [161]. Son et al. have shown that the ROS-inducible transcription factor NRF2 is constitutively highly expressed in Ni-transformed human bronchial epithelial cells [162]. NRF2 overexpression increases autophagy via STAT3 signaling, and upregulates the expression of antioxidant and antiapoptotic proteins, contributing to apoptosis resistance and tumorigenesis [162].

Epigenetic Mechanisms

Epigenetic mechanisms are considered more important than genetic changes in nickel-induced carcinogenesis (see also Chap. 3). 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 [74, 149, 163, 164]. Ni^{2+} is able to displace Mg^{2+} in the phosphate backbone of DNA and increase the level of chromatin condensation and subsequent DNA methylation and heterochromatinization [165]. Histone acetylation is necessary for transcriptional activation. Ni restricts the acetylation of histone H4 by binding with its N-terminal histidine-18 and by influencing histone acetyltransferase (HAT) activity [166–168]. Ni also increased histone H3K9 dimethylation ($H3K9me^2$) in a transgene when the transgene was integrated near the heterochromatin region [169]. Jose et al. [170] showed that Ni can disrupt $H3K9me^2$ domain structures genome-wide, resulting in spreading of $H3K9me^2$ into the active genomic regions and gene silencing. The group suggested a mechanism involving the inhibition of the insulator protein CCCTC-binding factor at the $H3K9me^2$ domain boundaries. Chen et al. [99, 100] demonstrated that Ni inhibits the activation of dioxygenase enzymes, such as histone demethylase MJD1A and DNA repair enzyme ABH2, by replacing the non-heme iron at their catalytic center. The loss of histone acetylation and de novo DNA methylation silence 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 [171]. Also, methylation has been observed in the enhancer regions of *RAR-β2*, *RASSF1A*, and *CDKN2A* genes of rat muscle tumors induced by nickel subsulfide [172]. Histone modifications have been studied in peripheral blood mononuclear cells of Ni refinery workers, steel workers, and Ni-smelting workers. In these worker groups, changes in histone H3 methylation and acetylation were observed as compared to non-exposed referents, and some of the changes correlated with the length of the employment [173–175].

Hypoxic Signaling

Activation of hypoxic signaling is another main alteration with significance in Ni-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 [176]. 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 Ni, avoids ubiquitylation and proteosomal degradation and accumulates in cells [86]. Hypoxic signaling is thought to be one of the pathways that Ni exposure can induce by disrupting cellular iron homeostasis [177, 178]. 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 [149].

DNA Repair

Nucleotide and base excision repair pathways are impaired by Ni compounds, at least partially by the damage of zinc fingers in DNA repair proteins [179]. Morales et al. [68] studied in a culture assay system how Ni exposure modifies DNA double strand break repair outcomes and found that $NiCl_2$ favors repair through non-allelic recombination events with a significant increase of non-templated sequence insertions at the repair site. Scanlon et al. [180] demonstrated that Ni exposure downregulates the DNA repair proteins which are involved in homology-dependent DNA double strand break repair (HDR) and mismatch repair (MMR) in human bronchial epithelial cells and in lung adenocarcinoma cells in a dose-dependent manner. Interestingly, these functional changes in DNA repair were similar to those induced by hypoxic stress.

Ni 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 Ni interferes with cellular metabolism by disrupting iron homeostasis and inhibiting the function of iron-dependent enzymes.

Mechanisms of Ionizing Radiation-Induced Carcinogenesis

Ionizing radiation-induced DNA damage is described in more detail in Chap. 3 and illustrated in Fig. 3.1. 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 [181]. 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 [182, 183].

Ionizing radiation (IR) produces reactive oxygen and nitrogen species that are responsible for oxidative stress and inflammatory response. The inflammatory reaction and oxidative damage is 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 [182, 184]. 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 [185–189]. High-LET alpha-emitters also induce genomic instability through the inactivation of DNA mismatch repair [190, 191]. 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 [192]. 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 [193, 194]. 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 [195]. 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 [196]. Belinsky et al. [197] 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.

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 metal carcinogenesis. In workplace air many carcinogens exist as complex mixtures, in which chemical compounds are bound to metal and mineral particles of respirable size. In lung cells, the components of complex mixtures induce oxidative stress as well as activation of chemical procarcinogens via intermingled pathways that may potentiate the DNA damage caused by either particle or chemical carcinogen alone. 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.

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Lung Cancer: Genetic Susceptibility

14

Ari P. Hirvonen

Genetic Susceptibility to Lung Cancer

Lung cancer is the most frequent malignant neoplasm in most countries and remains among the most lethal cancers globally. The use of tobacco cigarettes is the single greatest risk factor in the development of lung cancer, with up to 90% of lung cancers attributed to smoking [1, 2]. Lung cancer is, however, a complicated disease involving also numerous other environmental risk factors, including various occupational exposures [3, 4]. 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, 5, 6].

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%). Most of the genetic risk for lung cancer is likely to involve several variants in the last two categories. Such risk variants have mostly been tested on a candidate gene basis. However, during recent years the genome-wide association studies (GWAS) have been offered as an alternative for these studies.

This chapter presents these nowadays most commonly used approaches and the main results they have produced regarding the studies on genetic susceptibility factors for lung cancer. Since only very few reports have been published so far on studies of genetic risk factors for work-related lung cancer, the information in this section largely concerns the genetic risk factors of lung cancer caused by environmental exposure in general. However, these risk factors are assumed to be very similar to work-related lung cancer and smoking-related lung cancer. Moreover, the occupational exposures may well be expected to act in concert with tobacco smoking in shaping the descriptive epidemiology of lung cancer [1–4].

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Candidate Gene Studies on Lung Cancer

The candidate susceptibility genes for lung cancer have been extensively studied for over two decades already. Most of this work has been focused on mechanistically plausible single-nucleotide polymorphisms (SNPs) in carcinogen-metabolizing, DNA repair, and cell-cycle control genes. The most studied genes in these pathways and the role of their SNPs in susceptibility to lung cancer 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 [7–9]. The first CYP polymorphism was identified for CYP2D6 based on the occurrence of adverse drug reactions to the cardiovascular drugs debrisoquine and sparteine [10]. More than ten variant alleles of the *CYP2D6* gene have been characterized, which are partially or totally inactive. Individuals that are metabolically competent are referred as extensive metabolizers, and those that are incapable of metabolism of these drugs due to carriage of two defective alleles of *CYP2D6* are poor metabolizers. In addition, ultrarapid metabolizers carrying more than two copies of the functional gene exist [11, 12].

The CYP2D6 activity is assumed to be involved in lung carcinogenesis via 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 carriers of *CYP2D6* poor metabolizer genotype [13, 14].

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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 [10]. 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 [15–17].

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 [18–20]. Probably due to significant ethnic differences in the variant allele frequency, it was difficult to detect such an association in Caucasian populations before being examined in large meta- and pooled analyses [21–26].

A significant interaction has also been observed between several functional *CYP1A2* variants (*CYP1A2∗1D*, *CYP1A2∗1 F*, and *CYP1A2-T/delT* or *delT/delT*) and lung carcinogenesis [27, 28].

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 [29].

To date, numerous *CYP1B1* variant alleles have been identified, which presumably cause an altered function of the enzyme and thereby determine the individual differences in susceptibility to cancer [30–33]. In agreement with this, a meta-analysis supported the hypothesis that the *CYP1B1* C432G, G119 T, and C48G polymorphisms modify the risk of developing lung cancer [34].

CYP2A6 is an important hepatic enzyme that metabolizes approximately 3% of therapeutic drugs, environmental toxicants, and many procarcinogens [35–38]. The *CYP2A6* gene is highly polymorphic, resulting in extensive interindividual variation in CYP2A6 activity [35]. 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 [35, 39, 40].

CYP2E1 is a natural ethanol-inducible enzyme that is involved in the metabolic oxidation of low molecular weight carcinogens such as *N*-nitrosamines, benzene, and vinyl chloride. Several SNPs have been found in *CYP2E1* gene [41–45], and many studies have investigated associations between *CYP2E1* gene variation and lung cancer risk [46–49]. 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 meta-analysis [50] decreased lung cancer risk was found for subjects carrying *CYP2E1 Rsa*I/*Pst*I variant alleles. 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 [51–56]. 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 [53]. Genetic polymorphisms have been identified, e.g., within exons 3 and 4 of the *EPHX1* gene [57, 58], 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}) [58]. 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 [59].

Although the previous studies on *EPHX1* genotypes and susceptibility to lung cancer have given somewhat divergent results, data from a comprehensive review and meta-analysis supported a modifying role for the *EPHX1* polymorphisms in lung carcinogenesis [60, 61].

GSTs

Human glutathione *S*-transferases (GSTs) are a superfamily of phase II enzymes having broad and overlapping substrate specificities [62]. The known substrates for GSTs in cigarette smoke are those derived from 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 [62, 63].

Among the GST isoforms, *GSTM1* is of particular interest; it is expressed in only about half of Caucasians, due to a homozygous deletion (null genotype) of the gene in the other half [64]. 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 [65].

There is abundant evidence that the *GSTM1* null smokers are at increased risk of lung cancer. However, several conflicting reports also exist including some meta- and pooled analyses [66–69]. In light of the compiled data, it has been estimated that 17% of lung cancers may be attributable to *GSTM1* genotypes [70]. 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, in turn, is one of the most abundant GSTs in human lungs [71–73]. 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 [74]. The functional consequence of this is still unclear, but both negative and positive regulatory effects have been suggested [75].

Low pulmonary expression of GSTM3 was observed in adenocarcinoma patients [73], and subsequent genotyping studies indicated that the *GSTM3* gene polymorphism may modify the risk of smoking-related lung cancer [69, 76].

The third polymorphic *GST* gene of major interest, *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 [72], 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 [77–79], and individuals homozygous for the *GSTP1* low activity alleles have been suggested to pose an increased risk of lung cancer [69, 76, 80–83].

Lastly, a deletion polymorphism similar to that observed for *GSTM1* has also been discovered for the *GSTT1* gene [84]. GSTT1 participates in detoxification of potentially carcinogenic monohalomethanes and of reactive epoxide metabolites of butadiene [85], 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 [18, 83].

MnSOD and MPO

Manganese superoxide dismutase (MnSOD), located in the mitochondrial matrix, provides an initial defense against reactive oxygen species (ROS) [86, 87]. A polymorphism in the second exon of the *MnSOD* gene results in an Ala16Val amino acid change, which changes the structural conformation and mitochondrial transport of MnSOD and affects the MnSOD activity; the *MnSOD 16Ala* allele encodes a protein with 30–40% more activity than the protein encoded by the *16Val* allele [88–90].

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 [91, 92]. 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 [93].

The studies on *MnSOD* Ala16Val polymorphism and lung cancer risk have given somewhat contradictory results [94–97] and asbestos exposure seems not to modify the risk associated with Ala16Val polymorphism [94]. On the contrary, the *MPO* − 463G > A polymorphism has been associated with lung cancer risk in several studies [98, 99]. Heavy smoking and asbestos exposure increased lung cancer risk jointly in the homozygous G-allele carriers but not in A-allele carriers [98].

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 [100]. However, following *N*-oxidation, the *N*-hydroxyl metabolite undergoes *O*-acetylation (usually activation).

The human genome contains two widely studied *NAT* genes, which code for NAT1 and NAT2 enzymes [101–103]. A number of genetic polymorphisms with functional consequences have been observed in both *NAT1* and *NAT2* [100, 104–106]. These polymorphisms cause individual variations in biotransformation of various xenobiotics with a primary aromatic amine or a hydrazine structure [107–109].

The *NAT2* polymorphisms are well established as the basis of rapid, intermediate, and slow acetylation phenotypes. While very good *NAT2* genotype/phenotype correlations have been reported [110–114], the functional effects of *NAT1* alleles, genotypes, and haplotypes are yet not fully understood [115–117].

Previous phenotyping studies as well as subsequent genotyping studies have suggested a modifying role for *NAT* genotypes in all major cancer sites including lung [118–121]. However, the more recent studies indicated no substantial effect for the *NAT2* genotypes, whereas the NAT1 fast acetylator phenotype-associated genotypes remained significantly associated with increased lung cancer risk [121–123].

DNA Repair and Cell-Cycle Genes

The DNA repair system maintains the integrity of the human genome. Individual differences in capacity to repair DNA damage may therefore greatly affect the variability in susceptibility to environmental cancer; individuals who have lowered or negligible DNA repair capacity may accumulate mutations that modulate the cancer risk [124].

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 [125]. 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. Direct repair corrects methylated bases, base excision repair (BER) operates on small lesions, nucleotide excision repair (NER) repairs bulk lesions, mismatch repair (MMR) corrects replication errors, and double-strand break repair (DSBR) corrects double-strand breaks through two different pathways (homologous recombination and nonhomologous end rejoining) [126].

The most promising DNA repair and cell-cycle control genes as candidates for modifiers of lung cancer risk 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 [127, 128], and therefore, functional polymorphisms in *ATM* gene may have crucial effects in cancer risk. In agreement with this, meta-analyses have indicated 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 [129, 130].

APE1

Apurinic/apyrimidinic (AP) endonuclease 1 (APE1) is a multifunctional protein that plays a central role in the BER pathway through hydrolyzing the phosphodiester backbone immediately 5′ to the AP site [131, 132]. Numerous SNPs in *APE1* gene have been identified [133], of which two functional SNPs, −656 T > G and 1349 T > G, have been most widely investigated. Meta-analyses have suggested that the *APE1* − 656 T > G base change has a possible protective effect on lung cancer risk [134] and that the 1349 T > G base change contributes to the lung cancer risk among smokers [135].

BAP1

BRCA1 associated protein-1 (BAP1) is a nuclear ubiquitin carboxy-terminal hydrolase or deubiquitinating enzyme that plays a role in regulating several cellular functions, such as cell cycle, differentiation, DNA damage response, and cell proliferation. Germline *BAP1* mutations cause a familial cancer syndrome predisposing to malignant mesothelioma, malignant melanoma, clear cell renal cancer, and lung adenocarcinoma, among others [136]. A recent study genotyped common, germline SNPs for *BAP1* in a large population of cancer patients, and identified a significant association of rs12163565 SNP with risk of lung cancer [137]. This missense variant is located in the 3′ flanking region within 10 kb of *BAP1* and its functional role on *BAP1* remains unknown [137].

ERCC1 and ERCC2

Excision repair cross-complimentary groups 1 (ERCC1) and 2 (ERCC2) play an essential role in the NER pathway [126]; ERCC2 is also named as xeroderma pigmentosum complementary group D (XPD) gene.

Several common and putatively functional SNPs of *ERCC1* and *ERCC2* genes have been identified, of which *ERCC1* 19,007 T > C and 8092C > A SNPs have been reported to affect the *ERCC1* mRNA expression [138, 139], whereas *ERCC2* Asp312Asn and Lys751Gln SNPs are associated with a suboptimal DNA repair capacity [140, 141].

In addition to the previously mentioned *ERCC1* 19,007 T > 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 a meta-analysis, the 8092C > A SNP does not appear to have an effect on individual cancer proneness [142]. Moreover, 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* 19,007 T > C SNP [142].

As for *ERCC2*, meta- and pooled analyses have indicated slightly elevated lung cancer risk for carriers of the homozygous variant Gln751Gln genotype, whereas no significant association was found for the Asp312Asn genotypes [143–145].

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 [146, 147]. XPA, in turn, is involved in damage recognition following the initial damage recognition [148, 149].

The most studied *XPA* gene polymorphism is −4G > A (A23G) located four nucleotides upstream of the start codon [150]. A number of molecular epidemiological studies have evaluated the possible role of this SNP in lung cancer proneness with inconsistent or contradictory results [151].

Among all identified *XPC* SNPs, three are commonly studied, i.e., intron 9 poly (AT) deletion/insertion polymorphism (PAT−/+), Lys939Gln, and Ala499Val. The PAT−/+ and Lys939Gln polymorphisms have been demonstrated to affect the DNA repair capacity [152, 153], 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 the

XPC polymorphisms with lung cancer risk with contradictory results [154].

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 large meta-analysis and pooled analysis suggested that the homozygous carriage of the *XPA* − 4A variant allele poses an increased risk of lung cancer [151]. Similarly, another meta-analysis concluded that the homozygous carriers of the *XPC* 939Gln allele are at increased risk of lung cancer [154].

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) [155].

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 − 77 T > 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 [140, 156–160], whereas the functional significance of the Arg194Trp and Arg280His polymorphisms is yet unclear.

In a recent meta-analysis, the *XRCC1* Arg194Trp and − 77 T > C polymorphisms appeared as significant modifiers of individual lung cancer risk, whereas no associations were found for the Arg280His and Arg399Gln polymorphisms [161].

Genome-Wide Association Studies on Lung Cancer

An alternative to candidate gene approaches in studies on genetic risk factors for lung cancer has been offered by the GWAS analyses, which do not require prior knowledge of the functional significance of the variants studied [162]. These studies have been able to identify multiple genetic polymorphisms underlying lung cancer risk by utilizing up to a million tagging SNPs to identify common genetic variations. The three main susceptibility loci identified are in the 5p15, 6p21, and 15q25 regions [163–165].

The 5p15 region has been associated with lung cancer both in smokers and nonsmokers [164–166]. The susceptibility locus at 5p15.33 contains two biologically relevant genes for lung cancer, *TERT* (telomerase reverse transcriptase) and *CLPTM1L* (cleft lip and palate transmembrane-1-like), variants of which have been reported to be associated with lung cancer risk [167–169]. 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 [170]; 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 [171]. The functions of *CLPTM1L*, on the other hand, are less well understood.

Numerous studies have provided strong evidence of a lung cancer susceptibility region in 15q25.1 [163, 164, 169, 172–174]. 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); since nAChRs mediate sensitivity to nicotine, variant receptors may modify smoking habits and nicotine dependence and, therefore, exposure to tobacco carcinogens [174–176].

Variants in chromosome locus 6p21 have been found to confer markedly increased risk of developing lung cancer risk [165, 167, 177] although contrasting findings also exist [169, 178].

GWAS analyses have also found some evidence for lung cancer susceptibility locus in regions 3q28, 12p13.33, and 13q31.3 [164, 179–182]. Moreover, a recent large-scale association analysis combining the outcome data with existing data for an aggregated GWAS analysis of lung cancer identified 10 novel lung cancer susceptibility loci [183]. Gene expression quantitative trait analysis (eQTL) highlighted *RNASET2* (ribonuclease T2), *SECISBP2L* (SECIS binding protein 2 like), and *NRG1* (neuregulin 1) as the novel candidate genes. Other loci included genes such as *CHRNA2* (cholinergic receptor nicotinic alpha 2 subunit) and *RTEL1* (regulator of telomere elongation helicase 1).

Interaction Between Genetic and Epigenetic Factors in Susceptibility to Lung Cancer

Epigenetic mechanisms, especially DNA methylation, may also play a role in the genotype-related susceptibility to lung cancer; DNA methylation occurs primarily in the CpG islands of the promoter region and therefore SNPs in the promoter region can alter DNA methylation status and profoundly impact gene expression [184].

Some promoter region SNPs have indeed been shown to alter methylation in an allele-specific manner; a GWAS analysis showed that 38 SNPs in 12 CpG loci correlated with changes in methylation and expression of 10 genes [185]. Moreover, a variant (−48 G > A) in the CHEK2 (checkpoint kinase 2) promoter at a methylation site has been shown to relieve transcriptional repression and confer reduced risk of lung cancer [186, 187].

CpG SNPs have also been found to affect many non-imprinted autosomal genes in normal human tissues by allele-specific DNA methylation (ASM), allele-specific gene expression (ASE), and allele-specific transcription factor binding (ASTF) [188].

The epigenetic factors may also contribute to the gender-related differences in susceptibility to lung cancer [189]; although the methylation difference of a large number of CpGs analyzed on three human chromosomes identified a relatively small mean methylation difference (0.1%) between males and females [190], these small differences in methylation patterns, if present at critical regulatory genes, may exert significant impact on cellular response to environmental exposure. Different epigenetic mechanisms also appear to cross-influence and reinforce each other in the orchestration of cellular response to environmental stimuli and endogenous cues [191, 192].

Genetic Factors and Work-Related Lung Cancer

Although it is well known that occupational exposures play an important role in lung cancer etiology, as previously noted, there is only a limited number of reports on the potential role of genetic risk factors and work-related lung cancer [3, 4]. A reasonable data exists, e.g., for asbestos-exposure-related lung cancer, which is the most common asbestos-induced neoplasm, incidence of which increases with increased duration to asbestos exposure [193]. Asbestos exposure can induce lung cancer independently or synergistically with smoking, and the interaction between asbestos and smoking has also been found to be approximately multiplicative [194]. Adsorption of tobacco carcinogens by asbestos fibers could enhance the carcinogenic potential of the fibers and is one possible mechanism for the observed interaction between asbestos and smoking exposure [195].

Some studies have examined interactions between asbestos exposure and gene polymorphisms by using either candidate gene or GWAS approaches with some promising results. These studies have, e.g., provided evidence of the effect of functional polymorphism of *MPO* (−463G > A) in susceptibility to lung cancer in the asbestos-exposed workers [98]. Moreover, a recent discovery and replication GWAS suggested a significantly increased asbestos-related lung cancer risk for heterozygous and homozygous variant allele carriers of *MIRLET7BHG* (*MIRLET7B* host gene located at 22q13.31) rs13053856, rs11090910, rs11703832, and rs12170325 SNPs [196]. MicroRNA let-7 functions as a tumor suppressor in lung cancer and downregulates several oncogenes.

A reasonable data exists also, e.g., 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) [197]. 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).

In a subsequent study, 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) [198]. In addition, Nazar-Stewart et al. [199] evaluated the occupational exposure to arsenic, asbestos, and welding or diesel products as potential modifiers of the effect of *GSTM1*, *GSTT1*, and *GSTP1* genotypes in lung cancer susceptibility, but found no association.

Aside the *GST* genotypes, very scarce data is available for the other xenobiotic metabolizing enzyme genotypes and work-related lung cancer. In one of the above studies, the *CYP1A1∗2C* variant allele showed a possible interaction with occupation for workers exposed in following occupations: 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 [198].

Finally, a recent GWA analysis suggested a significant gene–radon interaction for marker rs12440014 located within the gene *CHRNB4* on chromosome 15q25.1 [200]. This study found no significant effect of the marker on the main lung cancer risk, but among the occupationally radon-exposed miners a lower risk was observed for carriers of the minor allele compared to non-carriers [200]. The locus 15q25.1 is a well-known lung cancer susceptibility locus observed in several previous GWA studies. As noted above, *CHRNB4* is one of the genes coding nicotine acetylcholine receptor subunits and has been suggested to associate with nicotine dependency. This study found no modification of risk across smoking categories [200].

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 able to generalize to, e.g., occupational PAH exposures, majority of the potential associations between genetic polymorphisms and occupational cancer remain to be elucidated.

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Epidemiology of Occupational Lung Cancer

15

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Introduction

Lung cancer is the most common cancer worldwide, with an estimated 1,600,000 new cases and 1,380,000 deaths annually [1, 2]. The most important risk factor for lung cancer is tobacco smoking, with over 90% of lung cancer in men attributed to smoking [3, 4]. Up to 10–20% of lung cancers have been attributed to occupational exposures and a synergistic effect has been observed between smoking and many of the occupational exposures. Occupational lung cancers represent approximately 75% of all occupational cancers [5] and are a major health burden. In most studies, the attributable proportion for occupational lung cancer is in the order of 10–15%, with one study from the UK providing a higher estimate [6]. Exposure level plays an important role. For some occupational exposures, an increased lung cancer risk is reported even at low exposure levels such as asbestos (OR: 1.76, 95% CI: 1.42–2.18), crystalline silica (OR: 1.31, 95% CI: 1.00–1.71), and nickel-chromium (OR: 1.18, 95% CI: 0.90–1.53). For polycyclic aromatic hydrocarbons (PAHs), an increased risk (OR: 1.64, 95% CI: 0.99–2.70) is found only for high exposures [7]. The mechanisms by which occupational exposures contribute to increased lung cancer risk are not well understood, but they likely differ between carcinogenic agents, and may include DNA damage, chronic increase in inflammatory cytokines or growth factors, and impairment in DNA repair [8]. Although industrial cohorts are useful for investigating particular exposures at high levels, they are not suitable to estimate their impact at a population level. Population-based case–control studies remain the most efficient epidemiological design to assess the impact of multiple occupational exposures among the broad range of industries and jobs occurring in a community.

Cigarette smoking is the predominant potential confounder in any analysis investigating the relationship between occupational exposure and lung cancer risk. For instance, a case–control study among 2584 cases exposed to diesel exhaust and 5099 hospital controls reported the crude odds ratio for lung cancer risk to be 1.31 (95% CI: 1.09 to 1.57). But adjustment for smoking and other confounders reduced the estimate to 0.95 (95% CI: 0.78 to 1.16). Similar results were observed for truck drivers, the only occupational category large enough for separate analysis [9]. Most individual studies and summaries of occupational lung cancer are based on data having a heavy preponderance of male smokers. Relatively little data are available concerning females and nonsmokers. Although many studies have been adjusted for smoking, there remains a significant potential for residual confounding because of the overwhelming role of smoking in the etiology of lung cancer [10].

High-Risk Occupations

The risk of lung cancer is increased among workers employed in a number of industries and occupations (Table 15.1). The responsible agent(s) have been identified for several, but not all, of these high-risk workplaces. A case-referent study assesses occupational risk factors associated with lung cancer, utilizing colon and rectum cancer referents. In 5935 incident lung cancer cases (and 3956 referents), there were significant elevated risks for excavating and mining workers (OR = 4.01), furnace workers (OR = 3.11), armed services personnel (OR = 3.10), agricultural workers (OR = 2.05), driver sales (OR = 2.21), mechanics (OR = 1.72), painters (OR = 1.96), and drivers (OR = 1.88). Industries with highest lung cancer risk included farming (OR = 2.21), mining

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Table 15.1 Occupational agents, groups of agents, mixtures, and occupations classified as human carcinogens (Group 1) by the IARC Monographs Program, Volumes 1–118, which have the lung as target organ

Agents, mixtures, occupations	Main industry, use
Agents and groups of agents	
Arsenic and inorganic arsenic compounds	Glass, metals, pesticides
Asbestos	Insulation, filters, textiles
Beryllium and beryllium compounds	Aerospace
Bis(chloromethyl)ether and chloromethyl methyl ether	Chemical intermediate
Cadmium and cadmium compounds	Dye/pigment
Chromium[VI] compounds	Metal plating, dye/pigment
Involuntary tobacco smoking	Hospitality
Nickel compounds	Metallurgy, alloy, catalyst
Plutonium	Defense
X- and γ-radiation	Medical
Radon-222 and its decay products	Mining
Silica, crystalline	Stone cutting, mining, glass, paper
Mixtures	
Coal-tar pitch	Construction, electrodes
Diesel engine exhaust	Mining, transportation
Soot	Pigments
Welding fumes	Welding
Occupations	
Acheson process (silicon carbide production)	–
Aluminum production	–
Coal gasification	–
Coke production	–
Hematite mining (underground)	–
Iron and steel founding	–
Painting	–
Rubber production industry	–

(OR = 2.98), and primary ferrous metals manufacturing (OR = 2.43) [11]. The IARC study was a multi-center case–control study included 2056 male and 576 female lung cancer incidence cases diagnosed from 1998 to 2001 and 2144 male and 727 female controls frequency-matched for sex and age. Industries with elevated risk among men included mining (OR: 1.75, 95% CI 1.20 to 2.57); manufacture of cement, lime, or plaster (OR: 3.62, 95% CI 1.11 to 12.00); casting of metals (OR: 2.00, 95% CI 1.17 to 3.45); and manufacture of electric motors (OR: 2.18, 95% CI: 1.24 to 3.86). For women, elevated ORs were found for medical, dental, veterinary doctors (OR: 2.54, 95% CI 1.01 to 6.31), librarians and curators (OR 7.03, 95% CI: 1.80 to 27.80), and sewer workers (OR: 3.63, 95% CI: 1.12 to 10.23) [12]. Construction workers also are at significantly high risk as they are exposed to many known or suspected carcinogens, including silica, asphalt fumes, PAHs, diesel exhaust, paints, asbestos, lead, metal fumes, and solvents [13]. It has been estimated that over half of all cancer deaths attributed to occupational exposures occurred among construction workers, and among these construction workers, lung cancer accounted for the largest proportion of occupation-attributable cancer deaths (47%) [14].

Asbestos and Other Fibers

The first evidence of increased risk of lung cancer following inhalation of asbestos fibers dates from the 1950s [15], and asbestos is responsible for a large number of occupationally related lung cancers. All different forms of asbestos—chrysotile and amphiboles, including crocidolite, amosite, and tremolite—are carcinogenic to the human lung, although the potency of chrysotile might be lower than that of other types [16]. All forms of asbestos have long been recognized as human carcinogens by IARC [17]. This conclusion is based largely on unequivocal evidence assembled from epidemiological studies that have found excesses of lung cancer and mesothelioma in highly exposed textile workers, miners, and cement factory workers [17]. Occupational exposure to asbestos has decreased dramatically over the past two decades due to bans in many countries; a substantial number of workers are still exposed, mainly in the construction industry especially in low- and medium-resource countries. The risk of lung cancer appears to increase by approximately 4% for a cumulative exposure of 1 fb/mL-year [18]; however, the estimates of risk are primarily based on studies conducted among highly exposed workers, and the extrapolation of results to low-level exposure circumstances is subject to considerable uncertainty.

The interaction between asbestos exposure and tobacco smoking in determining lung cancer risk has been subject to extensive research. The most widely accepted conclusion is that of an interaction intermediate between the additive and the multiplicative model [19]. A large pooled analysis provided additional results on the interaction between asbestos exposure and tobacco smoking on lung cancer risk. This was a combined data from 14 case–control studies conducted in 1985–2010 in Europe and Canada, including 17,705 lung cancer cases and 21,813 controls. A quantitative job-exposure matrix to estimate job-, time period-, and region-specific exposure levels was developed and fiber-years were calculated for each subject by linking the matrix with individual occupational histories. The fully adjusted OR for ever-exposure to asbestos was 1.24 (95% CI, 1.18, 1.31) in men and 1.12 (95% CI, 0.95, 1.31) in women. In men, increasing lung cancer risk was observed with increasing exposure in all smoking categories and for all three major lung cancer subtypes. In women, lung cancer risk for all subtypes was increased in current smokers (ORs ~two-fold). The joint effect of asbestos exposure and smoking did not deviate from multiplicative among men, and was more than additive among women [20].

Man-made vitreous fibers (MMVF) include glass wool, glass filaments, rock/slag wool (also referred to as mineral fibers), and refractory ceramic fibers [8]. They are widely used as substitutes for asbestos in insulation of residential and commercial settings, and they are structurally similar to asbestos fibers. This has contributed to the hypothesis that MMVF may cause cancer of the respiratory system. Two population-based case–control studies examined the effects of occupational asbestos as well as MMVF at low to moderate levels of exposure. Study I (1979 to 1986) comprised 857 cases and 1066 population and cancer controls. Study II (1996 to 2001) comprised 858 cases and 1295 population controls. A detailed job history was obtained to evaluate lifetime occupational exposure to 294 agents, including asbestos and MMVF. Low and moderate levels of exposure to asbestos were associated with excess risk of lung cancer (OR: 1.78; 95% CI: 0.94 to 3.36). Results for MMVF were inconclusive (OR: 1.10; 95% CI: 0.37 to 3.32) [21]. In 2002, IARC categorized MMVF (glass fibers and mineral fibers) in group 3, i.e., not classifiable as to carcinogenicity to humans based on inadequate evidence in humans and limited evidence in experimental animals [8].

Heavy Metals

Multiple studies have confirmed the association between occupational exposure to heavy metals such as arsenic, chromium, nickel, and cadmium (or their compounds) with lung cancer risk. Exposure to inorganic arsenic, a known lung carcinogen since the late 1960s, occurs mainly among workers employed in hot smelting. Other groups at increased risk include fur handlers, manufacturers of sheep-dip compounds and pesticides, and vineyard workers [22]. Chromium [VI] compounds increase the risk of lung cancer among chromate-production workers, chromate-pigment manufacturers, chromium platers, and ferrochromium producers. No such risk has been detected among workers exposed only to chromium [III] compounds. Studies of nickel miners, smelters, electrolysis workers, and high-nickel alloy manufacturers showed an increased risk of lung cancer [22]. There is debate on whether all nickel compounds are carcinogenic for humans; the available evidence does not allow a clear separation between different nickel salts to which workers are exposed. An increased risk of lung cancer has been demonstrated among workers in cadmium-based battery manufacture, copper-cadmium alloy workers, and cadmium smelters. The increased risk does not seem to be attributable to concomitant exposure to nickel or arsenic. Studies from the United States showed an excess risk of lung cancer among workers exposed to beryllium in the early technological phase of the industry [23] although the relevance of these results for current exposure circumstances has been debated [24].

Employment as either a welder or a foundry worker is associated with a non-significant increased risk of lung cancer (HR: 1.12, 95% CI: 0.91 to 1.37) and (HR: 1.09, 95% CI 0.85 to 1.39), respectively. Further, there is a joint effect in that those who are ever employed in both occupations with significantly increased risks (HR: 1.48, 95% CI: 1.08 to 2.04)) [25]. A study in Canada found that exposure to welding fumes was related to an excess risk of lung cancer in light smokers, but not heavy smokers [26]. Additionally, a study in Eastern and Central Europe found a significantly increased risk in those with more than 25 years of welding fume exposure adjusted for smoking [27]. The equivocal findings for welding may be attributed to differences in adjustment for smoking across studies. Smoking is a strong confounder because it is heavier and more common among metalworkers than the general population, and is an established risk factor for lung cancer. Welders and foundry workers are considered to be at high risk for lung cancer as fumes containing heavy and transition metals can induce local inflammation in lung tissue, lipid peroxidation of cell membranes, and oxidative damage to the genome. Welding fumes are complex mixtures formed by the filler material, gas flows, the metal surface to be welded and its coverings. Different carcinogens are found in welding fumes, but many studies focused on hexavalent chromium and nickel oxides [28].

Crystalline Silica

More than half of 11 million workers in the construction industry of the European Union are exposed to carcinogenic agents [29]. The most prevalent of these carcinogens is crystalline silica in the form of quartz dust (19% of the workforce exposed). In addition to construction workers, silica exposure is also high for miners and glass or ceramics industry workers. Crystalline silica is classified by IARC as carcinogenic to humans (class 1). An increased risk of lung cancer has been consistently reported in cohorts of silicotic patients [30]. Many authors investigated crystalline silica-exposed workers in foundries, pottery making, ceramics, diatomaceous earth mining, brick making, and stone cutting, some of whom might have developed silicosis. An increased risk of lung cancer was reported by some, but not all, studies, and in the positive studies the increase was small, with evidence of an exposure–response relationship [31].

Respirable crystalline silica is a highly prevalent occupational exposure and a recognized lung carcinogen. Two large population-based case–control studies of lung cancer were conducted in Montreal, one in 1979–1986 (857 cases, 533 population controls, 1349 cancer controls) and another in 1996–2001 (738 cases and 899 controls). Interviews provided descriptive lifetime job histories, smoking histories, and other information. Industrial hygienists translated job

histories into histories of exposure to a host of occupational substances, including silica. The OR for substantial exposure to silica was 1.67 (95% CI: 1.21 to 2.31) and for any exposure was 1.31 (95% CI: 1.08 to 1.59). Joint effects between silica and smoking appeared to be between additive and multiplicative. The study concluded that in this population, approximately 3% of lung cancers were attributable to substantial silica exposure [32].

Some specific occupations in the construction industry have higher silica exposure such as bricklayers. SYNERGY was a large international pooled analysis of case–control studies on lung cancer and the joint effects of occupational carcinogens. Among 15,608 cases and 18,531 controls, there were 695 cases and 469 controls who had ever worked as bricklayers and these participants had a significantly higher risk of lung cancer (OR: 1.47, 95% CI: 1.28 to 1.68) [33].

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are a complex and important group of chemicals formed during combustion of organic material. An increased risk of lung cancer has been demonstrated in several industries and occupations entailing exposure to PAHs such as aluminum production, coal gasification, coke production, iron and steel founding, tar distillation, roofing, and chimney sweeping [34]. An increased risk has also been suggested in other industries, including shale oil extraction, wood impregnation, road paving, carbon black production, and carbon electrode manufacture, with an exposure–response relationship in studies with detailed exposure information. In different cohort studies, a positive dose–response relationship between PAH exposure time and lung cancer has been described [35]. A significant risk of lung cancer has been reported in the coal/coke and related product industry to be 1.55 (95% CI 1.01–2.37) and the iron/steel foundry industry to be 1.52 (95% CI 1.05–2.20) [36]. Exposure to PAHs is one of the suspected causes of cancer in these industries. A population-based case–control using cases from the Cancer Registry of Norway (1980 to 1992) also reported higher risk for lung cancer (OR: 2.9, 95% CI: 1.2 to 6.7) associated with exposure to PAHs [37].

Motor Exhaust/Diesel Engine Emissions

Diesel engine emissions (also referred to as diesel exhaust) are highly complex mixtures that vary widely depending on engine type, fuel type, and operating conditions. The components of exhaust most often quantified in occupational setting are particles, carbon monoxide, and nitrogen oxides, but PAHs and aldehydes have also been measured in work environments [38]. In 2012, IARC reclassified diesel exhaust from Group 2A (probably carcinogenic to humans) to Group 1 (carcinogenic to humans) based on experimental findings and evidence of lung cancer in humans [39]. The Diesel Exhaust in Miners study (DEMS) was a nested case–control study in a cohort of 12,315 workers in eight non-metal mining facilities, which included 198 lung cancer deaths and 562 incidence density-sampled control subjects [40]. The study reported statistically significant increasing trends in lung cancer risk with increasing cumulative diesel exhaust exposure, represented by respirable elemental carbon (REC). Among the heavily exposed workers (above the median of the top quartile [REC $\geq$ 1005 μg/m^3-year]), risk was approximately three times greater (OR: 3.20, 95% CI: 1.33 to 7.69) than that among workers in the lowest quartile of exposure. The study also reported an interaction between smoking and 15-year lagged cumulative REC such that the effect of each of these exposures was attenuated in the presence of high levels of the other. The study thus provided further evidence that diesel exhaust exposure is associated with lung cancer.

A meta-analysis combined data from 19 studies and reported a significantly increased risk of lung cancer (pooled smoking-adjusted RR: 1.18, 95% CI: 1.05 to 1.33) among professional drivers. A higher pooled RR was observed among smoking-adjusted studies reporting 10 years or more of employment as compared with the study having a shorter duration of employment (6 years). This meta-analysis revealed that the 18% excess risk of lung cancer was linked to professional drivers who are potentially exposed to diesel exhaust, after adjustment for the confounding effect of smoking [41]. The SYNERGY project pooled information on lifetime work histories and tobacco smoking from 13,304 cases and 16,282 controls from 11 case–control studies conducted in Europe and Canada. A general population job-exposure matrix, assigning no, low, or high exposure to diesel motor exhaust, was applied to determine the level of exposure. Cumulative diesel exposure was associated with an increased lung cancer risk in highest quartile versus unexposed (OR: 1.31, 95% CI: 1.19 to 1.43), and a significant exposure–response relationship (P value <0.01) [42].

Wood Dust

Wood dust is one of the most common occupational exposures, with millions of workers exposed worldwide [43]. The amount and size of particles also differ according to the operations performed on wood. For example, shattering wood cells during sanding operations produces finer particle size than does chipping in sawing and milling industries [44]. Wood dust has long been recognized as a respiratory irritant,

with studies of dust from certain tree species demonstrating adverse effects on the lung, including asthma, chronic obstructive pulmonary disease, decline in lung function over the workshift, and decreased forced vital capacity, among woodworkers in a variety of jobs [45, 46]. Worldwide, about two-thirds of the wood used for industrial purposes is softwood (conifers) and one-third is hardwood (deciduous trees), where most of the harvested hardwood is consumed as fuel. In 1995, wood dust was designated by the IARC as a known human carcinogen (Group 1) based on increased sinus and nasal cancer rates among workers exposed to hardwood dusts. While sinonasal cancer has been clearly associated with hardwood dust, increased risks with softwood dust have not been ruled out.

Occupation exposure to wood dust is highest for occupations such as carpenters and wood workers. A population-based case–control study with 440 cases and 845 age-matched controls observed an increased risk of lung cancer associated with working in sawmills (OR: 1.5, 95% CI: 1.1 to 2.1), but found no evidence of increased risks with other wood-related occupations. This study provided somewhat reassuring evidence that softwood dust does not increase the risk of lung cancer [44]. Two population-based case–control studies in Montreal evaluated the association between wood dust and lung cancer. Study I (1979–1986) included 857 cases and two sets of controls (533 population and 1349 cancer controls), and Study II (1996–2001) comprised 736 cases and 894 population controls. There was an increased risk of lung cancer for substantial cumulative exposure to wood dust in Study I with cancer controls (OR: 1.4, 95% CI: 1.0 to 2.0) and in Study II (OR: 1.7, 95% CI: 1.1 to 2.7). There were no excess risks of lung cancer in any of the three datasets among workers whose cumulative exposure was not substantial [47].

Organic Dust

Organic dust consists of particulate matter from microbial, plant or animal origin. Organic dust is present in many work environments, such as in agriculture, sawmills, or the meat industry. The SYNERGY project pooled information on lifetime working and smoking from 13,300 lung cancer cases and 16,273 controls from 11 case–control studies conducted in Europe and Canada. A newly developed general population job-exposure matrix (assigning no, low, or high exposure to organic dust, endotoxin, and contact with animals or fresh animal products) was applied to determine the level of exposure. The study reported that occupational organic dust exposure was associated with increased lung cancer risk. The second to the fourth quartile of cumulative exposure showed significant risk estimates ranging from 1.12 to 1.24 in a dose-dependent manner ($p < 0.001$). No association was observed between lung cancer and exposure to endotoxin or contact with animals or animal products [48].

An increased risk of lung cancer has been reported for butchers and meat workers in several cohort studies [49, 50], although confounding from tobacco smoking could not be ruled out in any of these studies. A large case–control study with full adjustment for smoking evaluated more than 5900 subjects from 7 European countries. For each job, local experts assessed the exposure: (1) meat aerosols and (2) live animals. A small increased risk of lung cancer was observed with exposure to meat aerosols, after adjusting for smoking, (OR: 1.27, 95% CI: 0.92 to 1.75), which was most apparent for the upper tertile of cumulative exposure. A similar overall effect was observed for exposure to live animals, with an increased risk observed (OR: 1.69, 95% CI: 1.21 to 2.36), with significant trends for increasing frequency ($p = 0.012$), intensity ($p = 0.015$), and cumulative exposure ($p = 0.024$). In conclusion, this study provided evidence for an association between exposure to meat aerosols and lung cancer apparent in the highest tertile of exposure. The authors identified a more consistent association with exposure to live animals [51].

Chlorinated Solvents

Chlorinated solvents have many industrial applications and are used as degreasers, paint strippers, dry-cleaning solvents, spot removers, chemical reaction intermediates, aerosol propellants, and anesthetic gas. Two case–control studies of occupation and lung cancer were conducted in Montreal and included 2016 cases and 2001 population controls. The studies examined associations between lung cancer among men and six specific chlorinated solvents and two chemical families (chlorinated alkanes and alkenes). When the two studies were pooled, there was increased risk of lung cancer associated with occupational exposure to perchloroethylene (OR (any exposure): 2.5, 95% CI: 1.2 to 5.6; OR (substantial exposure) 2.4, 95% CI 0.8 to 7.7) and to carbon tetrachloride (OR (any exposure) 1.2, 95% CI 0.8 to 2.1; OR (substantial exposure) 2.5, 95% CI 1.1 to 5.7). No other chlorinated solvents showed both statistically significant associations and dose–response relationships [52].

Paint/Varnishes

Paint, varnish, and stain products contain thousands of chemical components that are used as pigments, extenders, binders, solvents, and additives. The chemistry of paint products has evolved over time. An increased incidence and mortality from

lung cancer has been observed in painters, an occupation that employs several million people worldwide. This has led IARC to classify occupational exposure as a painter as carcinogenic to humans (Group 1) [53]. A meta-analysis combined data from 47 independent cohort, record linkage, and case–control studies, including >11,000 incident cases or deaths from lung cancer among painters. The summary relative risk (meta-RR, random effects) for lung cancer in painters was 1.35 (95% CI: 1.29 to 1.41) and 1.35 (95% CI: 1.21 to 1.51) after controlling for smoking. The results remained robust when stratified by study design, sex, and study location and are therefore unlikely due to chance or bias. Furthermore, exposure response analyses suggested that the risk increased with duration of employment [54].

Proportion of Lung Cancers Attributable to Occupational Exposures

Several studies have estimated the proportion of cases or deaths from lung cancer that can be attributed to occupational exposures. Results among men are summarized in Table 15.2. The methodology used in these studies was slightly different, in particular in the selection of agents to include. In most studies, the attributable proportion is in the order of 10–15%, with one study from the UK providing a higher estimate [6]. That study, however, included also suspected lung carcinogens in the calculation. Corresponding figures for women are in the range of 2–5%. In these studies, asbestos, PAHs, and silica were the main contributors to the overall burden of occupational lung cancer. It should be stressed, however, that the results of studies of attributable fractions reflect the current burden of lung cancer, which is due to past exposures. The effect of current exposures is expected to be lower, because of the reduction in the number of workers exposed to occupational lung carcinogens, and reduced exposure levels.

Table 15.2 Proportion of lung cancer cases among men attributable to occupational exposures in selected studies

Study	Population	Method	PAF (%)
Doll and Peto [56]	USA	Review	15
Dreyer and Winther [57]	Nordic countries	Known carcinogens	13
Driscoll et al. [58]	Western Europe	Selected carcinogens	10
Boffetta et al. [59]	France	Known carcinogens	8
Rushton et al. [6]	UK	Known, suspected carcinogens	21
Wang et al. [60]	China	4 carcinogens	15
Azevedo et al. [61]	Brazil	Selected carcinogens	14

PAF population attributable fraction

Conclusions

Occupational exposures represent an important cause of lung cancer. The list of occupational agents causally linked to lung cancer is longer than for any other cancer. Among the possible reasons for the important burden of occupational lung cancer are the facts that inhalation represents an important route of exposure to occupational agents, and that tobacco smoking, the main cause of the disease, may exert an interaction with occupational carcinogens, thus enhancing their etiologic role.

Epidemiology and occupational medicine have been instrumental in identifying important causes of lung cancer, which in turn has led to prevention strategies involving technological changes and industrial hygiene measures. In several industries in which an increased risk has been shown among workers employed in the early part of the twentieth century, before the identification of occupational carcinogens, no residual risk of lung cancer has been detected among workers employed after preventive measures were implemented. For example, the excess risk of lung cancer among beryllium manufacturing workers appears to be restricted to workers employed in this industry before 1965 [24], and among silicon carbide workers only those involved in the Acheson process experienced an increased risk of lung cancer [55].

However, not all exposures to occupational lung carcinogens have ceased or have been adequately controlled, and priority for prevention should be given to the most prevalent agents, such as PAHs and crystalline silica. In addition, because of the long latency of lung cancer, the sequelae of past high-level occupational carcinogenic exposure will remain apparent for several decades, with important medical and economic consequences.

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Malignant Mesothelioma: Clinical and Imaging Findings

16

Naveed Z. Alam and Raja M. Flores

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. Eighty to ninety percent 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, 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

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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. 16.1) and possibly some pleural plaques indicative of asbestos exposure [10]. In more advanced cases, the CXR may also demonstrate pleural thickening and nodularity.

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. 16.2 and 16.3). Alternatively, the first presentation on CT may consist of subtle pleural thickening or one or more discrete pleural-based masses (Fig. 16.4). These masses may be on any of the

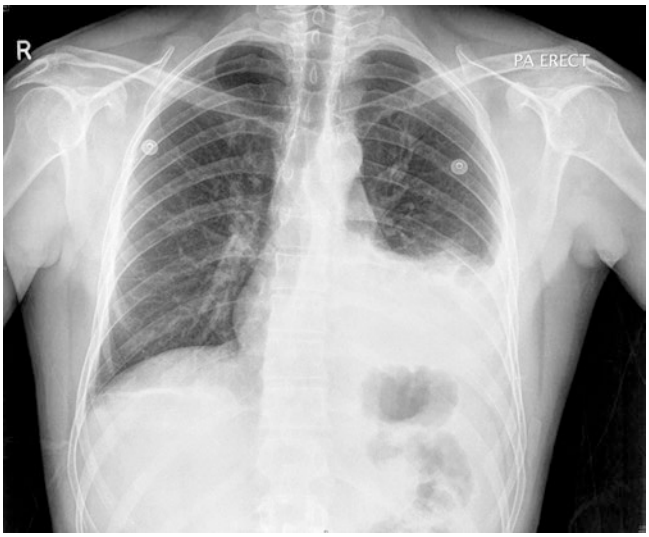

Fig. 16.1 CXR PA erect—early simple pleural effusion

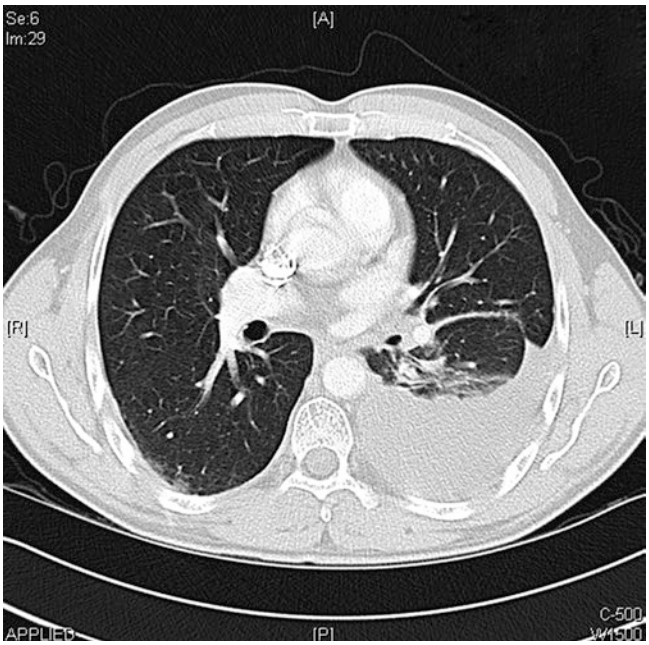

Fig. 16.2 CT—early disease—simple pleural effusion

pleural surfaces, including the visceral pleural reflections within the fissures (Figs. 16.5, 16.6, 16.7, and 16.8). As the disease progresses, larger masses are evident and may become confluent (Fig. 16.9). There may be associated multiloculated pleural effusions. Although a solitary dominant pleural mass may occasionally be present initially (Fig. 16.10a), the disease almost always progresses to a diffuse, thick, confluent pleural rind which encases the lung and obliterates the pleural space [12].

In advanced cases, the presence of mediastinal lymphadenopathy may be evident (Fig. 16.11). In addition to lymph node metastases in the usual lung cancer locations, e.g., paratracheal, para-aortic, and subcarinal, lymph node

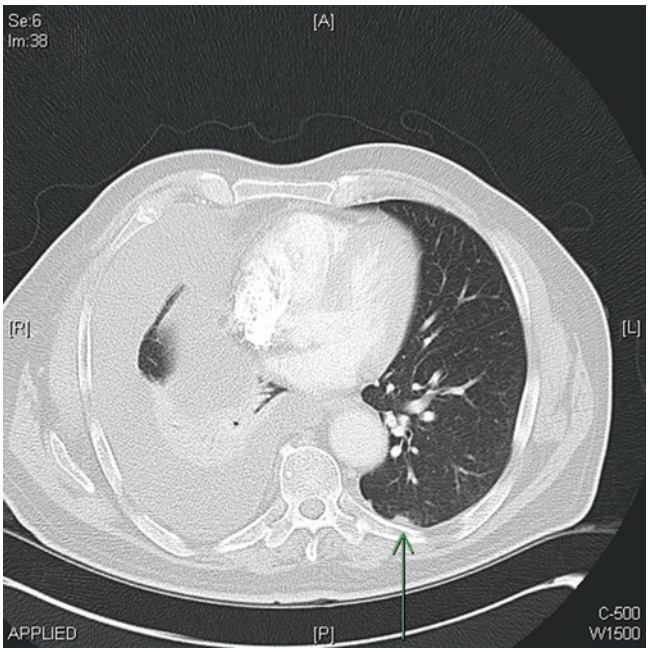

Fig. 16.3 CT—early disease. Simple pleural effusion with contralateral asbestos plaque (*green arrow*)

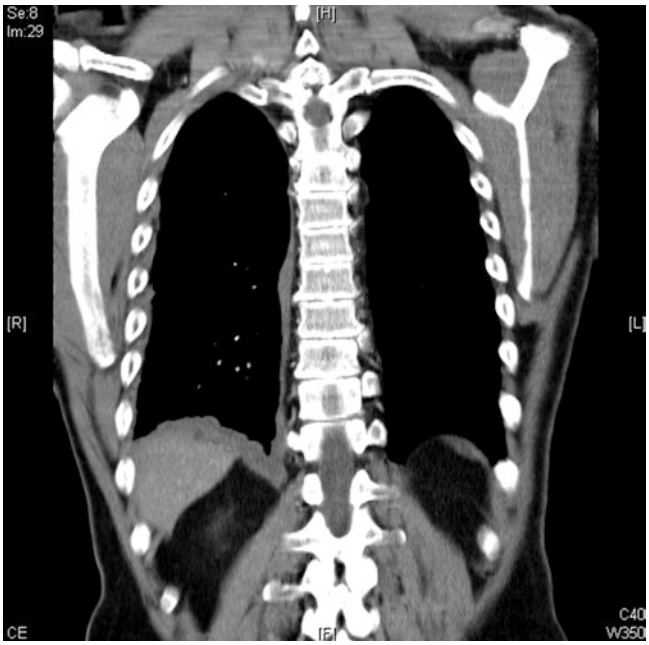

Fig. 16.5 Thickening of diaphragmatic and mediastinal pleural surfaces

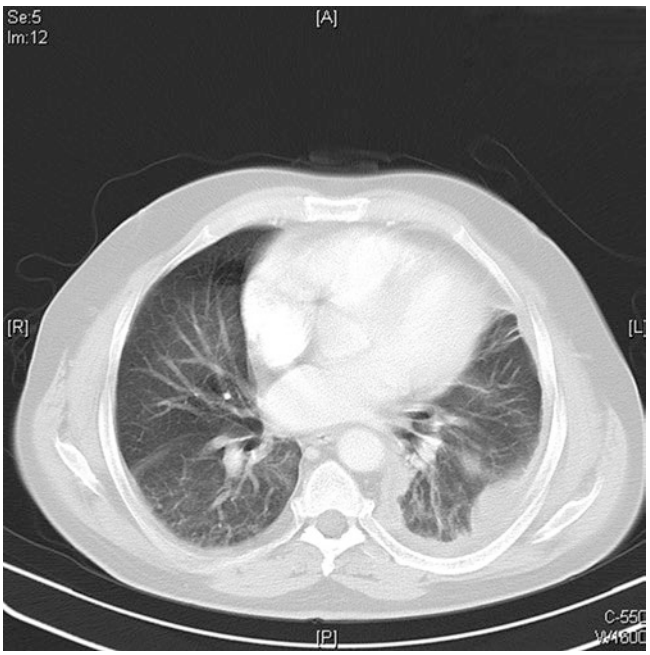

Fig. 16.4 Pleural mass with effusion

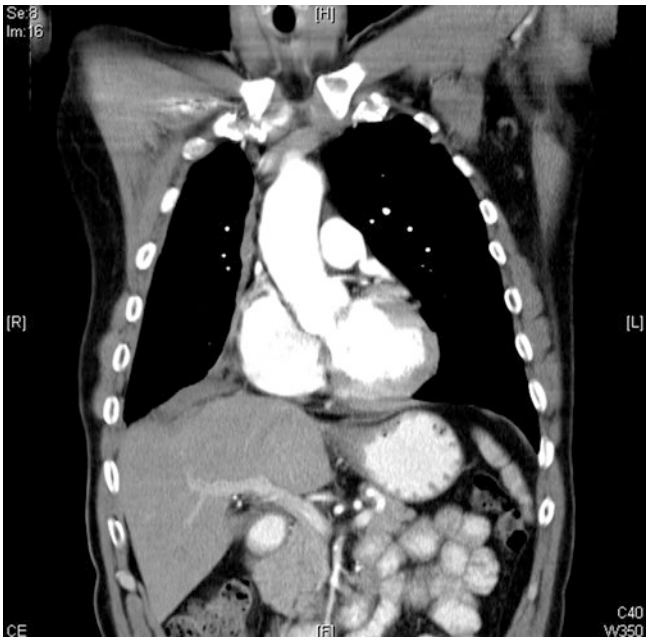

Fig. 16.6 Thickening of pericardium and mediastinal pleura. Note contraction of right hemithorax

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. 16.12). 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. 16.10a) [13].

Magnetic Resonance Imaging (MRI)

The main limitation of CT in evaluation of MM is related to assessing the presence of chest wall invasion (Fig. 16.10b) 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

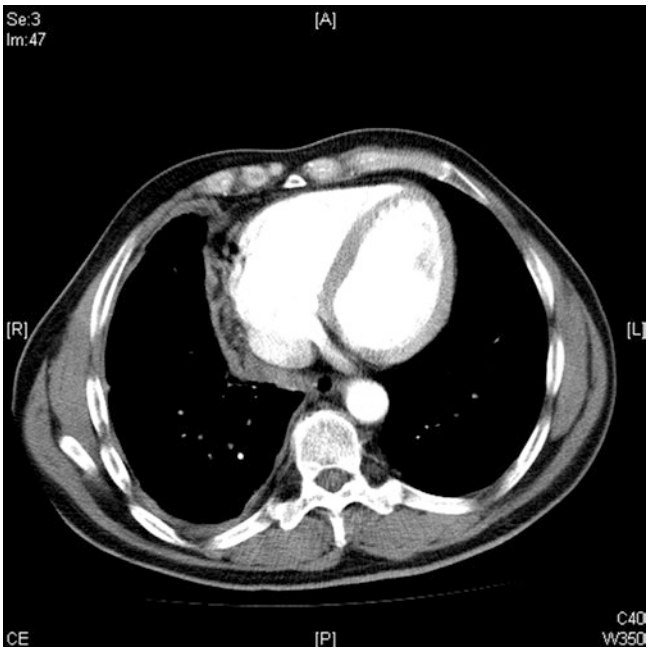

Fig. 16.7 Pericardial thickening

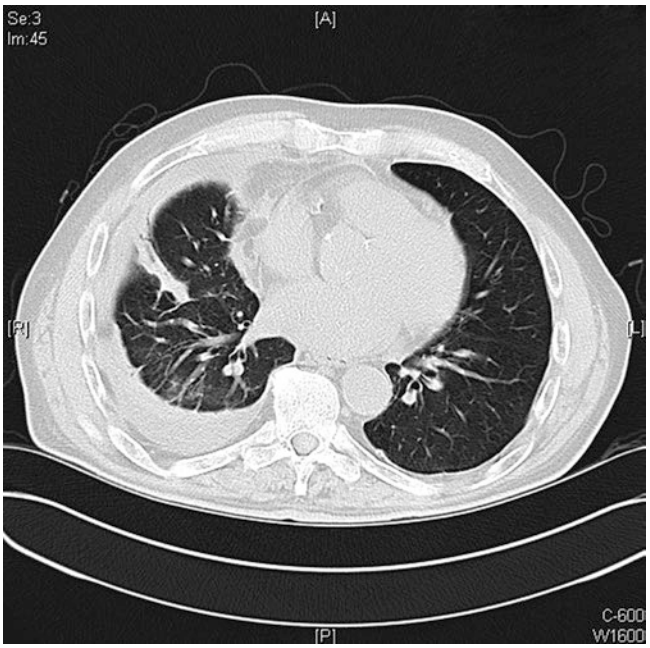

Fig. 16.8 Tumor in oblique fissure

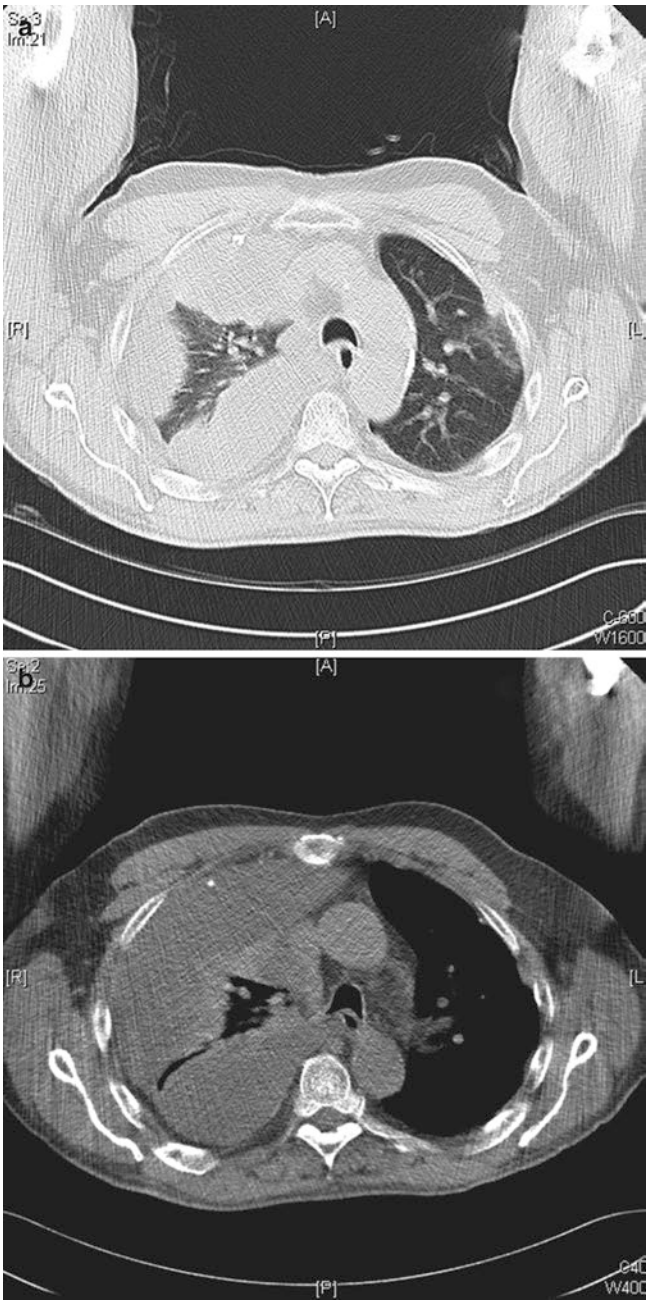

Fig. 16.9 (**a**) Multiple large, confluent masses. (**b**) Note mediastinal shift

pneumonectomy or pleurectomy/decortication. MM enhances with the use of gadolinium-based contrast, which aids in the discrimination of tumor from surrounding normal tissue. MM is typically slightly hyperintense on T1-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

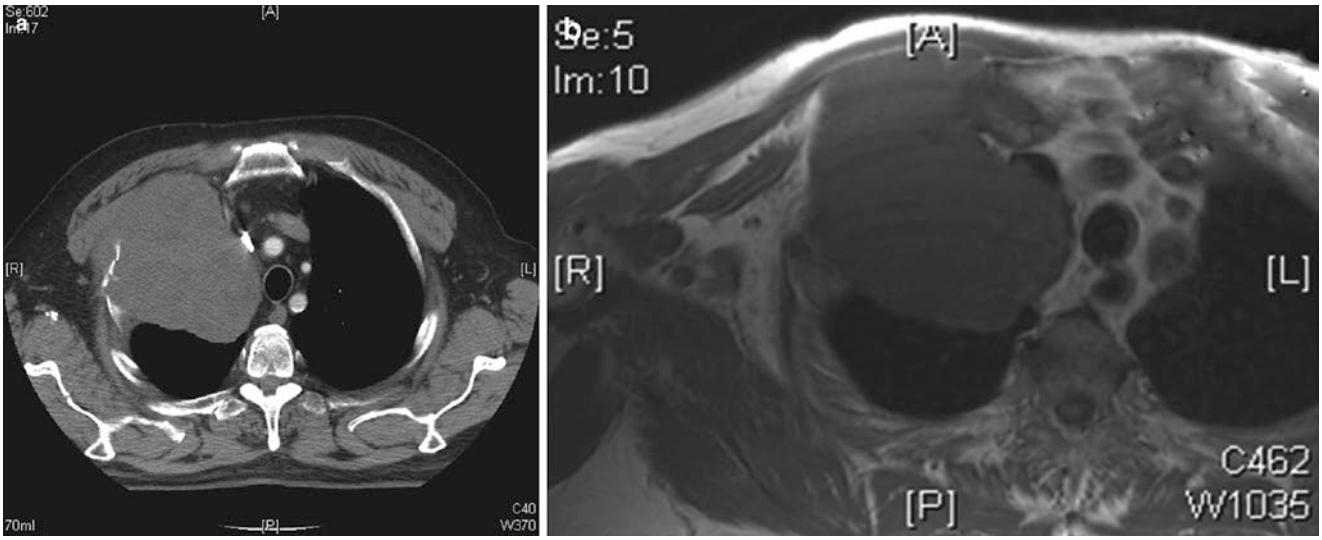

Fig. 16.10 (**a**) Unusual solitary dominant mass. Note chest wall invasion through intercostal muscles. (**b**) MRI showing chest wall invasion

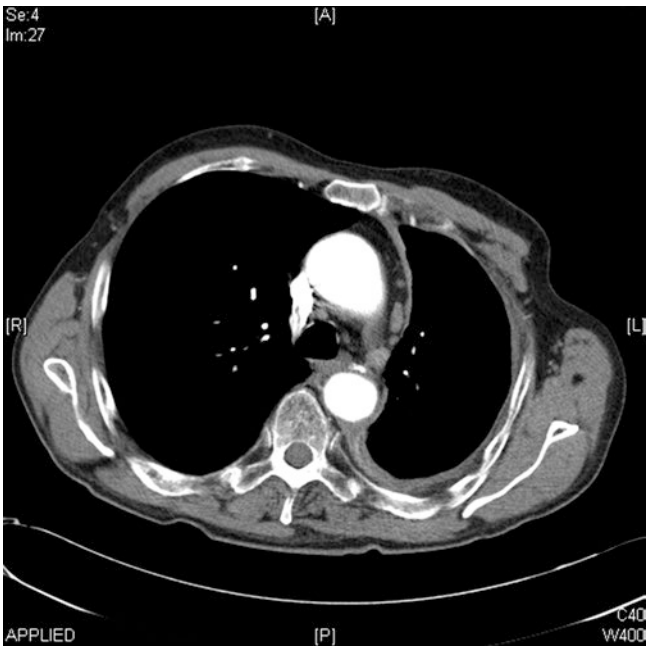

Fig. 16.11 Para-aortic lymphadenopathy

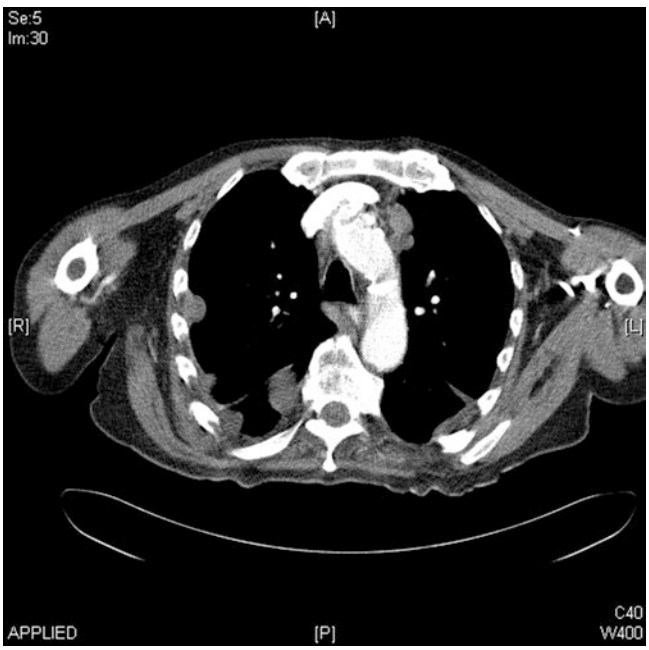

Fig. 16.12 Left internal mammary chain lymphadenopathy

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 prognosis 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 upbiting rigid bronchoscopy biopsy forceps 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.

Table 16.1 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

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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 16.1). 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 16.2).

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.

Table 16.2 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

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Malignant Mesothelioma: Pathology

17

Sisko Anttila

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 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. Until the present time, it has not been 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. However, a cytological MM diagnosis may be made when appropriate cytological features are present together with typical clinical and imaging findings of MM [2, 3]. New specific markers, such as loss of BRCA1-associated protein 1 (BAP1) immunostaining and homozygous deletion of 9p21 region (*CDKN2A*, *p16*) detectable by FISH or by immunostaining for methylthioadenosine phosphorylase (MTAP), may be used for differentiating benign from malignant mesothelial proliferations [4–6]. 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. 17.1). 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.

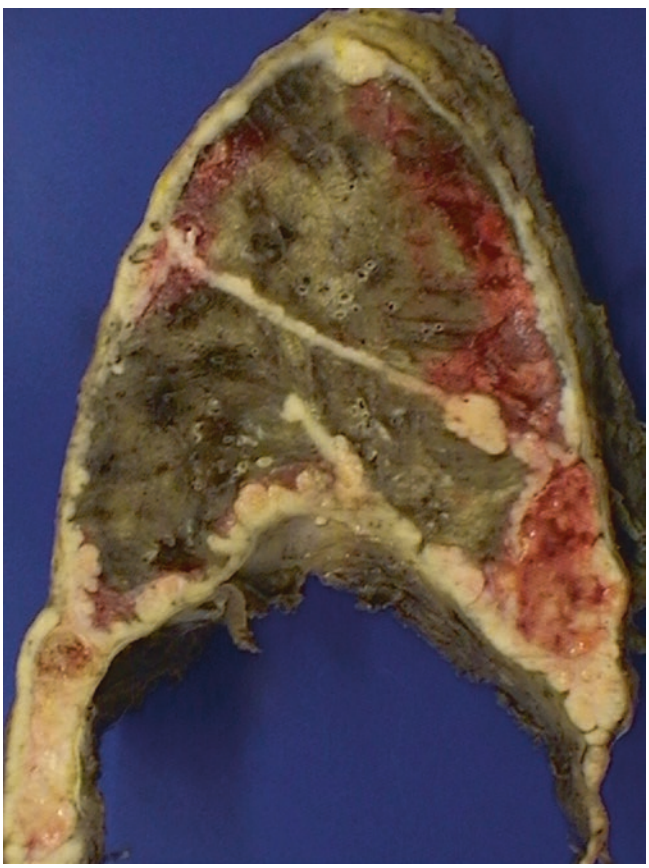

Fig. 17.1 Extrapleural pneumonectomy specimen. Malignant mesothelioma tumor tissue encases the lung and fills interlobar spaces (Photo courtesy of Dr. Mikko Rönty)

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Morphological Subtypes of Malignant Mesothelioma

MM is divided into epithelioid, biphasic, and sarcomatoid main morphological subtypes. Desmoplastic MM is classified as a variant of sarcomatoid MM in the present WHO classification of lung tumors [7]. Although the prognosis of all diffuse MM is poor, it is worse for sarcomatoid and biphasic MM than for epithelioid MM [8, 9], which makes it important to include the subtype in the pathologist's report. Furthermore, patients with a diagnosis of sarcomatoid MM do not benefit from extrapleural pneumonectomy [10–12]. Biphasic MM contains an epithelioid subtype together with a sarcomatoid component, and each component should cover at least 10% of the tumor tissue [7]. 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.

Recent research has shown that within epithelioid subtype, certain morphological patterns, such as myxoid, microcystic and tubulopapillary patterns are associated with a longer patient survival than solid, micropapillary and pleomorphic patterns [13, 14]. A few rare growth patterns of epithelioid and sarcomatoid MM are known, such as clear cell, deciduoid, signet ring, and small cell patterns of epithelioid MM and heterologous MM pattern of sarcomatoid MM [15, 16]. 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 [17–19]. 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 [15] (Fig. 17.2). Two patterns do not clearly belong to any main subtype, namely, lymphohistiocytoid and transitional, where epithelioid and sarcomatoid features bend in the same cells (Fig. 17.2). Pleomorphic MMs, consisting of anaplastic and giant cells in more than 10% of the tumor, are classified under epithelioid subtype in the present WHO classification of lung tumors [7, 20, 21]. Kadota et al. analyzed 232 epithelioid MMs by their predominant growth pattern and observed that 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 [14].

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. 17.2). 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 [22, 23]. 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 [24, 25]. PAS-positive glycogen granules occur commonly in epithelioid MM. Psammoma bodies may be observed in epithelioid MM.

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. A chronic persistent injury of the serosal surface leads to mesothelial cell hyperplasia and the proliferation of myofibroblastic cells. 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 [26, 27].

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. 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 [28–30]. 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.

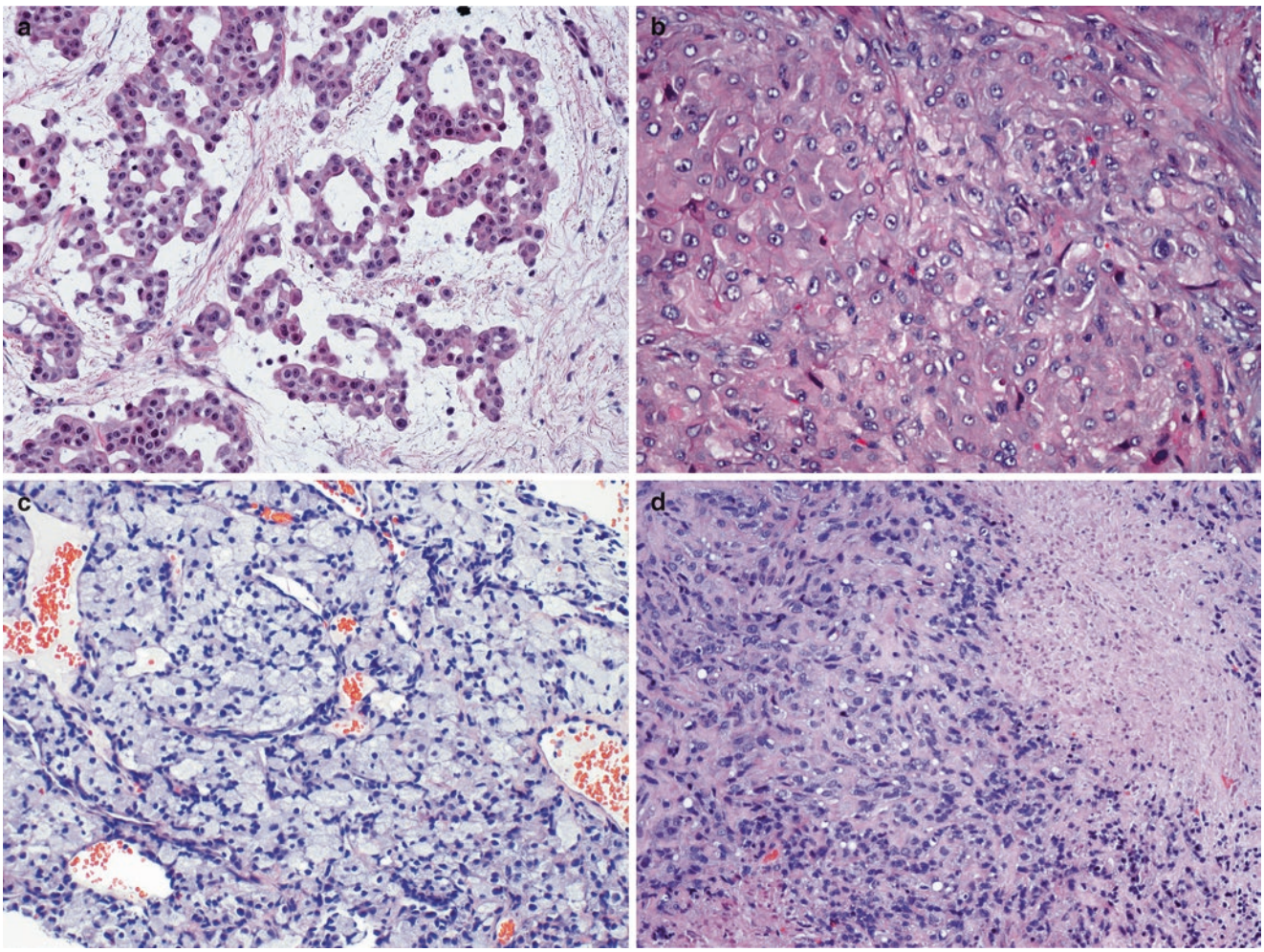

Fig. 17.2 Epithelioid malignant mesothelioma. Papillary structures in loose myxoid stroma (**a**). Solid pattern with deciduoid features (**b**), clear cell pattern (**c**), and transitional pattern between epithelioid and sarcomatoid type and necrosis (**d**) (H&E; medium magnification)

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. 17.3). Sometimes a population of cells that are considerably larger than their normal and hyperplastic counterparts can be observed [26, 31].

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 [29]. Recently found specific markers of mesothelial malignancy, namely, the loss of BAP1 immunostaining and homozygous deletion of 9p21 (*CDKN2A*) chromosomal locus, can be applied to effusion cytology specimens ([4–6]; see section Molecular Markers in the Diagnosis of Malignant Mesothelioma in this Chapter).

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]. 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 or specificity of 80% or more in the detection of MM [3]. Positive and negative markers for

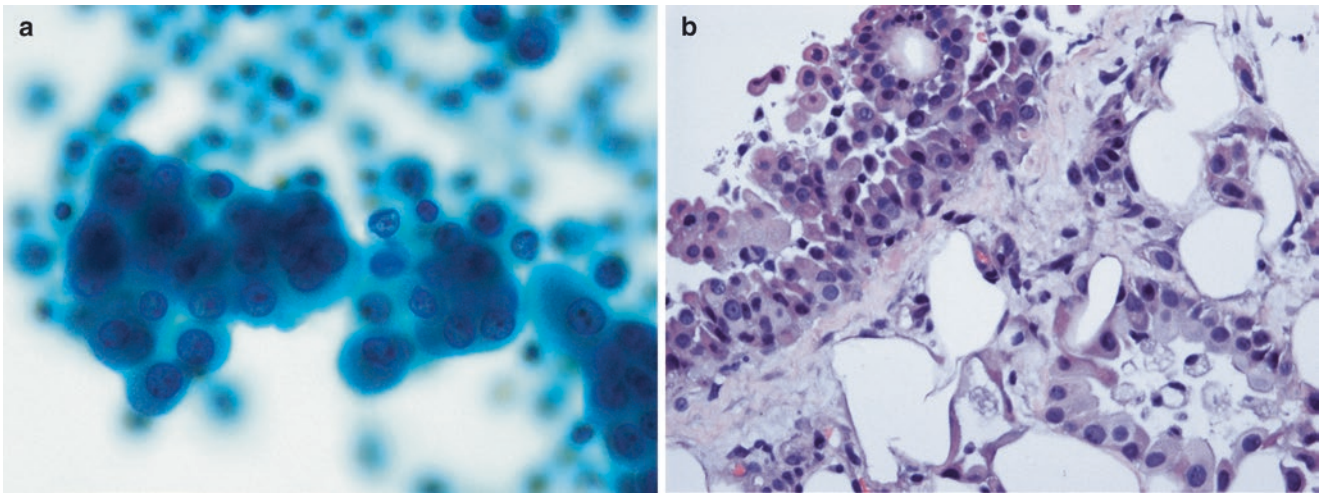

Fig. 17.3 Effusion cytology of epithelioid malignant mesothelioma. A cluster of tumor cells in a cytological specimen (**a**, Papanicolaou's stain, high magnification). Histology of the same mesothelioma case (**b**, H&E; medium magnification)

Table 17.1 Positive markers of epithelioid malignant mesothelioma

	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	4–23	4–39	0–10	39–52	4–13	0–7
Squamous cell lung carcinoma	22–40	87–100	0–2	16–31	71–100	0–50
Large cell lung carcinoma	37–38	47–50	0	14	13–50	0
Small cell lung carcinoma	40–49	27–49	0	0	11–27	0
Breast cancer, various types[d]	4–74	31–84	0–23	0–28	2–18	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

Comparison of immunostaining in epithelioid malignant mesothelioma and relevant other tumor types
Modified from [32]
Range of positive immunostaining, if more than one study (Data from Refs. [33–54])
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
[d]Mesothelial markers are commonly expressed in basal-like carcinomas of breast

the differential diagnosis of epithelioid MM and metastatic carcinomas of pleural and peritoneal cavity are suggested in Tables 17.1, 17.2, and 17.3. The proportions of tumors given in Tables 17.1, 17.2, and 17.3 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 [69, 70], whereas poorly differentiated, pleomorphic, or sarcomatoid MM may be negative or only partially positive with some or all mesothelial markers [71, 72]. 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 (Table 17.1). 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 [36, 37, 70, 73–77].

Table 17.2 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	[33, 35, 48–51, 55]
	Napsin A	80–83	0	[56, 57]
	CEA	83–97	0–5	[48, 49, 57]
	CD15 (LeuM1)	72	0–7	[48, 49]
	Ber-EP4	80–100	5–26	[48–50]
	BG-8 (Lewis^y)	93–100	2–7	[35, 48–50]
	MOC-31	93–100	5–13	[48–51]
	Claudin-4	95–100	0–14	[57–59]
	MUC4	83	0	[57]
Squamous cell lung carcinoma	p40	98	5	[57]
	p63	100	7–23	[46, 47, 60]
	MOC-31	91–97	5–13	[46, 47, 60]
	Ber-EP4	87	5–26	[46, 47, 60]
	BG-8 (Lewis^y)	80	2–7	[46, 47, 60]
	MUC4	89	0	[57]
	Claudin 4	98	0	[57]
Renal cell carcinoma	CD15 (LeuM1)[a]	25–100	0–3	[61]
	MOC-31[b]	38–75	5–13	[61]
	RCC Ma[c]	50–75	8–26	[61, 62]
	Ber-EP4	42	5–26	[61]
	PAX8	80–95	0–4	[63–65]
Breast carcinoma	BG-8 (Lewis^y)	96–100	2–7	[35, 50]
	Claudin-4	100	0	[54]

Modified from [32]
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

Table 17.3 Examples of negative markers for differential diagnosis of epithelioid MM and ovarian/peritoneal serous carcinoma

Marker	Positivity in serous carcinoma, %	Positivity in epithelioid MM, %
Ber-EP4	87–100	5–26
MOC-31	93–100	3–15
Estrogen receptor	60–100	0–2
B72.3	73–87	0–3
BG-8 (Lewis^y)	73	2–3
CA19-9	60–73	0
CD15 (LeuM1)	30–63	0–6
PAX8	93–100	0–12[a]
Claudin-4	98–100	0

Modified from [32]
Range of positive immunostaining, if more than one study (Data from Refs. [34, 36, 37, 43–47, 59, 60, 64–68])
MM malignant mesothelioma
[a]Peritoneal mesotheliomas may show weak immunostaining

Mesothelial Lesions Other than Malignant Mesothelioma

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 [78]. All of them are most common in the peritoneal cavity but may also occur in other body cavities. Well-differentiated papillary mesothelioma was originally known as a rare peritoneal tumor among young women but has also been described among men and in pleural, pericardial, and tunica vaginalis testis locations [79–83]. Histologically it is characterized by fungating papillary structures with a fibrovascular core and a single layer of mesothelial cells with benign appearance (Fig. 17.4). Although some reported patients have been exposed to asbestos, no epidemiological correlation between well-differentiated papillary mesothelioma and asbestos exposure has been established [81]. 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,

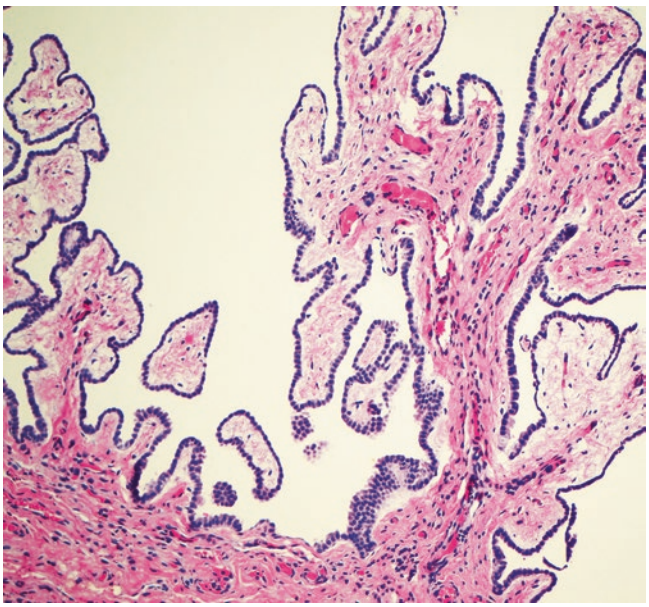

Fig. 17.4 Well-differentiated papillary mesothelioma. Fungating papillary structures on the serosal surface (H&E; low magnification)

intrahepatic, and intrapancreatic tumors with a serosal origin have been described [84–87]. Allen et al. [1] 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. 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. Several patients died of metastatic disease, but none of the patients had developed a diffuse MM at the time of death. 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 [7, 20, 25, 88, 89]. 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 [7, 25, 88, 89]. 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 [20]. In the 2015 WHO classification [7], the features of malignancy are divided into major criteria, which are stromal invasion, cellularity, type of papillary structures, growth pattern, zonation, and vascularity, whereas cytological atypia, necrosis, and mitoses are minor criteria. The features of benign and malignant mesothelial proliferations are listed in Table 17.4, and malignant features are illustrated in Fig. 17.5.

Table 17.4 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
Vascularity	Capillaries perpendicular to the surface	Irregular and haphazard
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. [7, 88, 89]

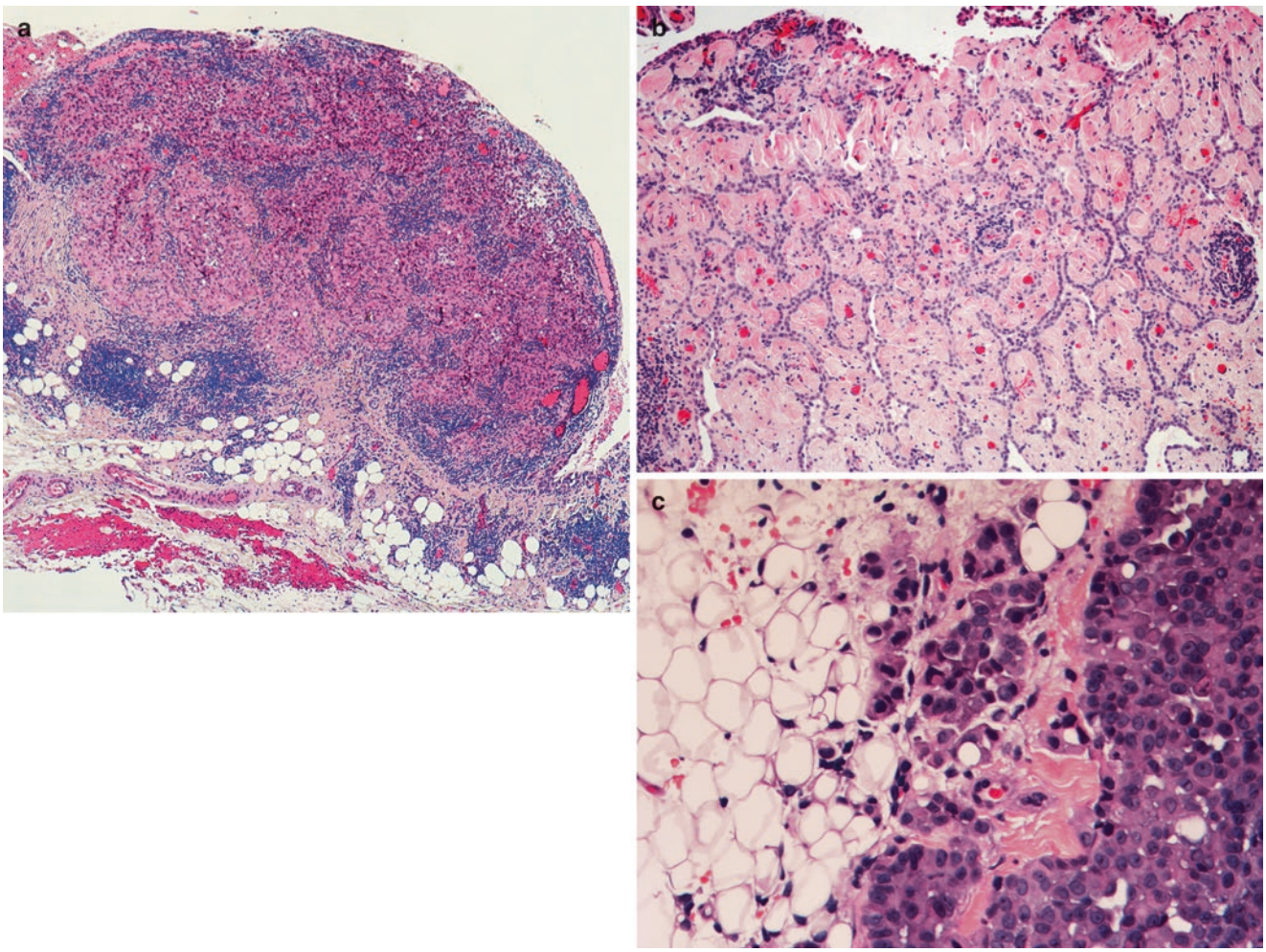

Fig. 17.5 Features of malignancy in the epithelioid mesothelial lesion. Large cellular nodules on the serosal surface (**a**), branching tubular structures (**b**), and invasion of parietal pleural fat layer (**c**) (H&E; **a**, **b**, low magnification; **c**, medium magnification)

Molecular Markers in the Diagnosis of Malignant Mesothelioma

Two common molecular alterations of MM, i.e., homozygous deletion of chromosomal region 9p21 (*CDKN2A* gene locus) and mutations or copy number changes of BRCA1-associated protein 1 (BAP1) resulting in loss of protein expression, have increasingly important role as diagnostic and prognostic markers of MM.

Previously, a large number of markers have been tested for their potential to aid in the differentiation between benign and malignant mesothelial proliferations. The most studied of those, such as desmin, epithelial membrane antigen (EMA), p53 protein, X-linked inhibitor of apoptosis protein (XIAP), and glucose transporter isoform-1 (GLUT-1), have all given inconsistent results in different studies and none of those can be applied to clinical practice [48, 49, 90–94].

9p21 (CDKN2A)

Homozygous deletion of 9p21 can be detected by FISH in tissue as well as in effusion cytology specimens in appr. 50–90% of epithelioid, 70–95% of biphasic, and 40–100% of sarcomatoid MMs, the proportion varying between different studies [4, 5, 95, 96, 99–103]. Chiosea et al. [95] were the first to apply 9p21 FISH to distinguish MM from benign mesothelial proliferations. The homozygous deletion of 9p21 appears to be specific to MM as benign mesothelial proliferations carrying this alteration have so far never been reported [96–98, 104].

The 9p21 region harbors several genes, i.e., methylthioadenosine phosphorylase (*MTAP*), *p14ARF*, *p15INK4B*, and *CDKN2A* (*p16INK4A*), which are often codeleted in MM [99]. So far, a FISH test has been applied to detect homozygous deletion of the *CDKN2A* locus as immunohistochemistry for p16 protein has shown unsatisfactory correlation with

deletion of the gene locus [e.g., [95, 96]]. Hida et al. [105] studied protein expression of the genes residing at 9p21.3 region and found best concordance between MTAP expression and homozygous deletion of 9p21. Later on, the group applied MTAP immunohistochemistry on pleural effusion cytology, and observed a sensitivity of 42% and specificity of 100% in distinguishing MM from reactive mesothelial proliferation, as compared to the sensitivity of 62% by 9p21 FISH [6].

Homozygous deletion of 9p21 chromosomal region and the deletions of *CDKN2A* and *MTAP* if studied separately are associated with poor prognosis of pleural and peritoneal MM, and the prognostic significance is independent of the histological subtype [106–108].

BAP1

Germline *BAP1* mutations were first discovered in two families with high incidence of MM [109]. Germline *BAP1* mutations, such as missense, nonsense, and frameshift mutations, were associated with a hereditary cancer syndrome causing high incidence of MM, ocular and cutaneous melanoma as well as renal, breast, and gastric cancers, among others [e.g., [110, 111]]. Ohar et al. [112] studied *BAP1* germline mutations in MM patients with a family history of cancer and found germline alterations in 6% of MM patients. *BAP1* mutation carriers developed MM at an earlier age, MMs were more often peritoneal, and mutation carriers had a better prognosis than MM patients without germline *BAP1* mutations. Asbestos exposure seems to influence cancer types in *BAP1* syndrome families so that asbestos-exposed persons develop MM more often than non-exposed mutation carriers [112, 113].

Somatic mutations of *BAP1* gene occur in both hereditary and sporadic MMs, leading to biallelic inactivation and loss of BAP1 protein expression [109, 114–116]. *BAP1* inactivation is readily detectable by immunohistochemistry as loss of BAP1 nuclear staining in cancer cells while normal inflammatory and stromal cells serve as internal positive control on the slide. BAP1 expression is lost in appr. 60–80% of epithelioid MM, in appr. 40% of biphasic MM, while only 0–20% of sarcomatoid MMs have lost BAP1 expression, the proportion depending on the study [4, 5, 115–117].

The loss of BAP1 is an excellent marker of malignancy in atypical mesothelial proliferations, showing a specificity of 100% and a sensitivity of 60–70% for distinguishing malignant from benign mesothelial proliferations in tissue and in effusion cytology specimens [4, 5, 97, 105, 114]. The combination of BAP1 immunohistochemistry and detection of 9p21 homozygous deletion by FISH increases the sensitivity for detecting malignancy up to over 80%, while applying MTAP immunostaining instead of FISH decreases the combined sensitivity by 10% [6, 97, 105].

The loss of BAP1 has been associated with a favorable prognosis of MM. However, no significant effect on survival has been observed independently of the epithelioid histological subtype, as loss of BAP1 associates with epithelioid rather than other MM subtypes [100, 108, 115].

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 [118]. Sometimes a stromal reaction may simulate a sarcomatoid tumor component [118]. 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 [70, 119]. Synovial sarcoma may express "mesothelial" markers calretinin and D2-40 [43, 44, 70], whereas bcl-2 and Ber-EP4 are commonly positive in synovial sarcoma and seldom in MM [70, 120–122]. 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 [120, 123].

The detection of homozygous deletion of 9p21 (*CDKN2A*) by FISH and/or loss of BAP1 by immunohistochemistry may aid the differentiation of biphasic from epithelioid subtypes. It has been shown that both genetic alterations are concordantly present or absent in epithelioid and sarcomatoid components, whereas neither markers are expressed in the fibrous stroma of epithelioid MM [102, 116].

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 [17–19]. 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 [72], only 2% of sarcomatoid MMs were of peritoneal origin. 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 [118].

The morphology of sarcomatoid MM is variable, and it may resemble any sarcoma or be a mixture of several morphological types (Fig. 17.6). Klebe et al. [72] 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. 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. 17.6a) [16, 122]. Some sarcomatoid MMs resemble pleomorphic malignant fibrous histiocytomas with tumor giant cells [72]. Sarcomatoid MM may also have leiomyoid features [72]. A very rare variant is sarcomatoid MM with heterologous elements which is characterized by malignant osteosarcomatous, chondrosarcomatous, or rhabdomyoblastic elements (Fig. 17.6b) [16]. 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 [16, 46, 47, 60]. Lymphohistiocytoid MM consists of discohesive proliferation of histiocytoid malignant cells with a marked infiltration of reactive lymphocytes and plasma cells (Fig. 17.6c) [124].

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

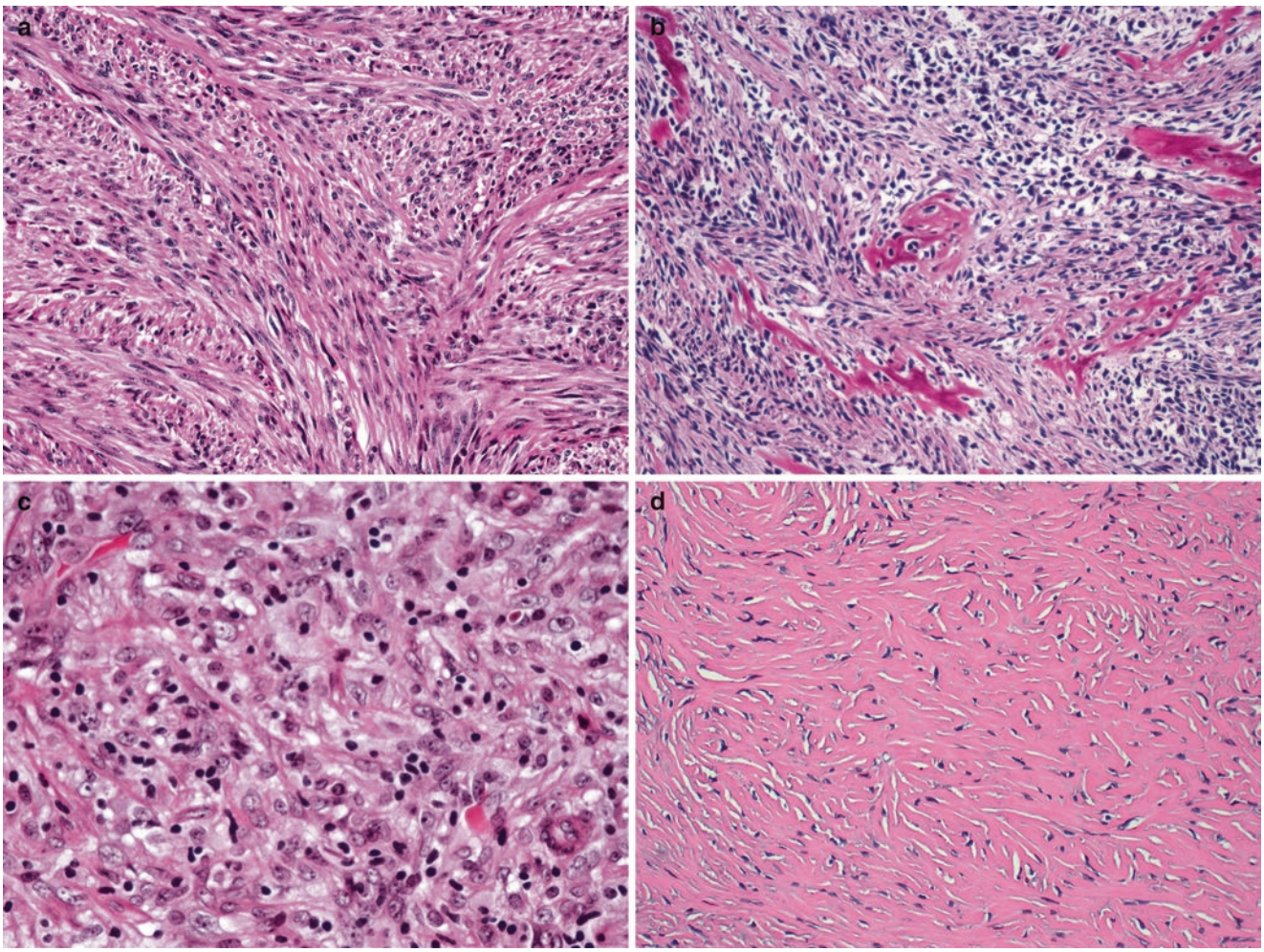

Fig. 17.6 Sarcomatoid malignant mesothelioma. Bundles of spindle cells arranged in fibrosarcomatous pattern (**a**), heterologous mesothelioma with osteoid formation (**b**), lymphohistiocytoid malignant mesothelioma (**c**), and desmoplastic malignant mesothelioma (**d**) (H&E; medium magnification)

spindle cell nuclei with minimal or no atypia are seen between the bundles of collagen (Figs. 17.6d and 17.7a) [7, 125, 126]. Desmoplastic features are common in sarcomatoid MM [72] and may occur in the sarcomatoid component of biphasic mesotheliomas [126–128]. 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 [125] 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. 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 [2]. 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. 17.7b). In contrast, myofibroblastic cells of fibrous pleuritis located close to the pleural surface stain with cytokeratins [20, 118].

The detection of homozygous deletion of 9p21 (*CDKN2A*) may be useful in the diagnosis of sarcomatoid and desmoplastic MM, whereas BAP1 is rarely lost in those subtypes. Hwang et al. [4, 5] studied 11 desmoplastic MMs for both markers: 8/11 showed homozygous 9p21 deletion and 1/11 had lost BAP1. Wu et al. [103] did not observe homozygous 9p21 deletion in any of 10 cases of fibrous pleuritis studied.

The morphological features separating desmoplastic MM from fibrous pleuritis are listed in Table 17.5.

Differential Diagnosis of Sarcomatoid 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

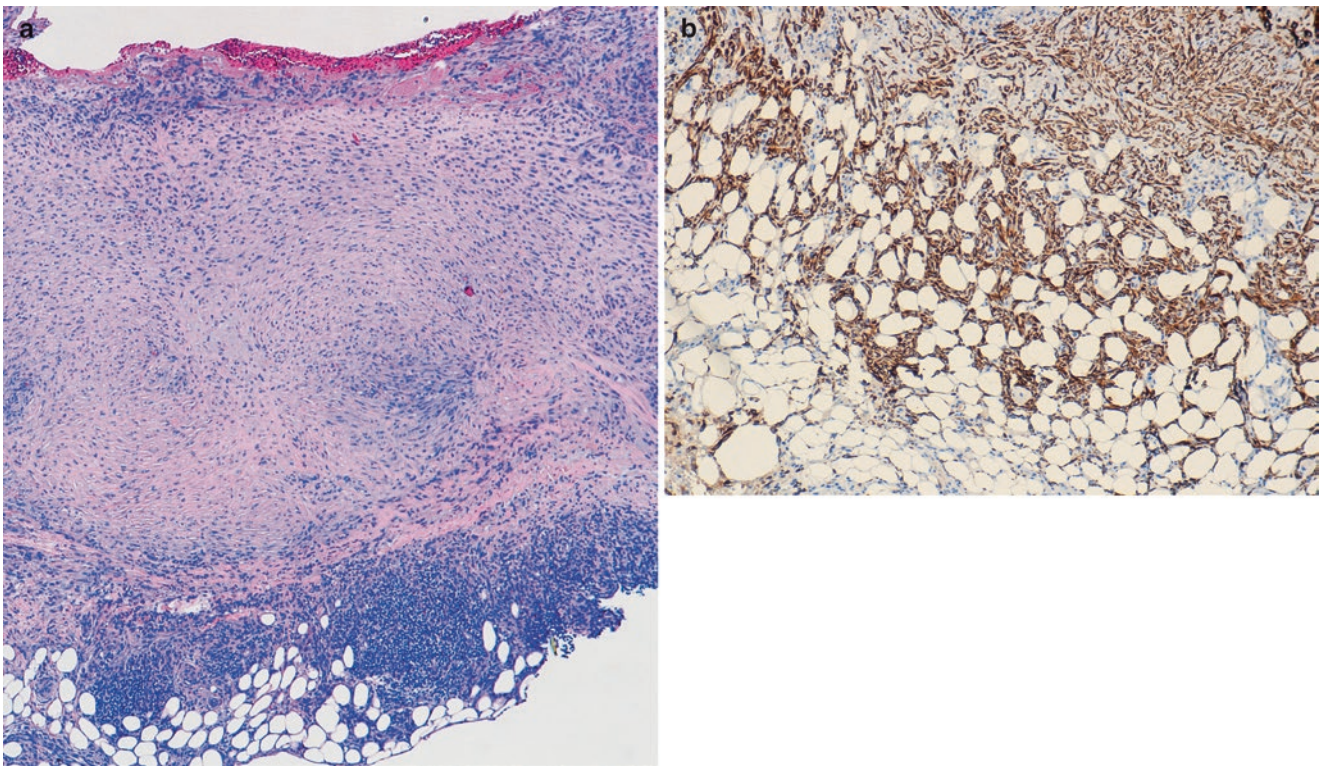

Fig. 17.7 Features of malignancy in mesothelial spindle cell lesion. Haphazard arrangement of cellular and acellular regions in sarcomatoid/desmoplastic malignant mesothelioma (**a**). Parietal pleural fat-invading cytokeratin-positive spindle cells in sarcomatoid malignant mesothelioma (**b**) (H&E; **b**, pancytokeratin immunostaining; (**a**) low magnification; (**b**) medium magnification)

Table 17.5 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. [88, 125]

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 [16, 70, 72, 129–133]. 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 (spindle cell or pleomorphic) carcinomas have shown at least focal positivity for calretinin [131–133]. 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 [70, 130, 131, 134, 135], but positive immunostaining for thrombomodulin, WT-1, and podoplanin may also occur in sarcomatoid carcinomas [135, 136].

Markers of pulmonary and kidney carcinomas may sometimes be useful for the differential diagnosis of sarcomatoid tumors. Unfortunately, less than half of pulmonary spindle cell or pleomorphic carcinomas express carcinoma markers, such as TTF-1, p63, p40, CEA, MOC31, or claudin-4 [21, 134, 136–139]. Recently two new markers have been proposed for distinguishing sarcomatoid MM from pulmonary sarcomatoid carcinoma. In the study of [137], MUC4 expression was observed in 72% of 29 sarcomatoid carcinomas, whereas none of the 31 sarcomatoid MMs expressed MUC4. Berg and Churg [140] detected strong and diffuse positive staining for GATA3 in all 19 sarcomatoid MMs studied and only weak, patchy, or no staining in 13 sarcomatoid carcinomas. The homozygous deletion of *CDKN2A* is not useful marker in distinguishing sarcomatoid carcinomas from sarcomatoid MM, as many carcinomas possess this alteration [4, 5, 101].

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 [62, 141].

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% [16, 72, 129, 133]. 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 [16, 72, 129, 133]. However, it is generally accepted that completely cytokeratin-negative sarcomatoid and desmoplastic MMs exist [72]. Cytokeratins are not helpful in the differentiation between sarcomatoid carcinomas and sarcomatoid MM, because both tumors normally express low-molecular-weight cytokeratins but rare cases may be completely cytokeratin negative [72, 118, 138]. 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 [118].

Conclusion

MM is divided into three main histological subtypes, i.e., epithelioid, biphasic, and sarcomatoid, 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. New markers, i.e., loss of BAP1 immunostaining and homozygous deletion of 9p21 (*CDKN2A*) region in malignant mesothelioma, may greatly benefit the diagnosis of difficult cases.

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Malignant Mesothelioma: Molecular Markers

18

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Introduction

Advances in molecular techniques have greatly increased our knowledge of the molecular features of malignant mesothelioma (MM). They have created new opportunities for identifying markers that not only facilitate early and differential diagnosis, but also assist in the evaluation of treatment options, disease prognosis, and the effectiveness of the treatment or disease monitoring. These developments have also shed light on the etiology of the diseases, for example, about exposures to different environmental factors. Nowadays the tumors can even be sub-classified based on their molecular features which have provided insights into the different molecular pathways leading to cancer development. Most importantly, the increased sensitivity and specificity of detection of molecular markers with the new advanced methodologies have led to the exploitation of these markers from more readily available body fluids like pleural effusions, plasma/serum, urine, sputum, and even exhaled breath condensate. This helps not only in the early detection but also in disease monitoring without the need for the primary tumor tissue for analysis.

This chapter describes the clinical significance of genetic, epigenetic, proteomic, and functional changes as biomarkers in MM. The causes of genetic changes in MM, especially the mechanisms behind the genomic alterations induced by asbestos, have been discussed in Chap. 19.

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Methods and Materials for Studying Genetic Changes in MM

The traditional karyotype analysis of MM is 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].

Copy number alterations (CNA) are mainly performed by the chromosome and the array comparative genomic hybridization (cCGH and aCGH), single nucleotide polymorphism (SNP) arrays, multiplex ligation-dependent probe amplification (MLPA) and recently also by next generation sequencing (NGS). NGS for studying genetic alterations is performed as: whole genome sequencing (identifies genetic alterations like mutations, CNA, genetic rearrangements), whole transcriptome sequencing (investigates the expression of genes, mutations in the expressed genes, expression of transcript variants and fusion transcripts), or targeted sequencing (detects mutations and small deletions/amplifications in exomes or targeted regions).

With respect to loss of heterozygosity (LOH) analysis with microsatellite markers, as well as the NGS and 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 that there has to be a tumor cell proportion of at least 30%. These systems can also utilize DNA extracted from formalin-fixed and paraffin-embedded (FFPE) tumor tissues.

RNA expression studies, performed mainly using microarrays, RT-PCR, or next generation RNA sequencing, generally require high quality intact RNA and the use of FFPE material is often challenging, due to the degradation of RNA that occurs during formalin fixation. However, RT-PCR with short amplicon design and targeted RNA amplification or

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NGS have been successfully employed in recent years to study the expression of specific transcripts [9].

Microarray and NGS methods create an enormous amount of genomic and functional data, and good collaboration between bioinformaticians, clinicians, and molecular biologists is needed to exploit properly the data from different sources so that it can be used for mining novel genetic changes.

Genomic Changes as Biomarkers

Chromosomal Imbalances

Standard chromosome banding and chromosome and array-based CGH have revealed the clonal and complex nature of the chromosomal abnormalities in MM. Around 100 cases with chromosomal alterations have been described [1, 2, 10–12]. The relatively small patient series for karyotype analyses are mainly attributable to the necessity of cell culture, the 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 [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 that chromosome is missing); +7 (the symbol "+" means that there is extra chromosome); −1, −3, −4, and 6q− (the symbol "q−" indicates that the chromosomal material in the long arm is missing); and −9, +11, and 3p− (the symbol "p−" means that the material in the short arm is missing).

Chromosomal and array CGH studies as well as LOH and FISH investigations [6–8, 13] have identified common gains observed at 1q, 5p, 6p, 7, 8, 11, and 17q, whereas the most common losses are located in 1p, 3p, 6q, 9p, 10, 12p, 13, 14, 17p, and 22p. Gains at chromosomes 1, 5, 7, and 17 are seen in 15% and losses at chromosomes 1, 3, 4, 6, 9, 13, and 22 in 25% of malignant pleural mesothelioma (MPM) in The Cancer Genome Atlas (TCGA) microarray dataset [14] (Fig. 18.1). The array CGH analyses have also revealed novel regions of genomic losses, gains, and high-level amplifications, such as gains at 1p32, 9p13.3, 7p22.2–p22.3, 12q13.3, and 17q21.32-qter [7].

The most frequent chromosomal alterations in MM are loss at 3p21 (*BAP1*), 9p21 (*CDKN2A*), and 22q12 (*NF2*) [15]. Although pleural (MPM) and peritoneal malignant mesothelioma (PMM) have different characteristics, the copy number alterations are rather similar in both types, with frequent losses at 3p21 (*BAP1*), 9p21 (*CDKN2A*), and 22q12 (*NF2*) [16, 17]. However, the deletion of *CDKN2A* is significantly more frequent in MPM than in PMM (35%) [15, 18]. Overall more losses are encountered in MPM, whereas more gains are seen in PMM [16]. Other regions with CNA reported in PMM include the deletion of 8p11.22 harboring the *ADAM3*, deletion of *CTNNB1*, amplification of the 15q26 region, and amplification of *VEGF-B* [17].

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 [7, 19, 20]. In MPM, 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% of cell lines [3, 21–24]. In contrast, similarly to the situation for PMM, the corresponding frequency is only 35% [18]. The deletion cases in PMM were exclusively detected in men who tended to be older than those without deletion and moreover, these patients had a significantly poorer prognosis than those without a deletion in their tumors [18]. *CDKN2A* deletion, which is seen at high frequency in MM, represents a good diagnostic marker for serous effusions by the FISH method [25].

In fact, this deletion has also been reported to be a sign of poor prognosis in MPM as in PMM [26]. The fact that immunostaining revealed a loss of p16 protein coded by *CDKN2A* in peritoneal tumors, in as many as 54% of cases, may indicate that mechanisms other than deletions, for example, methylation, may be silencing the gene [18]. However, the question still remains open whether these two inactivation mechanisms (deletion vs. methylation) may have originated from different exposure statuses. With regard to disease location, PMM has been reported to be associated with heavier asbestos exposure than MPM [27]. In familial MM cases, 9p deletions have also been reported to be recurrent [28, 29].

Some of the recurrent chromosomal abnormalities seen in mesothelioma have been found to be associated with the asbestos exposure or radiation exposure. Our cytogenetic analyses revealed an association of chromosome 1p deletion and monosomy 4 with a high asbestos burden [30]. A deletion at chromosome 14, one of the most recurrent alterations in MM, has been shown to be asbestos-related [31]. A significant difference in copy number alterations pattern is reported between mesothelioma patients with a history of asbestos exposure and radiation exposure. While mainly regions of gains (1q, 3p, 3q, and 5p) are associated with radiation exposure, asbestos exposure is more associated with

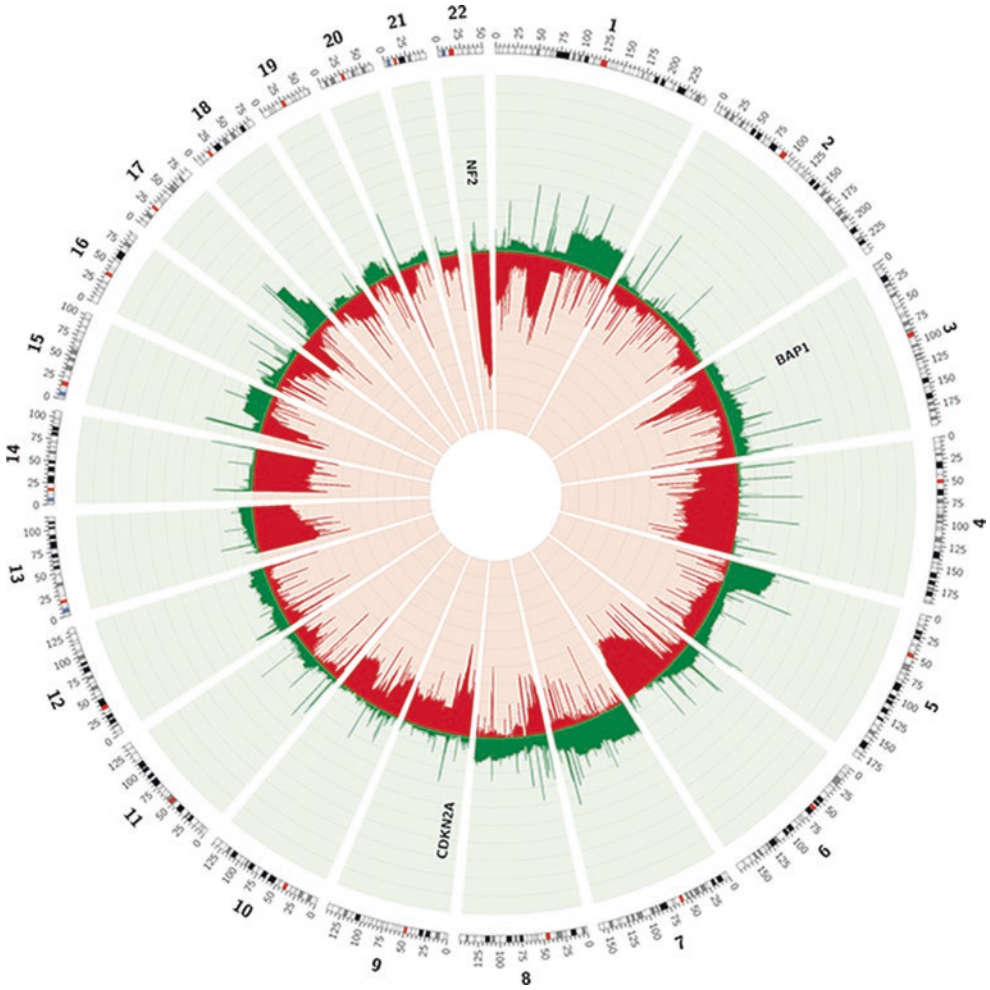

Fig. 18.1 Circos plot of the copy number variations (CNVs) observed in array data of 85 malignant pleural mesothelioma (MPM), available through the Cancer Genome Atlas (TCGA). Frequencies of copy number loss (red) and gain (green) are depicted for every chromosome position. (Reprinted from Hylebos et al. (2017) under the terms of Creative Commons Attribution License 3.0 (CC BY 3.0) [14])

regions of losses (14q, 22q, 17p, and 6q) although gains at 17q are also seen in asbestos-exposed patients [16].

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 [32].

Genomic profiling of MM has revealed clear-cut differences from the profiling of lung adenocarcinoma (Fig. 18.2). Losses at 4, 6q, 10, 14, and 9p are recurrent in MM, whereas gains at 8q, 1q, and 7p predominate in lung adenocarcinoma. Moreover, copy number gains of *EGFR*, *KRAS*, and *FGFR1* are significantly less common in MM than in lung adenocarcinoma [33]. The sensitivity of CGH analysis in differentiating MM from lung adenocarcinoma has been reported to be 81% with a specificity of 77% [13].

The improvements in resolution for detecting small copy number changes by the aCGH/SNP array, MLPA, and NGS in recent years has resulted in the identification of very small sized copy number alterations, even at the exon level, especially in the *BAP1* gene. A combined analysis of high resolution aCGH and NGS has shown common small multiple biallelic deletions in chromosome 3p21 which involve various genes. Multiple microdeletions and mutations in genes have been reported to result in biallelic inactivation of genes *SETD2* in 27%, *BAP1* in 48%, *PBRM1* in 15%, and *SMARCC1* in 6% of MM biopsies [34].

Bueno et al. (2016) [35] analysis of 95 MPM using SNP arrays and whole genome sequencing revealed recurrent copy number loss of *BAP1, NF2, CDKN2B, LATS2, LATS1,* and *TP53* as reported by most previous studies and recurrent copy number gains of *RPTOR* and *BRD4* that also showed increased gene expression. A higher proportion of tumor cells with *PDGFRB* copy number gain has been reported to indicate a better prognosis in resected MPM [36].

Gene Fusions

ALK rearrangements have recently been identified by FISH, IHC, and NGS in a subset of PMM patients, more commonly in younger women with no history of asbestos exposure or

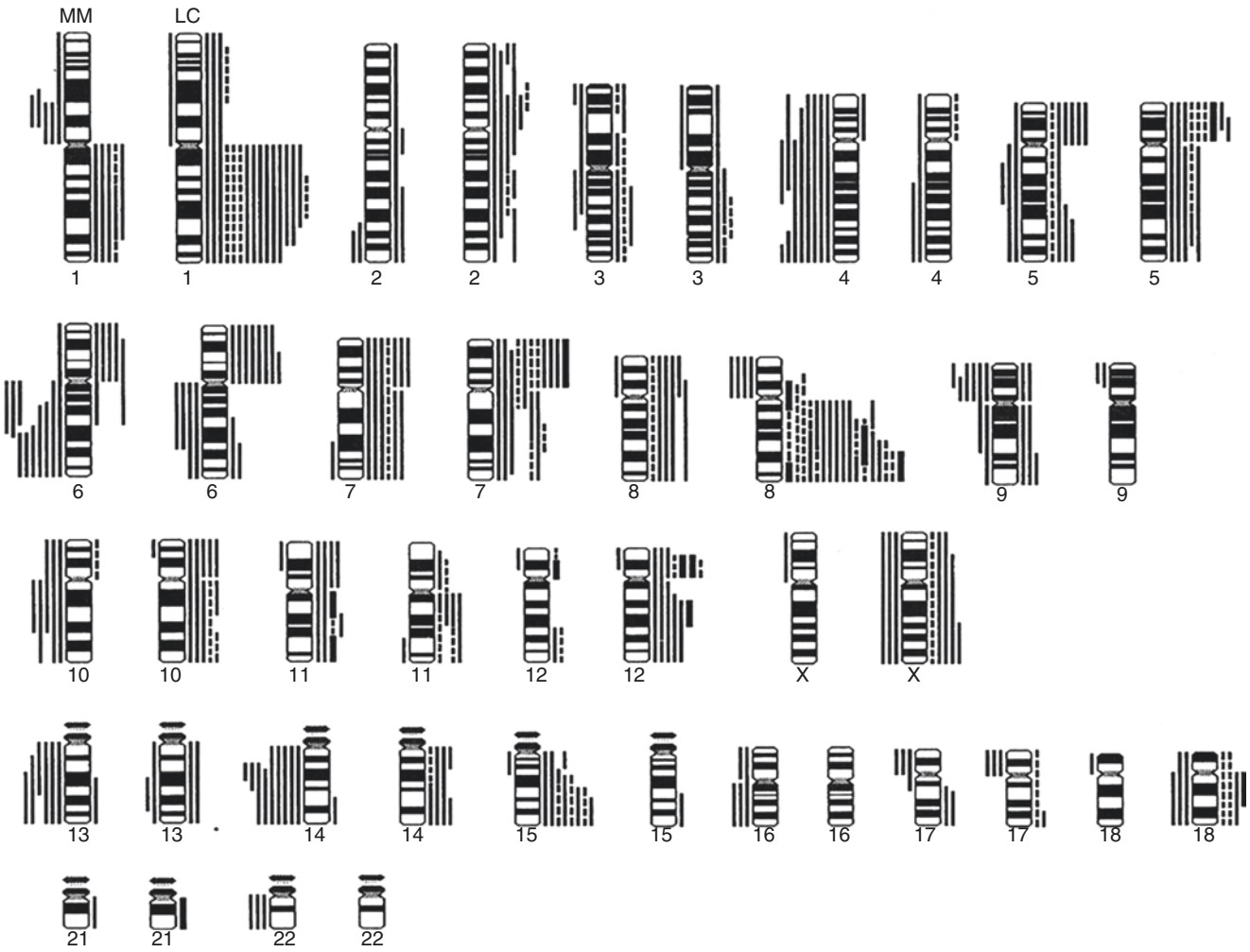

Fig. 18.2 Copy number changes in malignant mesothelioma (*MM*) and lung adenocarcinoma (*LC*) are so different that tumor types can be predicted in more than 80 % of cases (Adapted by permission from Springer Nature: on behalf of Cancer Research UK, Springer Nature, British Journal of Cancer: Björkqvist et al. [13], Copyright 1998)

radiation and lacking the other cytogenetic and molecular alterations associated with MM. The fusion gene partners seen were *ATG16L1, STRN,* and *TPM1* [37]. NGS analysis has also identified gene fusions involving tumor suppressor genes, rather than the commonly encountered fusions of oncogenes in other tumor types. These gene fusions involving *NF2, BAP1, SETD2, PBRM1, PTEN,* and *STK11* have been predicted to be inactivating gene alterations and exclusive of the other genetic alterations associated with these genes, thus indicating multiple modes of silencing these genes [35]. A fusion transcript of *YY1* and *EWSR1* has also been found in mesothelioma [38].

Mutations

Recurrent point mutations are relatively infrequent in MM. Recently, exome and transcriptome sequencing have however shed light on the mutational landscape of MM histological subtypes (Table 18.1). Mutations in *NF2* have been reported in a high percentage of MM and consist of both point mutations and deletions [39]. *TP53* has been found to be mutated at a lower rate in comparison with many other human cancers [40], especially in epithelioid subtypes, occurring with a frequency of less than 10% but associated with lower overall survival compared to patients with wild-type *TP53* [35].

Among the recently described mutations, those in *BAP1* tumor suppressor gene are most significant as they are recurrent (30–60%). Germline *BAP1* mutations predispose to a higher risk of mesothelioma development. Recently, a sensitive and high resolution analysis of *BAP1* locus has identified high frequency (60%) homozygous inactivating mutations in MM [41].

The *EGFR* activating mutations seen in lung adenocarcinoma are infrequent in MM, and the patients are insensitive to therapy with EGFR inhibitors [42]. However, MM with

Table 18.1 Genes reported to exhibit molecular alterations in malignant pleural mesothelioma (MPM)

Disrupted gene	Gene name	Disruption	Study
Genes involved in intrachromosomal rearrangements			
MAP2K6	Mitogen-activated protein kinase 6	Intrachromosomal rearrangement	Bueno et al. (2010) [49]
DPP10	Dipeptidyl-peptidase like 10	Intrachromosomal rearrangement	Bueno et al. (2010) [49]
Genes located in regions with copy number variations			
DHFR	Dihydrofolate reductase	Copy number gain	Bueno et al. (2010) [49]
PCBD2	Pterin-4-alpha-carbinolamine dehydratase 2	Copy number gain	Bueno et al. (2010) [49]
NF2	Neurofibromin 2	Copy number loss	Guo et al. (2015) [46]
Genes reported to be focally deleted			
CDKN2A/B	Cyclin-dependent kinase inhibitor 2A/B	Focal deletion	Guo et al. (2015) [46]
MIR31	MicroRNA31	Focal deletion	Guo et al. (2015) [46]
Genes with a differential exon junction expression between MPM and normal lung			
ACTG2	Actin gamma 2, smooth muscle	Differential exon junction expression	Dong et al. (2009) [50]
CDK4	Cyclin-dependent kinase 4	Differential exon junction expression	Dong et al. (2009) [50]
COL3A1	Collagen type III alpha 1 chain	Differential exon junction expression	Dong et al. (2009) [50]
TXNRD1	Thioredoxin reductase 1	Differential exon junction expression	Dong et al. (2009) [50]
Genes reported to exhibit missense or nonsense mutations			
ACTB	Actin beta	Missense mutation	Kang et al. (2016) [44]
ACTR1A	Actin related protein 1A	Missense mutation	Sugarbaker et al. (2008) [51]
CDH8	Cadherin 8	Missense mutation	Bueno et al. (2010) [49]
COL5A2	Collagen type V alpha 2 chain	Missense mutation	Sugarbaker et al. (2008) [51]
CUL1	Cullin 1	Missense mutation	Guo et al. (2015) [46]
GOT1	Glutamic-oxaloacetic transaminase 1	Missense mutation	Kang et al. (2016) [44]
KDR	Kinase insert domain receptor	Missense mutation	Lo Iacono et al. (2015) [52]
KIT	KIT proto-on cogene, receptor tyrosine kinase	Missense mutation	Lo Iacono et al. (2015) [52]
MXRA5	Matrix-remodeling associated 5	Missense mutation	Sugarbaker et al. (2008) [51]
NFRKB	Nuclear factor related to kappaB binding protein	Missense mutation	Bueno et al. (2010) [49]
NKX6-2	NK6 homeobox 2	Missense mutation	Bueno et al. (2010) [49]
PDZK1IP1	PDZK1 interacting protein 1	Missense mutation	Sugarbaker et al. (2008) [51]
PIK3C2B	Phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta	Missense mutation	Guo et al. (2015) [46]
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	Missense mutation	Lo Iacono et al. (2015) [52]
PSMD13	Proteasome 26S subunit, non-ATPase 13	Missense mutation	Sugarbaker et al. (2008) [51]
RAPGEF6	Rap guanine nucleotide exchange factor 6	Missense mutation	Kang et al. (2016) [44]
RDX	Radixin	Missense mutation	Guo et al. (2015) [46]
UQCRC1	Ubiquinol-cytochrome c reductase core protein 1	Missense mutation	Sugarbaker et al. (2008) [51]
XRCC6	X-ray repair cross complementing 6	Missense mutation	Sugarbaker et al. (2008) [51]
NOD2	Nucleotide binding oligomerization domain containing 2	Nonsense mutation	Kang et al. (2016) [44]
SETDB1	SET domain bifurcated histone lysine methyltransferase 1	Nonsense mutation	Kang et al. (2016) [44]
Genes reported to exhibit multiple mutation types			
BAP1	BRCA1 associated protein-1	Nonsense mutations, missense mutations, splice site mutations, and frameshift deletions	Guo et al. (2015) Mäki-Nevala et al. (2016) Lo Iacono et al. (2015) [45, 46, 52]

(continued)

Table 18.1 (continued)

Disrupted gene	Gene name	Disruption	Study
NF2	Neurofibromin 2	Nonsense mutations, missense mutations, splice site mutations, and (non)frameshift deletions	Guo et al. (2015) Lo Iacono et al. (2015) [46, 52]
TAOK1	TAO kinase 1	Nonsense and splice site mutation	Guo et al. (2015) [46]
TP53	Tumor protein p53	Missense and nonsense mutations	Guo et al. (2015) Kang et al. (2016) Lo Iacono et al. (2015) [44, 46, 52]

MPM malignant pleural mesothelioma
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G719C and S768I mutations in *EGFR* has recently shown positive results from treatment with the tyrosine kinase inhibitor, afatinib [43].

Largest exome sequencing study on 216 MPM [35] identified the ten most frequently mutated genes, *BAP1, NF2, TP53, SETD2, DDX3X, ULK2, RYR2, CFAP45, SETDB1,* and *DDX51*. Other exome sequencing studies have reported somatic mutations in *SETDB1, RAPGEF6, ACTB, GOT1, NOD2* and *TP53* [44] and in *BAP1, MRPL1, TTLL6, INPP4A, SEMA5B, STK11, EGFR, NF2, COPG1, EPHB1,* and *EPHB2* (unconfirmed somatic status; [45]).

Integrated analysis of somatic mutations and copy number analysis showed most prevalent mutations/inactivation of *BAP1, NF2, CUL1,* and *CDKN2A* [46], while targeted mutation analysis has revealed the most frequent mutations in *BAP1* (36%), *CDKN2A/B* (27%), and *NF2* (27%), with *CDKN2A* mutations only in MPM [47].

Similarly in PMM, copy number analysis, exome sequencing, and targeted sequencing have also shown 3p21 harboring *BAP1* to be the most frequently deleted with no alterations in *NF2* and *CDKN2A* commonly affected in MPM. Only *BAP1* showed recurrent mutations [48].

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 non-coding RNAs (ncRNAs), patterns of different chemical modifications of histones, and aberrant methylation of DNA at CpG islands often within gene promoter regions. Long ncRNAs (lncRNAs) and short ncRNAs such as micro RNAs (miRNAs), piwi-interacting RNAs (piRNA), and short interfering RNAs (siRNA) are involved in chromatin function/formation and the regulation of gene expression, e.g., by targeting DNA methylation.

MicroRNAs

MicroRNAs have attained an important role as molecular markers in MM. They have been shown to be differentially expressed not only in tissue but also in plasma and serum sampled from patients with MM. In addition to their role as diagnostic (Table 18.2) and prognostic markers, they are also attractive therapeutic targets.

We were the first to document the differential expression of miRNAs in MM compared to normal mesothelium. We 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, i.e., let-7e∗, miR-144∗, miR-203, miR-340∗, miR-34a∗, miR-423, miR-582, miR-7-1∗, and miR-9 were unexpressed or had severely reduced expression levels [54]. 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. Several miRNAs were located in those chromosomal areas known to be deleted or gained in MM, such as 8q24, 1p36, and 14q32. Specific miRNAs for each histopathological subtype of MM were also identified [54].

Subsequently, some of our results have been confirmed by other investigators [55], and the power of miRNA profiling to discriminate MM from lung adenocarcinoma [56] and different subtypes of MM [57] or the prognostic value of miRNAs [57, 58] has been reported.

Different diagnostic panels based on the expression of miRNAs in tumor tissues have been proposed that show high sensitivity of identifying MM. A panel of miR-193-3p, miR-200c, and miR-192 was demonstrated to have 100% sensitivity and 94% specificity of diagnosing MM [56]. miR-30d is reported to be downregulated in pleural MM cell line, plasma of asbestos-exposed individuals, asbestos-exposed mesothelial cells and suppresses pleural MM cell proliferation, migration, and invasion [59].

A recent meta-analysis of miRNA studies, including only qRT-PCR validated miRNAs analyzed in MM tissue and non-cancer tissue, found miR-145-5p, miR-126-3p, miR-16-5p, miR-192-5p, miR-193a-3p, miR-200b-3p, miR-203-3p, miR-143-3p, and miR-652-3p to be differentially expressed in MM compared to non-cancer tissue. This nine miRNAs meta signature was proposed as a diagnostic panel for MM [60].

The miRNA expression profile has also been found to be predictive of survival outcome in MM. Higher levels of miR 29c∗ [58] and reduced levels of miR 17-5p, miR-30c [57],

Table 18.2 Potential diagnostic miRNAs for malignant pleural mesothelioma (MPM)

miRNA	Ref	Source	Cohort	Number	MPM histological subtype	Statistical measure
200c, 141, 200b, 429	[69]	Tissue	1	15 MPM, 10 lung AD	N/A	AUC > 0.9 for each miRNA
			2	100 MPM, 32 lung AD	32 U, 39 Ep, 19 Bi, 10 Sa	
200c, 192, 193a-3p	[56]	Tissue	1	29 MPM, 140 carcinomas	22 Ep, 1 Bi, 6 Sa	Sensitivity 100%, specificity 94%
			2	48 MPM, 136 carcinomas	6 U, 29 Ep, 2 Bi, 7 Sa	
			3	14 MPM, 49 carcinomas	8 Ep, 4 Bi, 2 Sa	
126, 143, 145, 652	[70]	Tissue	1	5 MPM, 5 matched diagnostic biopsies, 5 matched non-neoplastic pleura	5 Ep	AUC 0.96 for miRNA combined
			2	40 MPM, 12 matched diagnostic biopsies, 14 matched non-neoplastic pleura, 5 non-neoplastic reactive mesothelium	27 Ep, 25 Bi	
625-3p	[71]	Serum	1	5 MPM, 3 healthy	3 Ep, 2 Sa	AUC 0.8
			2	5 MPM, 14 healthy	1 U, 9 Ep, 3 Bi, 2 Sa	
			3	30 MPM, 10 asbestosis	1 U, 29 Ep,	
		Tissue	4	18 MPM, 7 normal pericardium	15 Ep, 3 Bi	
103	[72]	Cellular fraction of peripheral blood	1	23 MPM, 17 asbestos exposed, 25 healthy	3 U, 12 Ep, 7 Bi, 1 Sa	AUC 0.75–0.87
126	[64]	Tissue	1	10 MPM, 5 normal mesothelium	9 Ep, 1 Sa	AUC 0.7
			2	27 MPM and adjacent normal tissue	23 Ep, 3 Bi, 1 Sa	
		Serum	3	44 MPM, 196 asbestos exposed, 50 healthy	30 Ep, 8 Bi, 6 Sa	Sensitivity 60–73%, specificity 74%
126, 132-3p	[65]	Plasma	1	21 MPM, 21 asbestos exposed	14 Ep, 4 Bi, 3 Sa	AUC ~ 0.8 for each miRNA and combination
			2	22 MPM, 44 asbestos exposed	4 U, 14 Ep, 2 Bi, 2 Sa	
197-3p, 1281, 32-3p	[66]	Serum	1	10 MPM, 10 asbestos exposed, 10 healthy	N/A	AUC ~ 0.7 for each miRNA
			2	20 MPM, 15 asbestos exposed, 14 healthy	N/A	
126, 21	[68]	Tissue	1	40 FFPE benign pleura, 51 FFPE MPM	34 Ep, 10 Bi, 75 Sa	AUC 0.92 for miRNA combination
		Archived cytology samples	2	24 Reactive mesothelium, 29 MPM	29 Ep	

U unknown, *Ep* epithelioid, *Bi* biphasic, *Sa* sarcomatoid, *N/A* not available, *FFPE* formalin-fixed paraffin-embedded
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and miR-31 in sarcomatoid mesothelioma patients [61] have been reported to be associated with a favorable prognosis. The miRNA signature based on six miRNA levels has been observed to predict survival with 72–90% accuracy for MPM patients [62]. Similarly higher levels of let-7c-5p and miR 151a-5p have been associated with a poor prognosis [63].

Circulating miRNA in Body Fluids

Serum levels of miR-126, in association with another MM serum marker soluble mesothelin-related peptide (see later), have been proposed as being a good candidate bio-indicator for the early detection marker of MM [64]. Combining miR-126 with another recently identified MPM marker, miR-132-3p was claimed to have a higher accuracy of discriminating MPM patients from asbestos-exposed individuals with 77% sensitivity and 86% specificity [65].

Circulating miRNAs miR-126-3p, miR-103a-3p and miR-625-3p in combination with mesothelin has been proposed for diagnosis and screening of high-risk asbestos-exposed subjects [60]. Higher serum level of miR-197-3p, miR-1281, and miR-32-3p have been speculated to be potential markers for MPM, with miR-1281 also higher in asbestos-exposed non-MM patients [66].

In pleural effusion cytology, miR-130A was reported as a diagnostic marker for differentiating MM from lung adenocarcinoma [67], whereas miR-126 and miR-21 levels in pleural effusions have been claimed to differentiate MPM from reactive mesothelial [68].

Long Non-coding RNAs

Deregulation of lncRNA in malignant tumors has recently been identified and their utility as screening markers is being assessed. A panel based on six lncRNA (AK130275, AK129685, EF177379, BX648695, NR_003584, and AF268386), upregulated in MPM tumors and detectable in both FFPE and fresh-frozen MPM tissues, has been reported to distinguish MPM tissue from benign mesothelium with high (71%) sensitivity and specificity (100%) [74]. *PVT1*, another lncRNA located in a frequently amplified 8q14 region along with C-MYC in MPM has been identified as an oncogene promoting MPM [75].

Histone Modification and DNA Methylation

Histone Modification

Covalent chromatin modifications include histone acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. Dysregulation of histone modification pattern can activate oncogenes and inactivate tumor suppressor genes leading to a pathological state. 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) have been identified [76]. Their detrimental effects could be reversed, thus inhibiting tumorigenicity, by treatment with a histone deacetylase (HDAC) inhibitor or by knockdown of EZH2, a core component of polycomb repressor complex-2 [76, 77]. Though some early-phase clinical trials with a single agent targeting HDACs have been discouraging in MM patients, HDAC inhibitors may be worthwhile evaluating in MM in combinations with different drugs [78].

Methylation

DNA methylation profiles vary extensively according to the tissue, with even the normal lung and pleura having distinct basal methylation profiles [79]. 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 [80, 81]. Nevertheless, DNA hypermethylation is a stable form controlling cell functions and as such, is a useful target in the search for MM biomarkers (studies listed in Table 18.3) [76, 79–97]. In relation to methylation in MM, also increasing numbers of miRNAs have been investigated, some showing pro-tumorigenic effects [82, 91, 98]. It has been suggested that miR-29c∗ is an important mediator of epigenetic regulation in MM through its role in regulating DNA methyltransferases and demethylating genes [58].

Indeed, most MM samples can be classified based on the CpG methylation profiles [76, 79]. Methylation classes accurately discriminated MM from the normal pleura and non-malignant pulmonary tissues as well as from lung adenocarcinoma (ADCA) [76, 79, 81, 84]. Several studies have shown that the amount of methylation of *APC* (adenomatous polyposis coli) was significantly elevated in ADCA in comparison to MM, whereas MM displayed higher methylation of *CDH1* (E-cadherin) [95, 96]. Moreover, methylation of *RASSF1* (Ras association [RalGDS/AF-6] domain family member 1) was associated with SV40 (simian virus 40)-positive MM (Table 18.3). Pathways involved in calcium signaling and Fc epsilon RI signaling were significantly enriched for methylation in MM in comparison to ADCA. The methylation level of mesothelin (*MSLN*) promoter has been shown to inversely associate with mesothelin protein expression in epithelioid mesothelioma [93, 94], whereas no such association was observed between the SMRP level and *MSLN* promoter methylation in asbestos-related diseased and healthy exposed subjects compared with healthy non-exposed individuals [99]. Methylation status or profiles of different genes have been shown to associate with different clinical correlates (Table 18.3). For instance, if one wishes to conduct the patient's prognosis, 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 should be used rather than examining changes in a single gene [88] (Table 18.3).

An increased asbestos fiber burden was associated with an increase in the 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 [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 in comparison 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

Table 18.3 Methylation studies performed on malignant mesothelioma

Study	Material	No. of subjects[a]	Studied genes[b]	Methylation frequencies in MM/results[c]	Observed associations[d]
Andersen et al. (2015) [82] Anticancer Res	Tissue	34 MM 14 non-neopl. pleura (NNP) 5 benign reactive mesothelial proliferation	*EGFL7*, includes *miR-126*	*EGFL7* hypermethylated in 71% of MM	*EGFL7* promoter hypermethylation associated with epithelioid histology and reduced survival
Kubo et al. (2011) [91] Clin Cancer Res	Cell lines, tissue	47 MM 10 non-neopl. pleura (LC) 2 mesothelial primary cultures 6 MM cell lines	*miR-34b/c, miR-34a*	miR34b/c from 85% (tumors) to 100% (cell lines); miR34a from 28% (tumors) to 33% (cell lines)	Epigenetic silencing was the major event in miR-34b/c in MM; Degree of serum miR-34b/c methylation with MM
Muraoka et al. (2013) [92] Lung Cancer	Circulating DNA (serum)	48 MM 21 BAP 41 healthy			
Cheng et al. (2013) [83] JTO	Cell lines, tissue	6+24 MM 2 mesothelial cell line	*ZIC1*	From 67% (tumors) to 100% (MM cell lines)	
Tan et al. (2010) [94] Hum Pathol	Tissue	39 MM 41 LC 26 non-neopl. pulm. lesions 12 normal lung	*MSLN*	The percentage of methylation of four CpGs significantly lower in MM; 21% in MM vs. 68% in normal pleura	Tumor *MSLN* hypomethylation with the presence of mesothelin protein in epithelioid tumor component; Tumor *MSLN* hypomethylation with the presence of serum SMRP
Nelson et al. (2011) [93] Epigenetics		36 MM 10 normal pleura samples			
Fujii et al. (2012) [89] Cancer Sci	Pleural fluid DNA	39 MM 46 LC 25 BAP 30 other	*CDKN2A(p16)*, *DAPK*, *MGMT*, *RARB, RASSF1A*	*RASSF1A* 31%, *RARB* 28%, *DAPK* 13%, *p16* 8%, *MGMT* 0% in MM	For *RASSF1A*, *p16,* and *RARB*, methylation significantly higher in LC (and AC) than MM; ≥30 years exposure to asbestos correlated with increased methylation in BAP
Toyooka et al. (2001) [95] 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)
Wong et al. (2002) [97] 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	

(continued)

Table 18.3 (continued)

Study	Material	No. of subjects[a]	Studied genes[b]	Methylation frequencies in MM/results[c]	Observed associations[d]
Tsou et al. (2005) [96] Lung Cancer	Cell lines, tissue	10 MM cell lines	14 loci such as *APC*, *CDH1*, *RASSF1*, *ESR1*	Potential candidate genes distinguishing between MM, ADCA, and non-cancer lung were revealed	*CDH1* showed high methylation in MM versus ADCA ($P < 0.002$) and *APC* showed low methylation in MM versus ADCA ($P < 0.0001$)
		8 ADCA cell lines			
		6 MM tumors			
		7 ADCA tumors			
		Non-tumor lung tissue			
		4 nonmalignant mesothelial primary cell cultures			
		SV40-infected human mesothelial cells			
		63 MM tumors			
Destro et al. (2007) [87] 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)
Tsou et al. (2007) [81] Lung Cancer	Tissue	52 MM tumors (of which 39 had self-reported asbestos exposure)	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
		38 non-tumor lung tissue from patients with lung cancer			
Christensen et al. (2008) [86] 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
Kohno et al. (2010) [90] Oncol Rep	Cell lines, tissue	8 MM cell lines	*WIF1 SFRP1*, *SFRP2*, *SFRP4*	*WIF1* in 74%, *SFRP1* 57%, *SFRP2* 62%, *SFRP4* 47% of MM (not specific for MM)	
		46 MM tumors			
Christensen et al. (2009) [79] Cancer Res	Tissue	158 MM tumors with quantitative asbestos burden data	1413/1505 CpG loci	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; 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
Christensen et al. (2010) [85] Cancer Res		57 ADCA tumors	773/803 cancer-related genes integrated analysis of methylation and copy number analysis by SNP array		
Christensen et al. (2009) [84] Cancer Res		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			

(continued)

Table 18.3 (continued)

Study	Material	No. of subjects[a]	Studied genes[b]	Methylation frequencies in MM/results[c]	Observed associations[d]
Goto et al. (2009) [76] 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
Christensen et al. (2009) [80] 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
Fischer et al. (2006) [88] 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

Full names of gene symbols and their synonyms can be found at http://www.genenames.org

[a]*MM* malignant mesothelioma, *ADCA* adenocarcinoma of the lung, *BAP* benign asbestos pleurisy

[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, *EGFL7* EGF like domain multiple 7, *ESR1* estrogen receptor 1, *GSTP1* glutathione s-transferase pi1, *KAZALD1* Kazal-type serine peptidase inhibitor domain 1, *LZTS1* leucine zipper tumor suppressor 1, *MAPK13* mitogen-activated protein kinase 13, *MSLN* mesothelin, *MGMT* O-6-methylguanine-DNA methyltransferase, *MT* metallothionein, *NAE1* APPBP1, HPP1, NEDD8 activating enzyme E1 subunit 1, *RARB* retinoic acid receptor beta, *RASSF* Ras association (RalGDS/AF-6) domain family member, *RASSF5* NORE1A, *SFRP* secreted frizzled-related protein, *SLC6A20* solute carrier family 6 member 20, *SYK* spleen tyrosine kinase, *TMEM30B* transmembrane protein 30B, *WIF1* WNT inhibitory factor 1, *ZIC1* Zic family member 1 (zinc finger protein)

[c]The methylation frequency percentages were rounded to the nearest whole number

[d]SMRP soluble mesothelin-related peptide

have been reviewed by Gray et al. (2009), Melaiu et al. (2012), and Gueugnon et al. (2011) [100–102].

In particular, if one wishes to devise diagnostic or prognostic tests, then several studies have identified either single genes or gene sets or the gene expression ratios which are claimed to distinguish tumor entities such as MM and lung adenocarcinoma or which may have some prognostic value in MM [103, 104]. Molecular diagnostic tests have also been developed to be performed on cells from pleural effusions [104]. Certain gene pair ratios or gene expression levels for use in prognostications of MM patients have been postulated [105–110]. Fine needle biopsy specimens of MM studied using a panel of 6 genes *CALB2, CLDN7, ANXA8, EPCAM, CD200,* and *NKX2-1* by RT-PCR as well as the calculation of expression ratios were considered suitable as a MPM diagnostic and prognostic test [111] and were shown to have 100% sensitivity and 90% specificity in distinguishing MPM from lung adenocarcinoma.

Serial analysis of gene expression (SAGE) has also been applied to reveal novel players in MM, with intelectin being one of the identified genes. Intelectin has also been shown to be induced in human primary mesothelial cells by exposure to crocidolite asbestos and SV40 infection [112]. Recently, higher expression of DAB2 and intelectin-1 at the mRNA level as well as at the protein level in epithelioid mesothelioma compared to lung adenocarcinoma is postulated as a potential future IHC marker for differentiating epithelioid mesothelioma from pulmonary adenocarcinoma [113].

Prognostic mRNA markers, as presented in the current literature, have only few overlapping genes [108]. In epithelioid MM, many genes have been implicated as being upregulated, e.g., those encoding matriptase, *ITGB4* (integrin beta 4), and P-cadherin [107, 114, 115]. 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 [108, 114–116].

Gene expression arrays and subsequent data mining procedures may be advantageous in the search for potential therapeutic molecular targets. In a data-driven approach, *SIM2s* was revealed as a novel MM-associated gene [117]. *CHEK1*, *RAD21*, *FANCD2*, and *RAN* have been proposed as new co-targets in MM [118]. When *CHEK1* siRNA was transfected into MM cell lines, the cells displayed enhanced apoptotic processes [119]. Furthermore, *UBE1L,* a component of the ubiquitin-proteasome pathway showed differential expression in MM cells compared to normal cells [119]. The ubiquitin-proteasome pathway is recognized as being implicated in PMM [120] as well as in asbestos-related lung tumors [121], which may mean that potential future markers relevant in MM may be found in the genes of this pathway.

Gene expression analysis by next generation RNA sequencing has recently identified four distinct molecular subtypes of MPM. Unsupervised consensus clustering of tumor RNA expression data of MPM patients showed four main groups based on their tumor gene expression profile: sarcomatoid, epithelioid, biphasic-epithelioid, and biphasic-sarcomatoid. Upregulated genes in the epithelioid cluster included *UPK3B, ELMO3, CLDN15* (known to be downregulated during epithelial-to-mesenchymal transition, EMT), *LRRN4, RSPO1, WT1,* and *MSLN. LOXL2* known to contribute to EMT and *VIM* believed to be upregulated during EMT were among the most significantly upregulated genes in sarcomatoid subtype. The *CLDN15/VIM* ratio was found to be capable of discriminating between subtypes [35].

Protein/Peptide Markers

Immunohistochemistry (IHC) is probably the most common method for assaying molecular markers in the verification and differential diagnostics of MM. Diagnostic IHC is based on the immunoreactive detection of mesothelial marker proteins and broad-spectrum or organ-associated carcinoma markers, in tissue sections or effusion cytological samples (immunocytochemistry) [122].

The identification of new potential protein and peptide MM markers is expected as a result of proteomic assays and broad proteome profiling performed in plasma, serum, pleural effusions and tissue biopsies. Exosomes are small membrane-bound secreted vesicles that participate in intercellular signaling by transporting different macromolecules, proteins, and lipids to target a recipient cell in normal state as well as in diseases [123]. Tumor exosomes have thus emerged also potential sources of novel protein biomarker candidates [123]. The techniques that can be exploited include enzyme-linked immunosorbent assay (ELISA), mass spectrometry (MS), and a multiplexed proteomic assay (SOMAmer technology) based on affinity capture. In MM, for instance, the cell surfaceome and secretome protein profiles have been studied [124–126]. Many marker and target candidates have been discovered but these still require future studies for validation [124–134].

Immunohistochemical Markers

Selection of suitable immunohistochemical (IHC) markers depends on the differential diagnosis. The most common situation is the need to differentiate between epithelioid MM and primary adenocarcinoma of the lung. Calretinin, keratin 5/6, WT1 (Wilms tumor 1) protein, thrombomodulin (CD141), and podoplanin (M2A antigen/D2-40) have been proposed as being putative positive MM markers in tissue for diagnosing epithelioid MM [122, 135, 136]. Calretinin, which is a calcium-binding protein of the EF-hand family, is expressed essentially by all epithelioid and mixed-type MM but only in 10% of lung adenocarcinoma [137]. Potentially DAB2 and intelectin-1 may prove useful positive MM markers but need validation [113]. In contrast to lung adenocarcinoma, MM stain negatively for carcinoembryonic antigen (CEA or CEACAM5) and Ber-EP4, a monoclonal antibody that recognizes cell surface glycopolypeptides on human epithelial cells. In the differential diagnosis of MM, other useful broad-spectrum positive carcinoma markers have been proposed, e.g., MOC-31, TAG-72 (B72.3), BG-8, CD15 (Leu-M1), and Claudin 4, and organ-associated carcinoma markers include TTF-1, Napsin A, PAX8, PAX2, GCDFP-15, mammaglobin, and CDX2 [122, 138, 139]. In addition, estrogen receptor and p63 may be useful in distinguishing MM from serous carcinomas and squamous cell carcinomas, respectively [122]. Commonly used markers in MM are shown in Table 18.4. Immunohistochemical markers are handled in more detail in Chap. 17.

Only a minority of sarcomatoid and desmoplastic MM exhibit positive mesothelial markers and about 30% are calretinin positive [138]. Sarcomatoid MM is keratin positive in 93% of cases [141]. However, also reactive mesothelial cells and reactive submesothelial fibroblasts are keratin positive [141]. Though not specific for MM, significantly higher PD-L1 expression has been detected in the sarcomatoid tumor component than in its epithelioid counterpart, with the expression associated with outcome [142, 143]. The suitable marker choice, thus, depends on the context and sample under evaluation. For a differential diagnosis between sarcomatoid MM and spindle cell/pleomorphic carcinoma, guidelines have been presented [144]. The case-specific diagnostic IHC labeling for MM with heterologous elements has been reviewed in detail by Klebe et al. [145].

The International Mesothelioma Interest Group (IMIG) has updated their consensus statement on recommendation guidelines for the pathologic diagnosis of MM panel selec-

Table 18.4 Commonly used markers and their expression pattern in the immunohistochemical classification of epithelioid malignant mesothelioma versus lung and breast adenocarcinoma

Marker class	Epithelioid MM	Lung AC	Breast AC
Mesothelial markers			
Calretinin	+	−/+ f	−/+ b
CK5/6	+/−	−/+ f	−/+ b
Podoplanin	+	−(+) f	−/+
WT1	+/−	−	−/+
Broad spectrum carcinoma markers			
CEA	−(+) f	+/−	+/−
Claudin-4	−	+	+
EpCAM	−/+ f	+	+
Lung AC marker			
TTF1	−	+/−	−(+) f
Breast AC markers			
ER	−	−/+	+/−
MG	−	−(+) f	+/−

+: >90% pos.; +/−: 50–90% pos.; −/+: 10% to <50% pos.; −/(+): 1% to <10% pos.; −: <1% pos.; f: focal when pos.; b: basal-like type in most cases when pos.
AC adenocarcinoma, *CEA*, carcinoembryonic antigen, *CK* cytokeratin, *EpCAM* epithelial cell adhesion molecule (e.g., detected with clone EP4 or MOC31), *ER* estrogen receptor alpha, *MG* mammaglobin, *MM* malignant mesothelioma, *TTF1* thyroid transcription factor-1, *WT1* Wilms tumor 1 (nuclear reaction); (Adapted from Panou et al. [140], Copyright 2015, with permission from Elsevier.)

tion for IHC markers [138]. The exact content of the IHC marker panel is dependent on the context of the differential diagnosis but should contain both positive and negative differentiating markers. The IHC markers should display either sensitivity or specificity greater than 80% [138].

Serum/Plasma and Effusion Biomarkers

Markers tested for the noninvasive diagnosis of mesothelioma have been systematically reviewed, covering studies on markers applied on serum or effusion cytological specimens, or using genetic or several types of markers [146]. There was substantial heterogeneity among the studies reporting a total of 54 different IHC markers. CEA, Ber-EP4, and calretinin performed best in differentiating epithelioid MM from adenocarcinomas [122, 146]. Epithelial membrane antigen (EMA), in addition to the serum marker soluble mesothelin-related peptide (SMRP, see below), was the most useful in distinguishing MM from nonmalignant pleural condition according to systematic review (Fig. 18.3) [146]. However, in individual cases, the value of EMA has been reported as only limited [135]. A meta-analysis for diagnostic performance of calretinin for MM in serous effusions showed pooled sensitivity and specificity of 0.91 (95% CI, 0.87–0.94) and 0.96 (95% CI, 0.95–0.96), respectively, and the area under the SROC curve 0.97 [147].

Mesothelin

Mesothelin, also called ERC/mesothelin, can be considered as a reference serum biomarker for MM and also it has been proposed as being one of the key molecules for targeted therapies [148, 149]. While the C-terminal fragment C-ERC/mesothelin is a membrane-bound protein, N-ERC/mesothelin or soluble megakaryocyte potentiating factor (MPF) is cleaved from the same precursor, and it was first isolated from the culture supernatant of the pancreatic cancer cells (HPC-Y5) [150]. Furthermore, a splicing isoform called soluble mesothelin-related peptide (SMRP), which lacks a GPI-anchoring signal, has been discovered [151]. A term "soluble mesothelin" has been used for molecules resulting from splicing or enzymatic cleavage events [152, 153]. Thus far, the SMRP assay MESOMARK™ is the only test approved by US Food and Drug Administration (FDA) for the diagnosis and monitoring of MM [154, 155]. In pleural disease, pleural fluid concentrations of SMRP are higher than in serum or plasma which displayed similar levels of SMRP [156]. Mesothelin has also been found in MM-derived small membrane-bound secreted vesicles, exosomes that transport signals between cells [157, 158].

Increased levels of SMRP have been shown in serum and pleural effusions of MM patients in comparison to other non-mesothelial malignancies and asbestos-exposed individuals with a nonmalignant disorder. However, in terms of the early diagnosis, the value of SMRP is limited due to its poor sensitivity; furthermore, a negative result cannot exclude MM [148, 159]. Retained methylation of mesothelin gene (*MSLN*) promoter restricting expression in part of the tumors may account for some of the poor sensitivity of the assay [93]. A meta-analysis indicated that serum MPF (cleaved N-ERC/mesothelin) was more accurate than serum SMRP in diagnosing MM [152]. Combining SMRP with miR-103a-3p biomarker may improve the detection of MM [160]. When serial measures are conducted rather than as a single baseline test, SMRP levels show potential for prognostication and for following up the treatment response in MM [159, 161, 162].

More than 40 years' asbestos exposure in an individual was associated with an increase in the SMRP levels (P = 0.0265) and frozen serum samples were shown to be suitable for analysis of SMRP in retrospective experiments [163]. Furthermore, genetic variants in mesothelin gene (*MSLN*) have shown a strong association with SMRP levels in non-MM subjects exposed to asbestos [164]. A possible screening approach of asbestos-exposed individuals without malignant disease for serum SMRP and MPF (cleaved N-ERC/mesothelin) would require individual adjustment for age and glomerular filtration rate [165, 166]. The results gathered so far do not, however, encourage routine screening using mesothelin [167, 168].

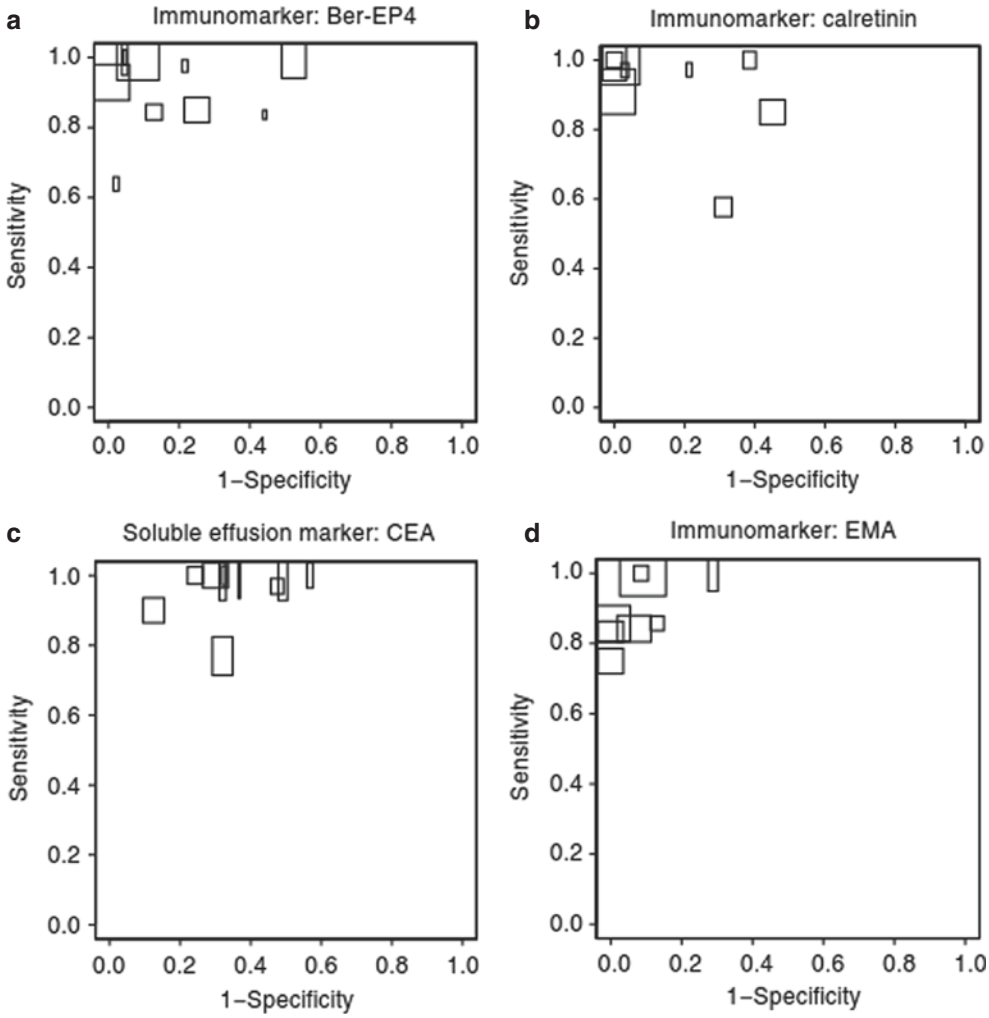

Fig. 18.3 Sensitivity against 1-specificity in receiver operating characteristic (*ROC*) space to best discriminate MM from other malignant diseases using (**a**) Ber-EP4, (**b**) calretinin, and (**c**) CEA and to discriminate best MM from nonmalignancy using (**d**) EMA, all applied to effusion cytology. 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 (MM no subjects) (**d**). (Adapted by permission from Springer Nature: on behalf of Cancer Research UK, Springer Nature, British Journal of Cancer: van der Bij et al. [146], Copyright 2011)

Osteopontin

The glycoprotein osteopontin (OPN) was identified as a potential marker for pleural mesothelioma but the diagnostic reliability of OPN is hampered by the fact that its overexpression has been detected in several cancer types [169]. Nonetheless, a meta-analysis on diagnostic performance of circulating OPN estimated the overall sensitivity as 0.65 (95% CI, 0.60–0.70) with a specificity of 0.81 (95% CI, 0.78–0.85), with the area under summary receiver operating characteristics curves of 0.83 [170]. In the diagnosis of epithelioid MM, OPN measurement may support the traditional radiological methods [171]. OPN may have a potential value as a prognostic marker but not as a marker of response [159, 172].

Serum OPN levels were increased in those individuals with asbestos-related disorders (ARD) in comparison to healthy exposed individuals, suggesting that OPN levels may be changed by nonmalignant processes as well [173]. Some discrepancy exists among the factors that have been reported to influence OPN levels although some differences may also exist between the available assays [171, 174, 175]. OPN is cleaved by thrombin and, thus, for measurements, plasma is preferred over serum [156, 171]. Renal failure has been reported to exert an effect on OPN level [176].

Other Markers

High-mobility group box 1 protein (HMGB1) has been suggested as a biomarker for asbestos exposure; it is released from mesothelial cells into extracellular space as a result of a cascade of molecular events induced by asbestos exposure [177, 178]. Elevated serum HMGB1 levels have been detected in MM compared to healthy controls [179, 180]. In particular, hyperacetylated HMGB1 outperformed other markers in distinguishing MM patients from asbestos-exposed subjects and unexposed controls [177]. Moreover, it has been postulated that serum HMGB1 possesses a prognostic capability in pleural MM [181].

Increased levels of a secreted glycoprotein, fibulin-3, or EGF containing fibulin like extracellular matrix protein 1

(FBLN3/EFEMP1) have been reported in MM plasma and effusion [182]. Effusion FBLN3 displayed some potential prognostic value in MM but less diagnostic value; however, some discrepancies have been shown between different studies and different cohorts [183–186]. It has also been suggested that FBLN3 may be helpful in evaluating the response to treatment in MM [187].

Tissue polypeptide antigen (TPA), hyaluronan, CA 125, Cyfra 21-1, and calretinin 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 [188, 189]. It is noteworthy that the CA 125 levels have been demonstrated to increase when serum samples were stored in the freezer for longer periods [163]. Although surveying markers in serum has the benefit of potentially revealing also asymptomatic patients at risk, many studies have explored the same markers in pleural effusion in attempts at achieving differential diagnostics [190–192]. For instance, the Cyfra 21-1/CEA ratio has been speculated to display diagnostic value in MM [191]. Moreover, the combination of some markers such as the Cyfra 21-1/CEA ratio with SMRP, present in pleural effusions, improved the diagnostic sensitivity from that of single markers, although at the expense of specificity [190].

Hyaluronan as a marker of mesenchymal origin may be useful in differential diagnosis of MM (reviewed in [193]). 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 possible with hyaluronan [194–196]. Thus, it has been claimed that effusion hyaluronan could serve as a prognostic marker [194].

A blood-based calretinin assay has been developed and verified in MM as supplementing other diagnostic markers [197]. Potential predictors such as renal dysfunction were reported to influence the diagnostic performance of calretinin blood test [198]. However, a further prospective validation is needed.

Measurements of vascular endothelial growth factor (VEGF), by ELISA, have been shown to increase the diagnostic performance of cytological examination of pleural fluid for malignancies even by as much as 24% [199]. Hence, it may serve as an adjunct to diagnostics in MM and also benefit in estimating the patient's prognosis. However, the specificity of VEGF at recognizing individuals at high cancer risk was not optimal [200, 201]. Overexpression of fibroblast growth factors (FGF2 and FGF18) and receptor FGFR1 have been shown in MM and responsible autocrine signaling suggested as therapeutic target [202, 203]. In addition, gremlin-1 has been identified as a potential target for therapy in MM; it is highly expressed and promoting invasion in MM [204, 205]. The activity of gremlin-1 action is partly dependent on the TGF-beta pathway [205]. It is noteworthy that MM-derived small membrane-bound secreted vesicles, i.e., tumor exosomes, were found to carry TGFbeta1 which had a greater potent antiproliferative impact than soluble TGFbeta1 [157].

Platelet-derived growth factor receptor (PDGFR) immunopositivity did not sufficiently differentiate between malignant and reactive mesothelial cells, whereas those MM patients with a shorter survival displayed higher levels of PDGF measured from serum, although no significant association was detected [206–208]. Epidermal growth factor receptor (EGFR) immunoreactivity has been shown in half of MM cases but without any prognostic value [209]. Furthermore, EGFR staining was significantly more prevalent in peritoneal MM compared with that of pleural [210].

Potential markers for MM, measured in pleural effusions, include the C-C motif chemokine ligand 2 (CCL2; also known as monocyte chemoattractant protein 1, MCP-1). A significantly higher level and a progressive rise of CCL2 were reported in effusions from MM patients, compared with the benign pleural effusions or effusion from lung adenocarcinoma [211, 212]. In an earlier study on rat pleural mesothelial cells, asbestos was shown to induce an elevated level of secretion of CCL2 [213].

Exhaled Breath Biomarkers

In order to improve the selectivity and feasibility of noninvasive diagnostic methods, the so-called breathprints, i.e., composite biomarker profiles, and the mean values of volatile organic compounds were recently examined in exhaled breath of the MM patients as well as in individuals with occupational asbestos exposure [214]. As a result, cyclohexane was claimed to be a possible marker distinguishing MM patients from asbestos-exposed patients without MM as well as from non-exposed healthy controls, while cyclopentane could distinguish asbestos-exposed individuals from the healthy controls and from the patients with MM [215]. In addition, the exhaled breath pattern has been found to differentiate healthy controls from those individuals with asbestos-related diseases based on α-pinene and 4-ethyltoluol concentrations [216]. Recent studies have shown promising results for the future application of breath markers/breathprints for the detection of MM [217, 218]. DNA/miRNA isolated from exhaled breath condensate (EBC) represents a noninvasive specimen for detecting the genetic changes associated with lung diseases [219]. We recently applied next generation sequencing to detect mutations in cancer genes from exhaled breath condensate and our results show promising potential of using NGS for screening driver mutations from EBC [220, 221].

Conclusion

Basic histology and immunohistochemistry using specific antibodies are the cornerstones when one considers the diagnosis of MM. Genetic alterations at 3p21 (*BAP1*), 9p21 (*CDKN2A*), and 22q12 (*NF2*) are the most recurrent genetic alterations in MM. Circulating levels of miRNAs miR-126-3p, miR-103a-3p, and miR-625-3p in combination with mesothelin can be included in a potential marker panel for the diagnosis and screening of high-risk asbestos-exposed subjects. Methylation patterns (e.g., *RARB* + *DAPK1* + *RASSF1*) have demonstrated prognostic value. Furthermore, profiling of DNA copy numbers, gene expression, methylation, and miRNAs as well as potentially assaying the levels of some serum markers and exosomal proteins may help in acquiring a differential diagnosis. The next generation of sequencing technology has already revealed new fusion genes in MM, and in the near future it is more than likely that this technology with the rapid innovations in bioinformatics will reveal not only novel prognostic and predictive markers but also therapeutic targets for new drug development and personalized patient treatment. There are also encouraging preliminary results from the use of serum, plasma, or pleural effusions for early diagnosis of MM. Our understanding about molecular mechanisms through which asbestos causes cancer is increasing; now, for the first time, there are potential biomarkers (copy number changes, miRNAs and methylation for lung carcinoma and methylation for mesothelioma) that can be used to decide whether the tumor is asbestos-related or not.

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Malignant Mesothelioma: Mechanism of Carcinogenesis

19

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Introduction

Our present knowledge of the mechanisms of mesothelial carcinogenesis originates from pathophysiological and toxicological research carried out in vivo in rodents and in mammalian cells in culture. The development of analytical tools allowed biological and molecular studies of malignant mesothelioma (MM) tissue tumor samples and cell lines from humans and experimental animals. Most experimental studies have been based on the cellular and/or animal, including genetically modified mice, responses to asbestos fibers. 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 molecular networks involved in the transformation of the mesothelial cell.

As this volume is devoted to occupational cancer, the studies reported here will focus on asbestos, the only known human etiological factor widely used in the occupational environment associated with MM, and early reported in asbestos mines regions [1]. Although epidemiological studies have clearly linked mesothelial carcinogenesis with both occupational and non-occupational asbestos exposure, no history of exposure can be found in about 10–20% of MM cases [2–5]. Some MM may be related to other fiber exposure or to other causes [6]. Indeed, other types of natural 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 CNT. In 2014, IARC reviewed the classification of other fibrous materials, fluoroedenite, silicon carbide fibers and whiskers, and CNT. Fluoroedenite, a fibrous amphibole, was classified as carcinogenic (Group 1) as asbestos and erionite, silicon carbide whiskers as probably carcinogenic (Group 2A), and a type of CNT as possibly carcinogenic (Group 2B) [7].

CNT are of particular interest because of similarities with asbestos, which are discussed in several reviews [8–10]. Recent studies investigating the effects of other elongated particles such as carbon nanotubes (CNT), and asbestos fibers as controls, have brought additional information on the mechanism of action of asbestos. In the field of investigation of the toxic potency of nanoparticles, the relation between the biological effects of asbestos and their properties led to the concept of high aspect-ratio nanoparticles (HARNs). In some parts of this review, we will mention CNT, which are a type of engineered HARNs that induces mesotheliomas and lung cancer in animal experiments [11]. The aim of the present chapter is to update the data on potential mechanisms of mesothelial carcinogenesis by integrating data based on cellular and molecular effects of asbestos fibers on mesothelial cells with data obtained on altered physiological and molecular features of MM [12].

Deposition and Translocation of Asbestos Fibers

The initial route of entry of asbestos fibers is by inhalation. Fibers deposit in the tracheobronchial regions, distal airways, and alveolar spaces of the lungs [13]. The major

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deposition mechanisms are by impaction, interception, sedimentation, and diffusion and are dependent on the physical characteristics of the particles [14, 15]. It results that asbestos and other elongated mineral particles have a greater inhalability than spherical particles having the same mass or volume [16]. 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 the penetration of fibers through the alveolar epithelium and subsequent translocation to the pleura and distant sites [17]. Fibers that enter the interstitium may cross the visceral pleura by paracellular migration or by direct penetration [18]. An alternative route of translocation to the pleural space is transport via lymphatics or the bloodstream [19].

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 [20]. The major route of drainage of fluid, protein, particulates, and cells from the pleural space is lymphatic stomata that open between mesothelial cells on the parietal pleural lining. Lymphatic stomata are communication holes between the pleural cavity and the parietal pleura lymphatics, where the particles are not cleared and concentrate, depending on their shape and dimensions [21–23]. The diameter of lymphatic stomata (~10–12 μm) limits the clearance of long fibers from the pleural space [19]. The translocation of asbestos fibers in the lymph nodes and in the pleura has been reported in animal experiments, a process also found in CNT-exposed animals [8, 24–27]. Asbestos persists in the lung regional lymphatics of mice 1 year after pharyngeal aspiration and giant cells formation is present in lymph nodes [28].

Systemic dissemination of fibers through lymphatics and the bloodstream has been described in humans following autopsy [29–31]. Asbestos fibers and asbestos bodies have been noted in the liver, mesentery, spleen, and abdominal lymph nodes [32, 33]. Several studies have demonstrated the presence of asbestos fibers in the human pleura [30, 31, 34]. The translocation of asbestos to the pleura is also suggested by the presence of pleural plaques that develop in the parietal pleura in asbestos-exposed subjects. Parietal pleura is also the location of early MM, although MM does not seem arise from pleural plaques. However, a statistically significant association was observed between mesothelioma and pleural plaques, consistent with the role of asbestos in these pathologies [35].

Diffuse peritoneal malignant mesothelioma is also associated with exposure to asbestos fibers [36, 37]. Fibers might 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 wall. A biodisponibility of asbestos fibers may account for the occurrence, not only of MM and lung cancer, but of other types of cancers, i.e., larynx, ovary, and possibly pharynx, esophagus, stomach, colon, and rectum [38–42].

The Mesothelial Cell In Situ

The mesothelium consists of a monolayer of mesothelial cells lying on a basement membrane and supported by connective tissue containing fibroblasts and macrophages. It provides a protective barrier for frictionless interface for the free movement of apposing organs and tissues, and in fluid transport across the pleura [43]. Mesothelial cells may have specialized functions at different anatomical sites, as demonstrated by morphological studies at the ultrastructural level [44]. Mesothelial cells play a role in the resolution of inflammation and tissue repair after pleural injury [45]. 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 remains poorly understood, mostly in the context of serosal injury following dialysis. However, some controversial hypotheses have been formulated. Comprehensive reviews summarize our present knowledge of these potential mechanisms [46, 47]. 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 (6) bone marrow-derived circulating precursors [47]. The origin of these new mesothelial cells has not yet been confirmed, but according to Mutsaers et al. [47], mesothelial regeneration is not dependent on subserosal cells, but more likely results from implantation, proliferation, and incorporation of free-floating mesothelial cells [48]. Recently, floating mesothelial cells were identified in pleural fluid after lung surgery in human, in the vein of this hypothesis [49].

Effects of Asbestos Fibers in Wild-Type Animals

The relationship between mesothelioma and exposure to asbestos, or to other fibers, such as erionite and fluoro-edenite, has been well demonstrated by numerous experimental studies carried out in rodents. 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 [14, 39, 50]. 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 [51–54].

Some studies have investigated the pleural responses to asbestos fibers following 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. These growth factors were able to induce proliferation of mesothelial cells in culture [55]. An inflammatory response may be triggered by fiber translocation to the pleura as demonstrated in rodents exposed to glass fibers, RCF or CNT [56–59]. The pleural reactivity to asbestos was observed in mechanistic studies using CNT, and asbestos as control fibers. Shvedova et al. [28] reported the occurrence of pleuritis and mesothelial hyperplasia and/or atypia 1 year after pharyngeal aspiration of crocidolite in mice [28].

Chromosome and DNA Alterations

Chromosomal and molecular alterations have been studied in mesothelial tissue and in MM developed in rats exposed to asbestos by intraperitoneal injection. Chromosome losses and rearrangements were observed in rats exposed to crocidolite and chrysotile [60]. Significantly enhanced mutation rate of *lacI* gene from omenta in Big Blue rats (a model to detect mutation potency) was found 12 and 24 weeks post-exposure to crocidolite, and significant enhanced level of 8-Oxo-2′-deoxyguanosine (8-OHdG), a major product of DNA oxidation, in DNA from 10 to 20 weeks post treatment of Wistar rats [61, 62]. 8-OHdG in DNA was also enhanced in rats and hamsters after intratracheal instillation 1 day after the exposure to crocidolite [63].

The type of mutations has been poorly investigated in animals. No mutations were found in *Trp53* (exons 5–8) or *Kras* (exons 1, 2) [60, 64, 65]. Additionally, no hot spot point mutation in *Kras* was detected, 1 year after pharyngeal aspiration of crocidolite in mice [28]. In MM from Big blue rats, transversions G>T were predominant (29%) followed by deletion (26%), G>A (20%), G>C (12%), A>T (6%), and A>G and insertion (3%), while in controls spontaneous mutations were G>T (19%), deletion (5%), G>A (57%), G>C (14%), A>T and A>G (0%), and insertion (5%) [61]. Recently mutational signature was investigated in human malignant pleural mesothelioma (MPM) [66]. The authors found a highest rate of mutations C>T, which C>T mutations can be generated by spontaneous deamination of methyl-cytosine bases in 5′-CpG, and by APOBEC-catalyzed deamination of cytosine bases to uracil [67]. One of the signature in human MPM may be associated with reactive oxygen species (ROS) but no significant difference in the mutational signature was found between asbestos-exposed and nonexposed patients [66].

DNA mutations in asbestos-exposed cells may occur through generation of ROS by surface reactivity of particles, by asbestos uptake, or by inflammation. Oxidative DNA damage has been reported in several studies [68–71]. Moller et al. [72] reported a critical assessment of the association between pulmonary exposure to particles, considering carcinogens carbon-derived particles, quartz, and asbestos and levels of oxidatively damaged DNA in lung tissues from animals [72]. The authors mentioned that the results show that asbestos can generate genotoxicity in a dose-dependent manner and without a clear threshold and that measurements of oxidatively damaged DNA, as marker of particle-induced genotoxicity in animal tissues, did not show evidence that inflammation is a prerequisite for generating DNA oxidation [72].

Inflammation

Inflammation plays a role in cancer. Asbestos-related MPM pathogenesis is associated with fibroproliferative response [73]. This process partly involves IL-1, as reported in a study comparing inflammation in wild-type (WT) and IL-1α/β/KO mice following injection of crocidolite or carcinogenic CNT fibers in the pleural cavity [74]. Both types of mice developed mesothelial cell hyperplasia, leucocyte infiltration, granulomas, and fibrotic responses, but fibrosis-specific genes were downregulated in the IL-1/KO mice in comparison to WT mice [74].

Induction of inflammation was confirmed by transcriptomic and proteomic analyses. Inflammatory response to asbestos, crocidolite and tremolite, was studied at the acute (1 day) and subacute (7 days) phase in lung of mice exposed by oropharyngeal aspiration [75]. Gene expression demonstrated inflammatory response (increased cytokine and chemokine release) and tissue damage (LDH release in the broncho-alveolar fluid) [75]. Fifty six days post exposure perivascular and parenchymal inflammation, granulomas

and fibrosis were moderate to severe [75]. A proteomic analysis was carried out in lungs of mice exposed to crocidolite, single-walled CNT, and ultrafine carbon black by pharyngeal aspiration [76]. The overall pattern of protein changes was similar across treatments, and GO functional categories were related to inflammation/immune response, fibrosis, and tissue remodeling [76].

Global Gene Expression

In the previously mentioned transcriptomic study [75], apart from genes of the inflammatory response, differentially expressed genes were involved in several other pathways regulating cell movement, death and survival, growth and cell proliferation, in comparison to control. In another study where amosite asbestos fibers and CNT were instilled into the pleural cavity of mice, transcriptomic microarray analysis showed a common molecular signature of inflammatory lesions, and antibody-based array analysis showed activation of pro-oncogenic signaling pathways, including Src family kinases, Akt, mTOR, ERK1/2, and STAT3 [77]. Progression of fiber-induced lesions is characterized by increased proliferation and oxidative DNA lesions [77].

Gene mutations and signal pathway dysregulation were studied in 15 MM cell lines obtained from crocidolite-induced murine MM in three different mice strains, BALB/c, CBA, and C57BL/6 [78]. Whole exome analysis reported homozygous deletions in *Cdkn2a* in 14/15 cell lines and deletion in *Trp53*, *Setd2*, or *Lats2* in 1–3 cell lines, as well as a frequent amplification of *Myc* [78]. The genes significantly mutated belonged to pathways Wnt, Mapk, and Jak/Stat, and mutations were also detected in genes from the Hedgehog and Notch pathways [78]. A differential response depending on the mice strain must be noted, as the BALB/c MM cells had higher average number of mutations than MM cells from the other strains, and only mutation in one sample in the Mapk signaling pathway [78].

Exposure of laboratory mice to carbon nanotubes mimics exposure to asbestos, from initial and chronic inflammation, through loss of the same tumor-suppressor pathways and eventual sporadic development of MM. These data support that fibers of a similar nature may pose significant health risks to MM [79].

Immunological Effects

Pathogenesis of asbestos, also shared by carcinogenic CNT, may be linked to their immunosuppressive effects, as reported in different studies [80–82].

MM Induction in GEM

To investigate the role of specific genes in MM development, several models of MM have been developed using genetically modified mice (GEM) unexposed or exposed to mineral fibers. A recent review analyzes the different studies [83].

GEM Unexposed to Asbestos Fibers

A few studies investigated the development of MM in conditional mutant mice carrying either heterozygous (Htz) or homozygous (Hom) inactivated genes in the absence of asbestos exposure [84–87] (see [83] for review). Gene inactivation was carried out by injection of Ad*Cre* (adenovirus expressing *Cre* recombinase) in the pleural or peritoneal cavity of mice carrying floxed relevant genes. All targeted genes were tumor suppressors, *Nf2*, *Cdkn2a/Ink4a*, *Cdkn2a/Arf*, *Trp53, Rb*, *Tsc1*, *Pten*, or *Bap1* alone or in combination. A high rate of thoracic MM was observed after injection of Ad*Cre* in the pleural cavity of double mutants *Nf2* and *Cdkn2a*, *Trp53*, or *Rb* and in triple mutants *Nf2*, *Trp53*, and *Ink4a* (almost 100%) [85]. After injection of Ad*Cre* in the peritoneal cavity or in the bladder of double Hom *Trp53/Tsc1* mutants, a high rate of MM developed, but none in Htz/Hom mutants showing a higher contribution of *Trp53* [84]. Involvement of *Pten* was also reported in the occurrence of pleural MM, as Hom *Pten* mice developed a frequency of 7% MM, but when coupled with Hom *Trp53*, 56% of mice developed pleural MM [87]. Of note, genetic alterations in *Tsc1* and *Pten* are found at very low frequency in MM. Kadariya et al. [86] investigated the role of *Bap1*, a gene predisposing to the development of MM and frequently mutated in human MM [88, 89]. Interestingly, the authors generated mice with point mutations in *Bap1* identical to germline mutations found in two human families with a *BAP1* cancer syndrome, and presenting mesothelioma in several family members [86]. They also studied Htz mice (knockout in exons 6 and 7). The results showed that Htz mice developed numerous types of cancers, but few or no MM [86]. The tumor type with the highest incidence was ovarian sex cord stromal tumors, found in 63% *Bap1* mutant mice [86].

GEM Exposed to Asbestos

Several studies investigated the development of MM in mice carrying Htz mutation in genes homologous to the most frequently inactivated in human MM, *NF2*, *CDKN2A/INK4A*, *CDKN2A/ARF*, *BAP1*, and *TP53* [83]. Studies were carried out on mice Htz for one tumor suppressor *Trp53*, *Nf2, Cdkn2a/Ink4a*, *Cdkn2a/Arf*, or *Bap1*. A higher level of MM

was found in asbestos-exposed Htz mice (crocidolite) in comparison with asbestos-exposed wild type (WT) mice. No MM was observed in untreated mice [54, 86, 90–93].

Interestingly MM cells obtained from ascites in *Trp53*$^{+/-}$mice exhibited *Trp53* LOH and polyploidy [94]. A loss of heterozygozity (LOH) of the *Nf2* gene was found in *Nf2*$^{+/-}$ mice, suggesting a common mechanism for loss of the WT allele [54, 91]. Moreover, in *NF2*$^{+/-}$ mice, two other TSG, *Cdkn2a/Ink4a* and *Cdkn2a/Ink4b*, were deleted at a high rate, while *Trp53* was mutated at a much lower rate similar to human MM [91, 92]. A loss of the WT allele was also observed in MM Htz *Bap1* mice exposed to asbestos [86].

Gene alteration and expression were studied in mesothelioma cells from asbestos-treated MexTAg transgenic mice carrying SV40 large T Antigen (SV40Tag), in comparison with WT mice [95]. Analysis of the *Cdkn2* locus revealed deletion in WT animals, but not in MexTAg mice [95]. As SV40Tag protein targets and impairs the p53 protein, this is consistent with different pathways of mesothelial cell transformation involving *Cdkn2a/b* and *Trp53*. Differentially expressed genes were involved in cell cycle regulation and DNA replication [95].

Murine MM closely mimics the human disease characterized by peritoneal ascites, a long latency between fiber injection and MM appearance, and histological subtypes, epithelioid, sarcomatoid, and biphasic, similar to human MM. The results obtained with GEM show that in most cases, MM progression could follow several routes involving different TSG with *Cdkn2a* and *Trp53* as independent key players. This is consistent with the specific clinical features and molecular alterations in human MM.

Collectively, results obtained in the different GEM experiments with or without asbestos exposure show that the most frequently altered murine genes homologous to the human genes, *NF2*, *CDKN2A*, and *TP53*, are important in the neoplastic transformation of mesothelial cells, consistent with findings in human MM. The potential of other genes, *Rb* and *Pten*, is dependent on the inactivation of other key MM genes. *Bap1* plays a role as cancer predisposing gene and is not specifically linked to the development of MM. The data obtained with asbestos-exposed mice are consistent with this observation.

Effects of Asbestos Fibers on Mesothelial Cells in Culture

While early studies have been carried out with cells of different species and tissues, human and rodent normal mesothelial cells have been most widely used to study the response of mesothelial cells to asbestos fibers [96].

Genotoxicity

In cultures of normal rat pleural mesothelial cells, asbestos induces chromosome alterations and abnormal mitoses [97–102]. DNA breaks, base oxidation, and stimulation of DNA repair were also evidenced [68, 103–108]. Furthermore, DNA breakage and cell cycle arrest were detected in rabbit pleural mesothelial cells exposed to crocidolite [68]. Interestingly DNA breakage was related to the phagocytosis of fiber by mesothelial cells as reduction of phagocytosis reduced the level of DNA breakage [68]. When incubated in the absence of serum or in low levels of serum concentration, cell proliferation was observed [109, 110]. However, in proliferating mesothelial cells, asbestos provoked a p53- and p21-dependent cell cycle arrest consistent with the induction of a DNA damage-induced response [102]. P53 was also induced in serum-deprived G0-synchronized mesothelial cells exposed to asbestos, but failed to block cell cycle progression [111]. Comparison between different studies showed that significant effects were found with doses of 0.5–1 μg/cm^2 [71].

To summarize, studies on genotoxicity of asbestos fibers demonstrate that asbestos fibers are genotoxic for 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. 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 [112]. Several studies with mesothelial cells in culture have emphasized the occurrence of apoptosis [68, 102, 113]. However, some cells can survive with genetic 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 some cells could pass through cell cycle checkpoints with unrepaired DNA and chromosomal damage. Recent findings suggest that BAP1 could play a role as reducing apoptosis [114].

Inflammation

The ability of mesothelial cells to interact and internalize asbestos fibers is an important feature that is linked to the deleterious effects of asbestos, especially production of inflammatory factors by these cells, and interaction with the dynamic of mitosis. Activation of the Nalp3 inflammasome that triggers inflammation is observed in mesothelial cells exposed to asbestos [73, 115].

Epigenetic Changes

Recently, some data on epigenetic changes in asbestos-exposed cells in culture were reported. DNA methylation profiling and gene expression were studied in Met5A cell line exposed to asbestos (chrysotile and crocidolite) [116]. Only 26 CpG sites were differentially methylated after treatment by both asbestos types, and methylation changes were the same for 15 of them [116]. Results did not show correlation between methylation and gene expression, except for *DKK1,* an inhibitor of Wnt signal pathway, whose expression is upregulated by chrysotile treatment. With chrysotile, differential methylation occurred in genes involved in cell response to stimuli, cell adhesion, and cellular matrix [116]. With crocidolite, several genes from the DNA damage response were downregulated, and upregulated genes were involved in metabolic process [116].

Effects on Signaling Pathways

Two studies investigated the response of human mesothelial cells to crocidolite asbestos by transcriptomic analyses [117, 118]. Gene expression was investigated in normal pleural human mesothelial cells, and in LP9, an h-TERT immortalized human mesothelial cell line exposed to crocidolite by transcriptomic analysis [118]. Several genes were upregulated (*ATF3*, *PTGS2*, *FOSB*, *IL8*, *NR4A2*, and *TFPI2*). Among them the transcription factor *ATF3* regulated levels of asbestos-induced inflammatory cytokines, IL-1b, IL-13, G-CSF, and the growth factor, PGDF-BB, in LP9/TERT-1 cells [118]. *ATF3* silencing by specific siRNA reduced cytokines and PGDF-BB expression levels [118].

The response of Met-5A cells to crocidolite was investigated using a Protein Pathway Array, which assesses proteins and phosphoproteins functionally linked to proliferation, apoptosis, cell cycle regulation, DNA repair, signaling, and transcription activity [119]. Three pathways were only affected by crocidolite, ILK signaling, PPARa/RXRa and G1/S phase checkpoint regulation [119]. Interaction between pathways, investigated by Ingenuity Pathway Analysis, identified several proteins regulating the networks, P53, CCND1, RB1, and CTNNB1 in asbestos-treated Met-5A cells in comparison with untreated cells [119]. These results confirm the effects of asbestos on cell cycle progression. Concerning the role of P53, it must be noted that Met-5A are SV40-transformed cells, which show a basal accumulation of nuclear P53 [120].

An upregulation of genes involved in invasion, including *MMP2*, was reported in a transcriptome microarray analysis of Met-5A mesothelial cells exposed to CNT and crocidolite at subcytotoxic concentrations [121]. Gene signaling network analysis found other genes involved in the asbestos- or CNT-induced invasion network as potential regulators of *MMP2* [121].

Fiber Properties in Relation to the Biological Effects and Carcinogenic Potency

These paragraphs summarize the biological mechanisms leading to the development of diffuse malignant mesothelioma, focusing on the physiochemical properties of asbestos fibers, and other carcinogenic natural mineral fibers known to induce MM in human. Several recent mechanistic studies have been carried out with CNT providing new perspectives to account for the mechanism of action of elongated particles. The reader is referred to comprehensive reviews for details on the fiber properties in relation to the biological effects and carcinogenic potency [8, 10, 11, 19, 122]. Several fiber parameters are of importance in the mechanism of asbestos toxicity (see also Chap. 12).

Physico-Chemical Properties of Asbestos Fibers and Elongated Particles

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 [123, 124]. Fluoro-edenite is a fibrous amphibole not used in the industry, but naturally occurring present in quarry stones [125]. Erionite fibers are a form of the mineral zeolite characterized by a high internal surface area. They are associated with the development of diffuse malignant mesothelioma in epidemiological studies [126–128]. These naturally occurring fibrous minerals are variable with respect to chemical composition, associated minerals, and trace contaminants depending on their geographic origin [129]. Asbestos fibers may contaminate other mineral deposits, for example, talc [126, 130] and vermiculite from Libby, Montana [130, 131], and exposure to these mixed materials has also been linked with diffuse malignant mesothelioma [128, 132]. The physiochemical properties of mineral fibers associated with biological activity include shape and dimensions, surface chemistry and reactivity, and biopersistence [8].

Shape and Dimensions

Shape and dimensions are fiber parameters modulating the biological effects of asbestos and elongated fibers. Fiber

length and diameter determine the respirability and site of deposition in the lungs, and clearance mechanisms. Short fibers are taken more easily by macrophages than long fibers and can be eliminated by the clearance mechanisms. In experimental studies, it was generally found that the fiber dimensions are important, with long and thin fibers more active that shorter fibers on cultured cell and with a greater carcinogenic potency in animals.

Phagocytosis is an important function of macrophages and other cells as it determines the intracellular availability of the fibers and possible interactions with cell components [73, 115]. A recent study investigated phagocytosis of CNT according to their geometry and demonstrated that geometry and volume influence the efficiency of phagocytosis [133].

Fiber length has been associated with the induction of aneuploidy and chromosomal damage due to direct physical interference with the mitotic apparatus or by binding to cell cycle regulatory proteins [134–136]. Chromosome damage and mitosis impairment are also features of CNT as observed in several types of rodent and human cells [137–139].

Surface Chemistry

Surface chemistry determines interactions between the fiber and the molecules present in the fiber vicinity. Fibers may interact with macromolecules in the biological fluids (proteins, phospolipids, etc.) [128]. Surface iron, especially on amphiboles surface, may be released, which could catalyze the formation of reactive oxygen species (ROS) and may be associated with biological effects of mineral fibers including lipid peroxidation, oxidative DNA damage, and activation of intracellular signaling pathways [140–143].

Biopersistence

Biopersistence is considered as a major determinant of fiber pathogenicity in the lungs [144]. It is dependent on fiber clearance and on the ability of fibers to be broken, split, or attacked by the biological medium in the lungs [144]. Differences in biopersistence of asbestos fibers have been linked with carcinogenic potency, as biopersistent fibers could sustain a local inflammatory response [145]. Amphibole asbestos fibers are more potent than chrysotile asbestos fibers due to their increased biopersistence in the lungs [8]. However, chrysotile fibers are detected in autopsic lungs several years past exposure to asbestos, and their biopersistence and effects could be linked to the surface modification of the fibers [146–148]. Additionally, these fibers should be stable regarding the lung pH [149]. 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 [150, 151].

High aspect ratio and biopersistence 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 [19, 152]. A long-term study, after intratracheal instillation of CNT in rats, reported that pulmonary lung burden did not decrease significantly over time up to more than 1 year after instillation [153].

Summary Hypotheses on the Mechanism of Action of Asbestos Fibers to Generate MM

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. The most important properties of asbestos fibers related to carcinogenicity are fibrous shape and dimensions, surface chemistry and reactivity, and biopersistence [39].

Interactions between mesothelial cells and fibers can cause genetic and chromosomal changes. There is a great body of evidence that (1) asbestos fibers can directly interfere with chromosomes and the mitotic spindle and (2) they induce the formation of reactive ROS resulting in DNA breaks, oxidation, and mutations [154–157]. 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, and they are well known to initiate signal transduction pathways that are, in turn, linked to inflammation, proliferation, and apoptosis [157, 158]. Free radical scavengers decrease genotoxic endpoints such as micronucleus formation induced by fibers, and antioxidant enzymes can protect cells against genotoxicity induced by chrysotile fibers [159, 160].

Prolonged interaction between pleural inflammatory cells and adjacent mesothelial cells causes persistent release of chemokines and cytokines, inflammatory mediators, ROS and reactive nitrogen species, and growth factors, which trigger repeated episodes of inflammation resulting in mesothelial cell injury, death, and/or proliferation [161]. This may also be linked to altered gene methylation patterns and to epigenetic gene silencing identified in human MM [162–164]. Genomic instability and acquired gene and chromosomal alterations in mesothelial cells may lead to altered cell cycle and growth regulation, resistance to apoptosis,

impaired repair of DNA and chromosomal damage, activation of oncogenes, and inactivation of tumor suppressor genes [134, 135, 163, 165]. This persistent inflammatory microenvironment in combination with oxidative stress and cell division impairment generates a strong selective force for mesothelial cells that have acquired genetic and epigenetic changes that promote their survival, proliferation, and tumor progression [164].

Molecular Alterations in Human MM

Carcinogens provoke several types of somatic gene mutations, consisting of DNA and chromosome alterations. Some mutations are the signature of past exposure to 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.

Chromosomal Imbalance

Structural and numerical chromosomal abnormalities are numerous and complex in MM. A detailed review can be seen in Chap. 18 [166]. It can be summarized here that one of the most frequent alterations are losses in the 3p21 region including the frequently inactivated gene *BAP1*, and other less frequently altered gene *SETD2* [167]. Frequent losses also occur in 9p21, which encloses the *CDKN2A*(*INK4A/ARF*) locus, encoding both the $P16^{INK4A}$ and the $P14^{ARF}$ proteins, and the *CDKN2B* locus, encoding P15 protein, and in 22q12 which encloses the *NF2* locus, which encodes the protein merlin.

Gene Mutations

In MPM, there are a limited number of genes known to be recurrently mutated in a high percentage of MM.

Inactivation of *CDKN2A* and *CDKN2B* TSG are mostly due to large deletions [168–170]. *CDKN2A* deletions have been considered as a marker of asbestos exposure in a study of non-small-cell lung carcinomas [171]. In MM, DNA methylation of *CDKN2A* and *CDKN2B* have been reported at a frequency of 13% (nine patients) and 4% (three patients), respectively, and positively correlated with asbestos body counts in the lung [172, 173]. The average methylation frequency of these genes in the literature is about 10% [92, 172, 174–178]. It was also suggested that mesotheliomas express microRNA (miRNA) that could inhibit *P16*/*CDKN2A* expression, based on an in silico analysis for miRNA target gene prediction [179]. Interestingly, a recent experimental study of instillation of either long asbestos fibers (amosite) or long CNT showed hypermethylation of *Cdkn2a*(*Ink4a/Arf*) in early lesions that precedes mesothelioma [77]. Both $P16^{INK4A}$ and $P15^{INK4B}$ are inhibitors of the kinase function of cyclin/cdk complexes involved in cell cycle progression. 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 $P14^{ARF}$. In murine models of asbestos-induced mesothelioma, the orthologous genes, *Cdkn2a*/*Ink4a* and *Cdkn2b*, are also inactivated by deletion (83, 91, 92, 180).

TP53 mutations occur at a lower rate in comparison with other human cancers, they are mainly due to non- or missense substitutions [66, 168, 170, 181, 182]. Different frequencies of 7.4% and 16.3% are reported in two studies respectively [66, 170]. No *TP53* mutation was reported in the epithelioid molecular MM subtype, in a whole exome analysis of 202 MPM [66], but TP53 mutations were found in MM of epithelioid histologic type in other studies [170, 183]. The protein P53 is activated in response to DNA damage and is a regulator of senescence, apoptosis, and autophagy. In animal models of MM (see above), 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 WT allele was found at a high rate in MM induced by asbestos fibers [90].

In large-scale analyses alterations of *NF2* TSG are frequently found, in about 20% of MPM [66, 170]. Higher percentages were previously reported in smaller series [184–187]. *NF2* has pleiotropic functions, being involved in the regulation of cell proliferation, apoptosis, and endocytic trafficking and acting upstream of several signaling pathways including the Hippo signaling pathway [188]. Mutations in *NF2* consist of both point mutations and deletions [189]. In $Nf2^{WT}$ and $Nf2^{+/-}$ FVB mice, *Trp53* alterations were infrequent. *Nf2* mutations were detected in mice exposed to asbestos and exposed to ceramic fibers [92, 180]. Alteration in the chromosomal region of the *Trp53* locus was infrequent [190]. 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.

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 [188]. Merlin is a component of the adherens junctions and other types of cell-to-cell contacts [191, 192]. 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.

Somatic *BAP1* mutations are frequent in MM. A frequency of about 20% was reported in several studies, although higher rates, up to 60%, are reported [88]. Bueno et al. [66] reported a frequency of mutations in 23% in MPM, that was the highest rate of mutations in comparison with the other predominantly mutated genes *NF2*, *TP53*, and *SETD2* [66]. In another series including MPM tumors and cultured MPM cells, a higher percentage of *BAP1* mutations was found in the subgroup of epithelioid MPM (subgroup C1) in comparison with subgroup including both epithelioid and sarcomatoid MPM (subgroup C2) [169]. *BAP1* germline mutations were found in a few cases of sporadic mesotheliomas [193]. However, no germline mutations in *BAP1* was found in a cohort of patients in Australia [194]. So far, the weight of germline *BAP1* mutations in asbestos-induced MM is not clear.

Until recently, *BAP1* was the only gene reported as possibly conferring an increased susceptibility to MPM. A recent paper reported a gene sequencing analysis of 85 cancer susceptibility genes on germline DNA of patients with pleural, peritoneal, and tunica vaginalis MM [195]. Twelve percent of patients with MM carried mutations in genes such as *BRCA2*, *CHEK2*, *CDKN2A*, and *ATM*, especially those with peritoneal MM, minimal asbestos exposure, young age, and a second cancer diagnosis [195].

So far, no recurrent mutations have been reported in oncogenes. However, a "hot spot" of mutations in the *TERT* gene core promoter has been reported in 15% of MPM [196]. *TERT* promoter mutations were significantly more frequent in MPM with sarcomatoid histologic subtype [196].

Regulatory Pathways in MM 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 deregulation in MM has been shown by gene sequencing and gene expression profiling [197, 198]. Alterations were recurrently reported in several pathways: hippo, MAPK, PI3K/AKT/mTOR hedgehog, Wnt signaling pathways, cell cycle, P53/DNA repair, apoptosis, and ubiquitin/proteasome system due to the frequent alteration of the deubiquitinase, BAP1.

The Hippo Pathway

The Hippo pathway is of special interest regarding the high frequency of mutations detected in merlin encoded by the *NF2* gene. As mentioned above, merlin negatively regulates cell proliferation and other cell functions [199, 200]. Its activity is affected by interaction between extracellular signals and membrane proteins, and activated merlin transduces signals suppressing the transcriptional activity of YAP coactivator for TEAD and other transcription factors [168, 201]. YAP and LATS1/2, regulator kinases of the hippo pathway, may mediate proper organization of cytokinesis machinery and mitosis progression [199]. *NF2* coinactivation with *LATS2* led to loss of cell contact inhibition in human MM cells [202]. *LATS2* gene was found to be deleted in three out of six MM cell lines and in one out of 25 tumors by DNA sequencing analyses [203]. A more recent study reported *LATS2* mutations in 11% (7/61) MPM cells [202]. 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 [204].

In an integrated analysis of genomics data, hippo pathway was identified as altered in all histological type of MPM due to gene alterations in several members of the pathway [66].

Cell Cycle

The alteration of CDK inhibitor genes located at the *CDKN2* (*CDKN2A* and *CDKN2B*) locus, as mentioned above, contributes to uncontrolled cell proliferation. 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 [205–207]. Overexpressed genes were involved in the regulation of all phases of the cell cycle and cell replication and control of cell cycle progression [205].

Several genes involved in the control of entry in mitosis and mitosis progression were also detected. Overexpression of aurora kinases (AURK) has been reported in several studies [206, 208]. In a recent study, higher expression of aurora kinase A (AURKA) mRNA expression was reported in a subset of MM with poor prognosis [170]. 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, possibly by an epigenetic regulation [209–211].

These results can account for the complex, even chaotic, chromosomal alterations mentioned above, as the result of a defective control of cell cycle progression through different phases of the cell cycle, including dysregulation of mitosis.

P53/DNA Repair and Apoptosis

Mutations in *TP53* and *BAP1* play a role in MM pathogenesis. *TP53* has multifunctional tumor-suppressor response, including the DNA damage response (DDR) function and regulation of senescence and apoptosis [212]. Additionally, *BAP1* encodes a multifunctional ubiquitin C-terminal hydrolase, which is also involved in DNA repair and stress response [213, 214]. Epigenetic mechanism was identified as a mechanism involved in gene silencing in DDR responses [215]. A nanostring analysis reported that mRNA expression of 12 target genes involved in different DDR pathways was significantly associated with expression levels of miRNAs in a series of 24 epithelioid MPM [216].

Otherwise, specific regulators can contribute to MM resistance to apoptosis, such as 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 [217–220]. Approaches to control MM proliferation have focused on the resistance of MM cells to apoptosis [221, 222]. Integrated analysis of the genomics data identified alteration of P53 signaling pathways [66].

From several studies, 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 [223–226]. 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 [227]. 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 [227, 228].

MAPK and PI3K/AKT/mTOR Signaling Pathway

The MAPK and PI3K/AKT/mTOR signaling pathway control various cellular processes, cell proliferation and differentiation, cell migration, survival, apoptosis, and response to stress and mitogens and is deregulated in solid cancers [229]. In normal cells, these pathways are 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.

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) [230–233]. VEGF expression was enhanced in a large proportion of MPM in comparison with nonneoplastic specimens [234]. An autocrine role for VEGF in cell proliferation has been suggested [232, 235].

MM cell growth may also be linked to autocrine or paracrine stimulation growth factors such as PDGF [236–242].

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 other types of cancer [243].

Human MM cells express insulin growth factor (IGF) and insulin growth factor receptors (IGFR), and the activation of IGFR activates downstream signaling [244, 245]. IGF-I appears to function as an autocrine growth factor in human mesothelial cells [246]. IGF-binding proteins also regulate IGF-dependent growth [245, 247, 248].

Hepatocyte growth factor receptor (MET) is a proto-oncogene and the receptor for the ligand hepatocyte growth factor/scattering factor (HGF/SF). Both MET and HGF/SF proteins are expressed in some MPM suggesting the establishment of an autocrine loop [249]. In vitro HGF/SF increases spreading, motility, and/or invasiveness of mesothelial cell lines, and inhibition of MET reduced cell proliferation [250–252]. The activation status of MET and other RTKs, EGFR family, 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 was investigated on cell lines [253]. 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 [253].

The MAPK signaling pathway is constitutively activated in MM as demonstrated by the phosphorylation and activation of downstream proteins of the MAPK cascade, ERKs, Jun amino-terminal kinases/stress-activated kinases (JNKs/SAPKs), and p38 MAPK and inhibition of cell proliferation and induction of apoptosis by inhibitors of the pathway [254–256]. 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. The relative levels of tyrosine phosphorylation of 42 distinct RTKs were determined in MM cell lines established from surgical specimens. A coordinated activation of several RTKs—EGFR, ERBB3, AXL, and MET—was reported [257]. No recurrent mutations were identified in members of MAPK signaling pathway in MM.

Activation of RTKs also induces activation of other downstream signaling cascades including PI3K-AK pathway. PI3K/AKT/mTor is activated in MM [258]. Phosphorylation of AKT protein, the active form of the protein, and activation of the Akt pathway have been demonstrated in MM cells [198, 219, 259]. In MM cells, PTEN, a TSG and negative regulator of the PI3K-AKT pathway, homozygous deletion has been reported in a very small subset of MPM cell lines [260, 261]. Integrated analysis of the

genomics data identified mTOR pathway as deregulated in MPM [66]. Upregulation of PI3K and mTOR signaling pathways were associated with poor prognosis [170].

Other Signaling Pathways

Other signal transduction pathways Wnt, Hedgehog, and Notch are activated in MM cells. These pathways are important in embryonic development and also as regulators of cancer stem cells (CSC), a side population which is resistant to chemotherapy and radiotherapy [262, 263].

The Wnt signaling pathway regulates cell proliferation and cell polarity, its activation prevents beta-catenin inactivation, a coactivator of transcription, allowing the expression of a variety of genes exerting pleiotropic effects [264]. However, cell growth inhibition and apoptosis of MPM cells were observed according to a beta-catenin-independent inhibition of Wnt signaling [265, 266]. In MPM, the Wnt pathway could be altered as a result of promoter hypermethylation of regulatory genes [265, 267, 268]. 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 [269]. These results suggest that deregulation of the Wnt signaling pathway is involved in mesothelial carcinogenesis. Hedgehog signaling pathway is inactive in normal mesothelium, it can be reactivated in some MM and targeted to reduce the stemness-related cell population [270–272]. Mutations in genes of these pathway have been suggested in MM [273]. The deregulation of Notch signaling pathways has been reported in MM, with expression levels of Notch1 and Notch2 being elevated and reduced, respectively, in human MM cell lines [274]. These proteins act as positive and negative modulators, respectively, of PI3K/Akt/mTOR signaling pathway.

Epigenetic Pathways

More recently, alterations in epigenetic pathways, DNA methylation, histone modification, nucleosome remodeling, and RNA-mediated targeting (noncoding RNAs) have been reported in MPM. These pathways are important as they are connected to cancer [275]. Modifications of DNA methyl transferases, chromatin remodelers, and differential expression of noncoding RNAs in comparison with normal mesothelium are found in MM. DNA methylation was associated with silencing TSGs [276]. Mutations in genes *SMARCA4*, *ARID1A*, and *ARID2* involved in the chromatin remodeling SWI/SNF complexes have been found in a low percentage of MM and in the histone methyl transferases *SETD2* and *KMT2D* [66, 276]. Promoter methylation was associated with alterations of gene expression and an upregulation of several DNA methyltransferases in MM [276, 277]. High-throughput integrated analysis of the genomics data identified histone methylation; RNA helicases pathways are altered in MPM [66].

Immune Checkpoints

Immune checkpoints are modified in cancer cells. In normal tissue, they permit the maintenance of a self-tolerance function. In cancer cells, the expression of immune-checkpoint proteins is modified, allowing tumor evasion, and blockade of the immune checkpoints is a developing field in anticancer immunotherapy [278]. Among them inhibitory T-cell receptors, CTL4 and PD1, or ligand PDL1 are presently targeted using specific antibodies to enhance immune recognition [279]. Studies have investigated the level of expression of checkpoints proteins in MM, and a heterogeneity between tumors of their expressions and also of the immune cell content has been reported [66, 170, 280]. Further studies should improve the knowledge of immune microenvironment of tumor cell and improve targeted immunotherapy [281].

Human MM Molecular Heterogeneity

MM heterogeneity appears to be one cause of the limited efficiency of treatments [282]. Histological diversity reflects various morphological patterns of MM defined through detailed classifications of the tumors [283]. Immunohistochemical markers are useful for differential diagnosis of MPM and molecular markers, e.g., BAP1 protein expression and deletion of *CDKN2A* locus are currently used [284]. CGH arrays and gene mutation analyses of MM have added a level of complexity in MM heterogeneity. DNA sequencing have revealed numerous copy number alteration and gene mutations [166]. Moreover, within tumors, mutations are not detected in every mesothelioma cell in the tumor, possibly linked to polyclonal evolution [282, 285].

Recently comprehensive genomic analyses allowed classifying MM in different subtypes through transcriptome analysis alone or coupled with other analysis such as sequencing [66, 169, 170, 202, 208, 286]. One transcriptomic study reported a clusterization of MPM in two subtypes loosely correlated with tumor histology, consistent with a molecular diversity partly related to morphological pattern [286]. In another study, gene expression profiles of epithelioid versus sarcomatoid MM were analyzed, and led to the identification of genes related to lower survival expressed in sarcomatoid MM, such as aurora kinases A and B and functionally related genes involved in mitosis and cell cycle control [208]. The authors developed a prognostic classifier

based on their microarray data, but found a limited predictive value [208]. However, the identification of diagnostic markers is of potential interest for better patient management [208]. Another transcriptomic analysis defined two robust molecular MPM subtypes, C1 and C2, only partly related to histologic types but closely related to prognosis [169]. Interestingly, epithelioid MPM were found in both groups, with a worse survival prognosis in the C2 subtype. These MM groups also exhibited differential rate of mutations, with more frequent *BAP1* alterations in C1 subtype. Pathway analysis revealed that EMT was differentially regulated between MPM subtypes, C2 subtype being characterized by a mesenchymal phenotype [169]. A subtype of C2, the $C2^{LN}$ subtype, characterized by the double inactivation of *NF2* and *LATS2* TSG, was identified by coupling transcriptomic and genetic analyses [202]. Another publication has identified four distinct molecular subtypes: sarcomatoid, epithelioid, biphasic-epithelioid (biphasic-E), and biphasic-sarcomatoid (biphasic-S) using RNA-seq data [66]. Exome analysis in the same tumor samples confirmed already identified and less commonly known mutated genes, *BAP1*, *NF2*, *TP53*, *SETD2*, *DDX3X*, *ULK2*, *RYR2*, *CFAP45*, *SETDB1*, and *DDX51*, and alterations in Hippo, mTOR, histone methylation, RNA helicase, and P53 signaling pathways without establishing a link with the four molecular subtypes [66]. Investigation of the immune microenvironment found highest rates of T cells and M2 macrophages in the sarcomatoid group [66]. Finally, one publication reported a comprehensive integrated genomic study providing histology-independent determinants of poor prognosis [170]. Four clusters, namely iCluster 1–4, were characterized. The authors also defined a genomic subtype with *TP53* and *SETDB1* mutations and extensive loss of heterozygosity, and a strong expression of the immune-checkpoint gene *VISTA* in iCluster 1 related to epithelioid MPM [170]. Gene methylation seems associated with prognosis as the methylation level is different between clusters and higher in better prognosis clusters [170].

The mechanisms of mesothelioma heterogeneity have been recently discussed, emphasizing the different levels of MM heterogeneity [287]. The recent publications on molecular characterization of MPM and the definition of distinct groups with specific molecular biomarkers linked to prognosis is of paramount interest to refine the diagnosis, to guide the therapeutic option, and to develop targeted therapies. In the future, it may be expected that integration of metabolic, epigenetic, and genomic data will succeed in proposing therapy adapted to the patient's tumor.

Conclusions

Recent studies brought some light on the mechanism of MM carcinogenesis, and some questions remain to be addressed. Carcinogenesis progresses through multi-dependent steps, from fiber inhalation to neoplastic transformation of mesothelial cells and tumor growth. Asbestos remains the major risk factor for MM, and past exposure can explain most of the MM, demonstrating a strong link between asbestos activity and mesothelial cell responsiveness. Lung, larynx, ovary, possibly stomach, colon, and rectum cancers are other cancers linked to asbestos exposure, but asbestos is not the unique cause for these cancers. Fibers can reach these organs via clearance, translocation, and ingestion mechanisms, after inhalation. The relationship with past asbestos exposure addresses the question of the specific sensitivity of mesothelial cells. The recent investigations carried out with CNT demonstrated a pleural translocation. Further studies would account for a more precise mechanism of particle translocation.

The *BAP1* gene was discovered and suggested as predisposing to MM in a context of asbestos exposure. In human, this gene is mutated in *BAP1* tumor predisposition syndrome (BAP1-TPDS), which increases the risk of a variety of malignant and benign tumors. In MM, *BAP1* mutation may be not a predisposing factor, as other cancers are associated with BAP1-TPDS families, but *BAP1* mutation is more likely a sensitivity factor in subjects exposed to asbestos, asking the question of the role of *BAP1* in mesothelial cell physiology. The results obtained with GEM are consistent with this hypothesis as no MM is found in unexposed $Bap1^{+/-}$ mice, in contrast with asbestos-exposed $Bap1^{+/-}$ mice. A recent study suggest the association of other germinal gene mutations associated with MM formation [195].

Carcinogenesis is defined by several capabilities that cells acquire during the neoplastic process [288, 289]. Asbestos can induce genotoxicity, an early step in mesothelial cell transformation, due to DNA oxidation generated by oxidative stress and inflammation, and chromosome aberrations generated by mitosis impairment. It seems that there is no evidence that inflammation is a prerequisite for generating DNA oxidation. Chromosome alterations are also reported in human cells exposed to CNT. Further studies carried out with HARNs should improve our knowledge of the mechanism of fiber-induced genotoxicity.

Studies of human MM cells and tissue samples have identified cellular and molecular changes in comparison with normal cells. MM is characterized by numerous copy number alterations including frequent deletions, gene fusions, and point mutations in a limited number of genes, most being TSG. In MM, genes are inactivated by mutation or by methylation. Apart from activating mutations in *TERT* promoter, no other recurrent oncogenic activation has been reported. Inactivated genes in MM are involved in the regulation of several pathways, cell cycle, hippo, P53/DNA repair, and MAPK and PI3K/AKT/mTOR regulatory pathways. Moreover, epigenetic changes in DNA methylation, histone modification, nucleosome remodeling, and miRNA-mediated targeting were more recently reported to occur in mesothelioma cells.

Ongoing researches will improve our knowledge on the molecular ways followed by mesothelial cells during neoplastic transformation.

Several recent clinico-biological studies have performed a molecular classification of MM, based on transcriptomic and multi-omic studies. The results have highlighted the molecular heterogeneity of MM, where tumors can be classified into different subtypes with different gene mutations, level of epithelial–mesenchymal transition, deregulated pathways, immunological microenvironment, and linked to survival outcome. These studies demonstrate that MM are heterogeneous tumors, not only clinically and morphologically but also on a molecular basis. The results are encouraging to go forward and define biomarkers to develop efficient precision medicine.

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Malignant Mesothelioma: Asbestos Exposure

20

Richard L. Attanoos

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]. Projections for the 1995–2029 period suggest that male mesothelioma deaths will double over the next 20 years to a peak of 9000 in 2018 and then decline, with an estimated 250,000 deaths up to 2025 in Europe [2]. There are marked geographic variations in mesothelioma rates. Age-adjusted mesothelioma mortality rates between 1994 and 2008 were (per million subjects): 16.0 in Oceania, 7.2 in Europe, 4.8 in Africa, 3.6 in The Americas, and 2.6 in Asia [3]. Within continents there are significant variations; in Europe, mesothelioma rates are higher in North West Europe (United Kingdom, The Netherlands) compared with South East Europe (excluding Italy). The highest incidence of malignant mesothelioma globally is presently in the United Kingdom relating to the protracted use of commercial amphibole asbestos amosite [4]. Annual pleural mesothelioma rates in males have been steadily decreasing in the United States since the mid-1990s although total mesothelioma rates are still increasing in many European, Asian, Central and South American, and African Countries, reflecting prior asbestos consumption.

It is most important to emphasize that while asbestos fibers are ubiquitous in air, water, and soil, there is no evidence to support the view that ambient exposures to asbestos from urban dwelling cause any asbestos-related disease. Indeed, there is now scientific evidence which shows that while considerable geographic variations in ambient asbestos air concentrations do exist between some urban and rural communities, these asbestos fiber variations do not translate into manifesting asbestos-related disease in the urban areas with higher ambient fiber concentrations [5]. It is also important to consider that the vast majority of adult persons in developed industrialized communities despite no known occupational asbestos exposure or evidence of any biomarkers of prior asbestos-related disease have detectable levels of asbestos fibers in their lungs on fiber burden analysis, reflecting some past exposure [6]. These are predominantly albeit not exclusively short (<5 micron) asbestos fibers. Mineral analytic laboratories establish these control populations to assist in individual disease causation in suspected asbestos-related cases of mesothelioma, lung cancer, and lung fibrosis (asbestosis) [7].

Fiber toxicity is governed primarily by cumulative fiber dose, fiber dimension (length and diameter), and fiber biopersistence (linked with fiber type—amphibole asbestos versus chrysotile). The scientific evidence correlating cumulative exposure to amphibole forms of asbestos and disease is extensively established in occupational settings which have cumulative asbestos exposures *orders of magnitude* above background ambient exposure levels [7]. Even after nonoccupational secondary exposures such as domestic/paraoccupational/"take-home" or neighborhood/environmental exposures from habitation close to industry, where cumulative asbestos exposures are typically somewhat lower than primary occupational exposures, the scientific literature extensively implicates commercial amphibole forms of asbestos [8–10].

Malignant pleural mesothelioma and benign pleural disease (pleural plaques and diffuse pleural thickening/fibrosis) develop after lower cumulative doses to commercial forms of amphibole asbestos than peritoneal mesothelioma, lung cancer, or lung fibrosis (asbestosis). The association, if any, between pericardial mesothelioma and asbestos is weak [11, 12]. These dose effects observed in different asbestos-related diseases in different anatomic locations are important to consider when evaluating disease causation.

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Tumor latency is an important temporal factor in cancer epidemiology and one determinant in estimating dose–response relationships, risk, and future disease trends. Asbestos-related mesotheliomas in occupational settings shows a long latent period in which the average is 30–40 years with no upper limit [13]. There is a body of scientific evidence which supports the inverse dose-latency hypothesis identifying longer latency in persons with lower cumulative asbestos exposures which have been generally reported in household contact, residential and environmental exposures which are proportionately more frequently observed in females [14].

In this chapter there is a discussion of the mineralogic aspects of asbestos, a review of varied relation of malignant mesothelioma with asbestos, and a guide to the evaluation of cases in suspected asbestos-related diseases.

Asbestos: Mineralogy

The term *asbestos* is a collective one that describes a *regulated* group of six naturally occurring fibrous silicate minerals. Not all *asbestos* is the same. There are two distinct mineral groups: amphibole asbestos and serpentine asbestos [15].

Amphibole and serpentine minerals may crystallize or grow in two forms or habits: a common non-asbestiform or massive habit (comprising over 90%) and a rare asbestiform habit (Table 20.1).

The amphibole asbestos minerals include commercial forms (amosite or brown and crocidolite or blue) and non-commercial forms (tremolite asbestos, anthophyllite asbestos, and actinolite asbestos). The serpentine asbestos group comprises chrysotile asbestos. (Elongate mineral particle (EMP) images Figs. 20.1, 20.2, 20.3, 20.4, 20.5, and 20.6).

Amphibole asbestos and chrysotile are distinct in their chemical, physical, and biological properties, and these factors transfer into significant differences in fiber toxicity and potency to induce diffuse malignant mesothelioma.

Physically, amphibole forms of asbestos are composed of firm, straight fibers with parallel sides which disaggregate easily to form matted sheets of fibrils. The asbestos fibers exhibit high tensile strength and flexibility, long fiber length, and fine fiber width and have curved splayed ends. Amphibole asbestos fibers are acid insoluble, do not breakdown after inhalation, and may persist for decades in tissue. Physically,

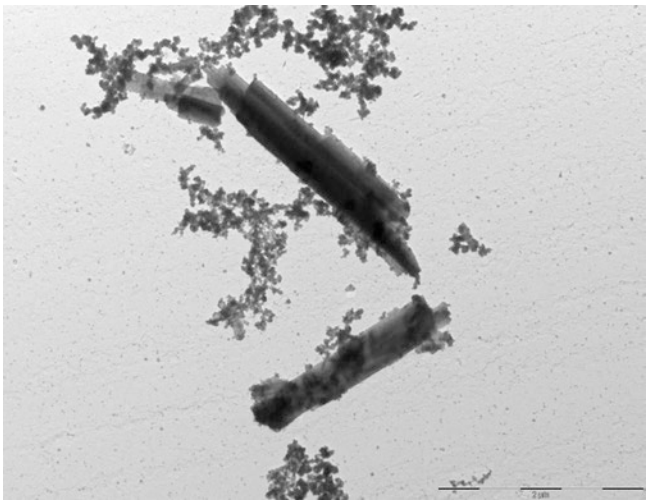

Fig. 20.1 Transmission electron microscopic image of actinolite EMP

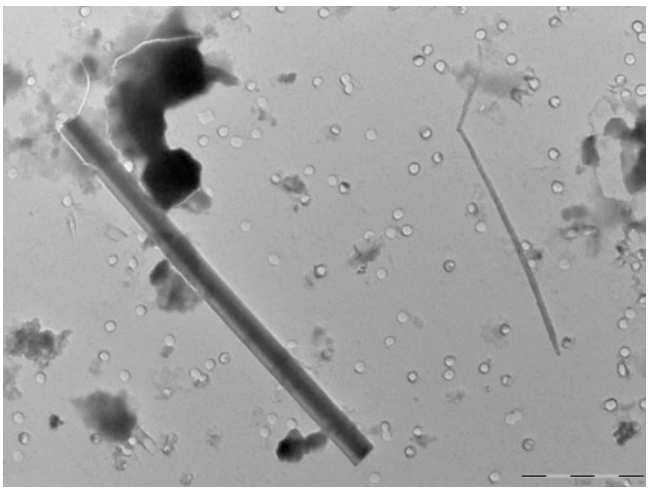

Fig. 20.2 Transmission electron microscopic image of amosite and glass fiber EMP

Table 20.1 Asbestos minerals and their non-asbestiform polymorphs

Mineral group	Asbestos	Non-asbestiform polymorph	Composition
Serpentine	*Chrysotile*[a]	Lizardite, antigorite	Mg_3 (Si_2 O_5) (OH_4)
Amphibole	Actinolite asbestos	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 asbestos[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 asbestos	Tremolite	Ca_2 Mg_5 (Si_8 O_{22}) $(OH)_2$

[a]Commercial asbestos forms, anthophyllite asbestos predominantly in Finland

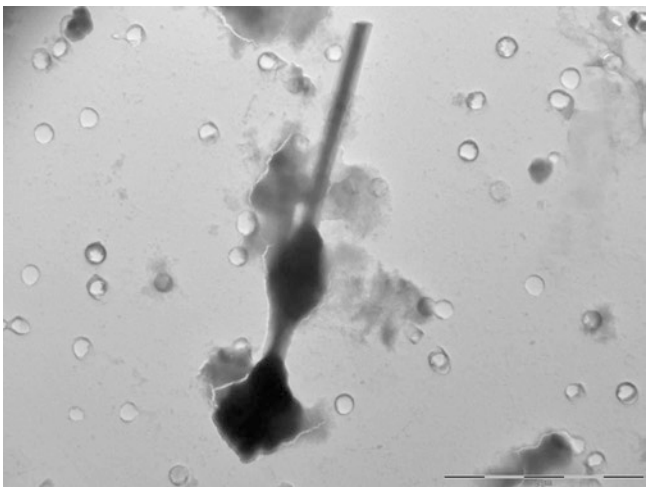

Fig. 20.3 Transmission electron microscopic image of amosite asbestos body

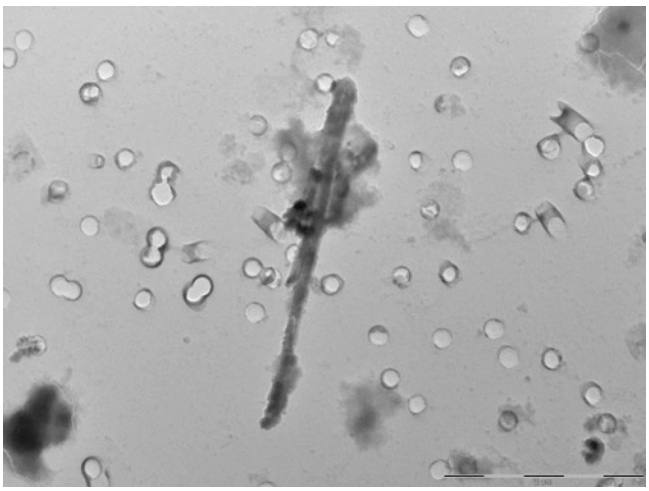

Fig. 20.6 Transmission electron microscopic image of crocidolite

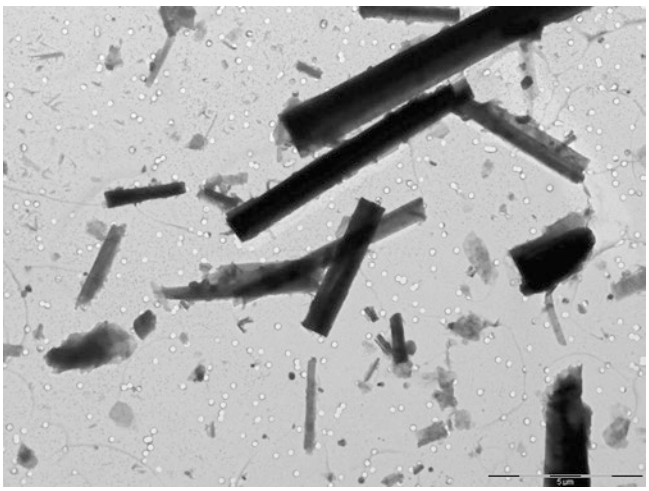

Fig. 20.4 Transmission electron microscopic image - anthophyllite EMPs

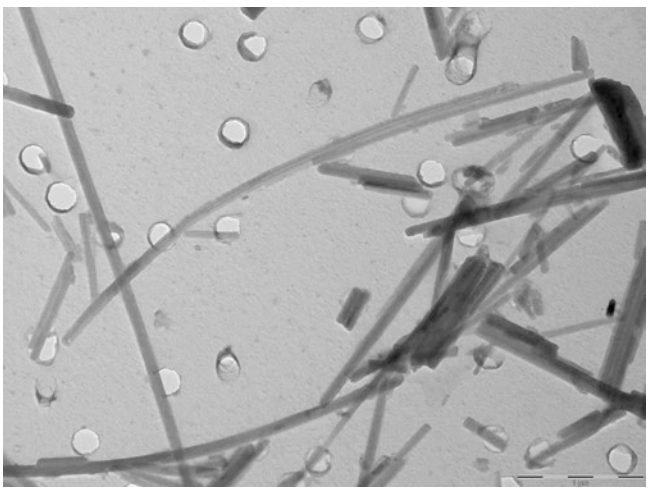

Fig. 20.5 Transmission electron microscopic image of chrysotile, note short fiber size

chrysotile comprises bundles of curled flexible fibers, which are acid soluble, and these do break down after inhalation with rapid clearance.

The more common non-asbestiform amphiboles (include riebeckite, cummingtonite/grunerite, tremolite, anthophyllite, and actinolite) and non-asbestiform serpentine minerals (lizardite and antigorite). Non-asbestiform amphibole minerals do not grow in the same crystalline habit as asbestos minerals. The non-asbestiform amphiboles are subject to fracture when physically crushed and form cleavage fragments which are shorter and thicker than counterpart asbestos fibers. Cleavage fragments may show varied morphologic features and have surface irregularities and low tensile strength. Cleavage fragments have diameters which, on average, are much larger than those of asbestos fibers of the same length. While these are chemically similar to their asbestos fiber counterparts, cleavage fragments are physically distinct, and these physical differences translate to significant differences in biologic effects in tissue systems with significantly lower, if any, toxicity [16–18]. Cleavage fragments of non-asbestiform minerals have not been associated with asbestos-related diseases and are not regulated as asbestos by the United States Occupational Health and Safety Administration (OSHA).

Asbestos and Mesothelioma: Site and Gender Variations

The proportion of malignant mesothelioma cases attributable to asbestos varies considerably according to fiber type, occupation and industry, tumor site, and gender. Although various factors are inter-related, in this section there is a discussion of anatomic site and gender variations with mesothelioma and asbestos.

Pleural Mesothelioma

Several epidemiologic studies have examined the broad relationship between asbestos production, use, or imports and the subsequent incidence of mesothelioma, on a countrywide basis [19, 20]. All have shown rises in the incidence of malignant pleural mesothelioma in men which parallel rises in the amount of asbestos in use after about 30–40 years. This reflects the long latent interval that occurs in human malignant mesothelioma. From North American registries, about 70–90% of pleural mesothelioma in men have a history of prior asbestos exposure [19, 21]. Among US female mesothelioma patients, the attributable fraction is ~20% [19, 21]. Gender-specific differences in pleural mesothelioma have also been observed in the United Kingdom and in mainland Europe although the attributable fraction to asbestos is higher compared to North America [4, 22–24]. It has been suggested that the constant incidence among women implies that either environmental exposure to asbestos is associated with a negligible risk or that the typical levels of environmental asbestos exposure will not exceed the threshold for mesothelioma risk [19, 25].

It is worth stating that when an occupational asbestos fiber-induced carcinogenesis exists, it most consistently creates a mesothelioma subject demographic predominantly of elderly men (median 70 + years) with pleural disease. The male: female ratio for occupational-induced pleural mesothelioma is usually around 4–5:1.

Peritoneal Mesothelioma

Peritoneal mesothelioma when asbestos related is associated with significant exposures to commercial forms of amphibole asbestos. Such heavy exposures are now uncommon, and currently the epidemiologic evidence correlating time trends, incidence in both sexes, and commercial asbestos use suggests that a much smaller fraction of peritoneal mesotheliomas in men are related to asbestos, and very few peritoneal mesotheliomas in women. The absence of any significant temporal trend has been observed in the United States (SEER data), Sweden, and The Netherlands [20, 26, 27].

In young (<50 years) subjects with malignant mesothelioma, there is no clear gender or anatomic site preponderance. In fact, <45 years mesothelioma is more common in women, and peritoneal disease predominates in this demographic pointing strongly against an asbestos fiber-induced carcinogenesis [28].

There is emerging scientific evidence that not all mesothelial cells are the same and that the molecular pathways of tumorigenesis in the pleura and peritoneum are different. This likely underlies the differences in the responses of pleural and peritoneal mesothelial cell surfaces to asbestos. Recent studies have shown that many mesotheliomas harbor somatic mutations of *BAP-1* and *NF2* and, to a lesser extent, *SETD2, TP53, DDX3X, ULK2, RYR2, CPAF45, SETDB1*, and *DDX* [29]. Deletions of the 9p21 region containing *p16INK4A*, *p15, p14*, and *MTAP* are common in mesotheliomas. Somatic *BAP1* mutations are more strongly associated with peritoneal mesothelioma with nearly 85% of peritoneal tumors harboring *BAP1* alterations versus only 60% of pleural tumors [30–32]. Gene profiling has demonstrated the differential expression of common genes in the pleural mesothelium (*ATF3, CXCL2, CXCL3, IL-8, IL-6,* and *GOS2*) compared to peritoneal mesothelium [33]. Analysis of genomic losses and gains in malignant mesothelioma demonstrate significant differences between pleural mesothelial cells (where losses are more common) and peritoneal mesothelial cells (where gains are more evident), suggesting that different genetic pathways may be implicated at the different mesothelial cell sites [34, 35].

In a proportion of young subjects with no asbestos exposure and malignant mesothelioma, autosomal dominant inherited germline *BAP-1* mutations have been implicated in disease causation [36]. In the recently described *BAP-1* hereditary cancer predisposition syndrome, other tumors may develop including uveal and cutaneous melanomas, renal cell carcinomas, cholangiocarcinoma, and basal cell carcinoma [37]. The mesothelioma prognosis appears somewhat more favorable in these subjects. Some reports note that in germline *BAP-1* mutated subjects with no asbestos exposure, peritoneal mesothelioma cases predominate [38]. This patient demographic suggests that *BAP-1* mutation can induce malignant mesothelioma *ex* asbestos via naturally-occurring mutations or, for example, by radiation. Some researchers proffer an alternate position that germline *BAP1* mutations may increase an individual's susceptibility to asbestos and the science in this regard is evolving and unresolved [39]. There is also clear evidence that other tumor suppressor genes such as *TP53* can induce peritoneal mesothelioma and sarcoma in subjects with no asbestos exposure [40]. More recently, *ALK-1* translocations have been implicated in the induction of a small number of peritoneal mesotheliomas with no asbestos exposures [41]. Overall, there appears a growing weight of evidence that a substantial proportion of peritoneal mesotheliomas appear unrelated to asbestos, particularly marked in young subjects and women and that there are emerging specific molecular markers at play in a proportion of these cases.

Pericardial and Tunical Vaginalis Testis Mesothelioma

With respect to pericardial mesothelioma and mesothelioma arising from the tunica vaginalis testis, these are very rare diseases and no epidemiologic studies exist. The weight of

scientific evidence indicates that for both pericardial mesothelioma and tunica vaginalis testis mesothelioma, the association, if any, between asbestos and the diseases is weak. Trends in the incidence of pericardial and tunica vaginalis testis mesothelioma do not match those of pleural mesothelioma, which are recognized to clearly correspond to historic trends of commercial asbestos use and to amphibole forms of asbestos [11, 12]. No analytic epidemiology (worker cohort studies or case–controls) exists demonstrating any association between pericardial mesothelioma and asbestos. Indeed, in numerous large occupational worker cohorts with historic heavy asbestos exposures to varied fiber types (including Canadian chrysotile miners, South African amosite/crocidolite miners, Australian crocidolite miners, asbestos cement factory workers, friction product manufacturers, North American insulators, and shipyard workers), no single case of pericardial or tunica vaginalis testis mesothelioma is reported.

The importance of the subject demographic in asbestos fiber-induced carcinogenesis has already been emphasized. Pericardial mesothelioma has a different subject demographic compared with pleural mesothelioma. The male: female ratio of pericardial mesothelioma is often reported as ~2:1 or less compared with pleural mesothelioma 4–5:1. The median age for pericardial mesothelioma is significantly younger (<50 years) than the median age for pleural mesothelioma (70 + years). Pericardial mesotheliomas have also been reported in young children (with too short a latency for asbestos-related disease) and in animals without known asbestos exposure. Interestingly, no study has identified asbestos fiber or asbestos bodies in pericardial tissue following inhalation, and further it has been suggested that lymphatic flow from the lungs into the pericardium requires retrograde flow which essentially precludes asbestos fibers entering the pericardium via stomata following inhalation [11].

Case reports of pericardial and tunica vaginalis testis mesothelioma occasionally do detail a prior asbestos exposure; however, most case reports note either no exposure or no known asbestos exposure. Case reports represent an interesting first enquiry but cannot prove causality as they do not address coincidental occurrence and have no control population.

The Role of Asbestos Fiber Type in Malignant Mesothelioma

There exists substantial evidence that the type of asbestos fiber to which exposure occurs is critical in determining the subsequent risk of pleural and peritoneal mesothelioma. Epidemiologic and mineralogic studies show that commercial amphiboles amosite and crocidolite can cause diffuse malignant pleural and peritoneal mesothelioma. There is no proven association between peritoneal mesothelioma and chrysotile asbestos or pericardial mesothelioma and asbestos irrespective of fiber type.

Wagner and his coauthors [42] are now credited with establishing the link between malignant pleural mesothelioma and crocidolite asbestos in 1960. Since then, several publications have documented mesothelioma in various occupational communities. For workers heavily exposed to commercial forms of amphibole asbestos, up to 18% (in crocidolite cigarette filter assembly workers) have developed pleural mesothelioma [43]. In comparison, following occupational exposures to chrysotile asbestos, the incidence of pleural mesotheliomas has ranged from 0% (cement manufacturers, friction product workers, civilian gas mask filter assembly workers) up to 0.47% (Quebec miners/millers) [44–46].

There exists epidemiologic evidence which shows a small excess risk of pleural mesotheliomas in workers exposed to high-dose chrysotile. This has been largely in the Canadian chrysotile mining industry and a few in predominantly chrysotile textile manufacturing workers. However, because in essentially all studies some level of amphibole asbestos (tremolite asbestos, anthophyllite asbestos) contamination was present, the results on workers exposed to uncontaminated chrysotile are too limited to allow a clear-cut conclusion.

There exist many epidemiologic studies which show no increased risk of pleural mesothelioma in workers exposed to low-dose chrysotile. Perhaps the most extensively studied are auto-mechanics handling friction products containing encapsulated chrysotile. Meta-analyses have recently reviewed the varied epidemiology undertaken by different researchers in different countries by different methods. The researchers observed consistently no increased risk of mesothelioma as a consequence of such exposures in the higher ranked studies [47].

Some authors have attempted to calculate a No-Observed Adverse Effect Level (essentially a level of exposure at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control) for pleural mesothelioma following occupational chrysotile exposure (with non-commercial amphibole asbestos contamination). The most recent evaluation of the "best estimate" for pleural mesothelioma was between 208 and 415 fibers/cc-years [48].

There is a clear and opposing view on fiber toxicity and mesothelioma induction. Some authors have suggested that chrysotile is the main cause for pleural mesothelioma while also recognizing that chrysotile did not cause peritoneal mesothelioma. This inference appears to be based on the premise that as chrysotile can be demonstrated in most mixed fiber exposures in which pleural mesotheliomas

rates are high, and chrysotile is the most frequently utilized form of asbestos, it somehow must be implicated in disease causation [49]. However, this analysis is incorrect because it ignores cumulative dose exposure, the profound fiber potency differentials which exist in persons exposed to mixed (commercial amphibole asbestos—chrysotile asbestos) asbestos and that amphibole forms of asbestos do exert a disproportionately significant effect in mesothelioma induction. Almost all authorities recognize that commercial amphibole asbestos is more potent than chrysotile.

The role of chrysotile in pleural mesothelioma causation is controversial. The presence of anecdotal case studies of mesotheliomas arising in subjects following exposure to chrysotile containing products does not indicate that either the exposures were significant or causal in the development of the said disease. This is because case reports and series lack an appropriate control population, thereby any observations may be simply coincidental. Analytic epidemiology (case–controls or worker cohort studies) is essential for causal attribution to be made in humans following asbestos exposures.

Peritoneal mesotheliomas are associated with heavy exposures to commercial forms of amphibole asbestos. The higher rates of peritoneal mesothelioma are observed in crocidolite-exposed workers, i.e., military gas mask manufacturing factory workers [50, 51], and amosite-exposed insulation workers [52, 53]. Peritoneal mesotheliomas are not reported in friction product manufacturing workers or cement manufacturing cohorts (absent crocidolite) [48].

Chrysotile asbestos is not a proven cause for malignant peritoneal mesothelioma.

No peritoneal mesotheliomas have been reported in several chrysotile mining cohorts (Canada, Italy, South Africa), civilian gas mask assembly workers in the United Kingdom, British cement factory workers, and friction product manufacturers or workers in the United States, Germany, Denmark, United Kingdom, or Spain [54].

It is important to note that the extensive epidemiological studies of chrysotile miners and millers in Quebec, Canada (approximately 11,000 men and 440 women) with the likely heaviest lifetime cumulative exposures to chrysotile (contaminated with amphibole asbestos) yielded the highest number of pleural mesotheliomas for any "chrysotile" cohort yet no malignant peritoneal mesotheliomas [46, 54].

There is conflicting scientific evidence of peritoneal mesothelioma in Chinese female textile workers utilizing chrysotile asbestos. The initial case series appears inconsistent with both the wider scientific literature and subsequent series from the same Chinese region which indicated that factors other than asbestos were important in inducing peritoneal mesothelioma in women [55, 56].

The relative ability of chrysotile and amphibole asbestos fibers to induce pleural and peritoneal mesothelioma has been studied for over 40 years. Meta-analytical epidemiological studies addressing the differential role of fiber type in the induction of mesothelioma have emerged since 2000.

The influences of asbestos fiber type appear much more marked for malignant pleural and peritoneal mesothelioma than for lung cancer. In a meta-analysis of the risk of mesothelioma from exposure to various fiber types [57], 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 noncommercial amphibole asbestos and chrysotile that is amphibole-free. In a subsequent publication [58] the same authors from the United Kingdom Health and Safety Executive modeled 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 [59] conducted a similar meta-analysis which demonstrated a substantial difference in the relative potency of commercial amphibole forms of asbestos and chrysotile toward the induction of mesothelioma, with combined commercial amphibole asbestos estimated as over 800-fold more potent than chrysotile on a fiber : fiber basis.

In an updated meta-analysis of 11 epidemiological studies, the researchers estimated risk for mesothelioma with models which address fiber size and mineral type. The statistical model that pure chrysotile is nonpotent for mesothelioma was not rejected. The best estimates for the relative potency for chrysotile ranged from zero to 1/200th that of amphibole asbestos (dependent on metric) [60, 61]. Amphibole absestos fibers >10 microns contribute most to the development of asbestos-related lung cancer and mesothelioma. More recently, it has been proposed that the best fiber metric predicting mesothelioma risk are those amphibole asbestos fibers >20 microns length and <1.5 microns diameter [62].

Given the recognized limitations of exposure assessment across different occupational cohort studies of asbestos and mesothelioma, the aforementioned authors in the United Kingdom and the United States performed their meta-analyses utilizing different statistical methodologies and found remarkably similar fiber potency estimates. These findings underpin the reliability of the findings. The UK Health and Safety Executive workers evaluated the relative fiber potency by using the fraction of mesothelioma deaths in a cohort as a function of mean cumulative exposure, then

compared exposure–response analyses across different cohorts. The North American researchers calculated individual level exposures for each cohort member and modeled risk of mesothelioma as a function of cumulative (intensity × duration) exposure using a Peto model. Both groups concluded that there was between a 2 and 3 orders of magnitude difference in fiber potency between commercial amphibole forms of asbestos and chrysotile (contaminated with noncommercial amphibole asbestos) in the induction of mesothelioma.

In an extensive meta-analysis of 71 asbestos-exposed cohorts to evaluate the role of asbestos fiber type relevant to industry and malignant mesothelioma [54], the author concluded that the epidemiologic studies show amphibole forms of asbestos, that most predominantly commercial amphibole asbestos forms cause mesothelioma in humans, and that epidemiology does not support the view that chrysotile, uncontaminated by amphiboles, cause mesothelioma. In eight large chrysotile-only cohorts (23,794 workers), no recorded mesotheliomas were found. In a further 14 cohorts exposed to chrysotile without identified amphibole asbestos, seven mesothelioma cases were found. Careful review identified that either the "chrysotile" exposures were likely mixed (with commercial or noncommercial amphibole asbestos), diagnosis was questionable or latency inadequate or unstated.

Fiber burden analyses undertaken in case–controls demonstrate strong support that mesothelioma risk is correlated with the retained commercial amphibole asbestos content with no contribution from chrysotile [8]. The differences in fiber toxicity of amphibole asbestos and chrysotile relates in part to differences in the individual fiber types' bio-durability in 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, commercial amphibole forms of asbestos are far more potent in inducing malignant mesothelioma. It is recognized that both the fiber dimensional characteristics determine the respirability, deposition, and retention of inhaled particulates and that both chrysotile and amphibole asbestos can be widely distributed within the lung and pleura. The differential role of fiber length is discussed below.

Noncommercial forms of amphibole asbestos comprise anthophyllite asbestos, tremolite asbestos, and actinolite asbestos. The potency of these forms of amphibole asbestos is less well defined than commercial amphibole asbestos. Anthophyllite asbestos miners have been reported to have a lower rate of pleural mesotheliomas (three cases) and one peritoneal mesothelioma, all with asbestosis [63]. In a further update of the heavily exposed anthophyllite asbestos miners, a total of eight mesotheliomas have been reported between 1967 and 2012 [64]. Anthophyllite asbestos is recognized to have a lower aspect ratio with large numbers of wider fibers compared with commercial amphibole forms of asbestos which may explain diminished respirability and low fiber potency for mesothelioma [63, 65].

Tremolite is a noncommercial form of amphibole which is most commonly present in non-asbestiform habit and rarely in an asbestiform habit. The mineral may be present in some chrysotile, talc, and vermiculite deposits. The inhalation of asbestiform tremolite is suspected to have caused an increased incidence of pleural mesothelioma in certain mining settings [66]. The capacity of a trace component of the mineral to induce disease following end product exposure is highly questionable.

Actinolite asbestos is mineralogically similar to tremolite asbestos with some elemental chemical differences. There is presently insufficient scientific evidence to specifically evaluate the potency of actinolite asbestos alone.

Asbestos Fiber Size and Malignant Mesothelioma

The importance of fiber length in relation to asbestos-induced neoplasia in vivo was demonstrated in the United States [67, 68] and in West Germany [69]. These workers independently showed that following 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 in inhalational animal models [70, 71], emphasizing the rapid clearance of short fiber chrysotile and lack of lung tissue injury. The results were later corroborated by Bernstein and coworkers [72, 73].

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. Some studies have sought to evaluate cancer outcomes associated with elongate mineral particles of non-asbestiform cleavage fragments which are, in general, shorter and thicker than counterpart asbestos fibers, with lower aspect ratios.

Scientific evidence shows that elongate mineral particles of non-asbestiform habit/shorter cleavage fragments have no clear carcinogenicity in humans, and this emerges from a number of publications:

1. Minnesota mine workers [74]. The workers were exposed to cummingtonite-grunerite, and the vast majority of elongate mineral particles were reported less than 10 μm

in length. The study found no increase in overall mortality or mortality from respiratory cancer. Subsequent studies do not correlate geographic locations where elongate mineral particles of non-asbestiform cleavage fragment are recorded with disease [75].
2. South Dakota gold mine workers exposed to cummingtonite-grunerite. On long-term follow-up, they had no increased risk of respiratory cancer. In this study 94% of airborne elongate mineral particles were less than 5 μm in length representing non-asbestiform cleavage fragments [76].
3. Cosmetic talc mine and mill workers in Europe and North America [77–84]. There is no increased risk of mesothelioma observed among the cosmetic talc miners and millers in Italy, Austria, France, Norway, or Vermont. This is consistent with the position that any exposures to non-asbestiform amphiboles or serpentine minerals did not induce mesothelioma after high-dose exposures in these workers.

The Agency for Toxic Substances and Disease Registry convened an expert panel which considered the influence of asbestos fiber length on malignant disease and concluded that asbestos fibers shorter than 5 μm were unlikely to cause cancer in humans [85].

In contrast, a number of case–control studies have shown that mesothelioma risk is considerably higher for individuals with larger amounts of long asbestos fibers retained in their lungs. In a case–control study of 78 Canadian mesotheliomas and age-matched referents, McDonald and co-workers [86] 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 [87] found that the best-fit relative risk for mesothelioma was greatest for amphibole asbestos fibers longer than 10 μm.

The identification of short chrysotile fibers in human tissues and pleura has been reported [88] and has been postulated to be associated with mesothelioma induction [89, 90], but this is of questionable relevance. There exists no convincing scientific evidence base that short chrysotile fibers are pathogenic.

Long commercial amphibole asbestos fibers have been identified in the peritoneum and mesentery [91]. In 1996 Boutin and coworkers [92] showed that the 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. The delivery of long thin bio-durable amphibole asbestos fibers to the parietal pleura represents a key first step in the pathogenesis of malignant mesothelioma. The subsequent limited clearance of such long dimension biopersistent fibers via mesothelial stomata results in secondary inflammatory changes, fibrous scarring, and stoma blockage. This role of long high aspect ratio biopersistent amphibole asbestos fibers may explain the emerging epidemiological evidence that initial early dose exposures to commercial amphibole asbestos are highly significant and that subsequent exposures or cessation of asbestos exposure plays little role on the subsequent mesothelioma risk [93].

In vitro experimental data provide compelling supportive evidence that long fibers are far more toxic than short fibers with low aspect ratio. Cleavage fragments have also been shown to have limited bio-durability and consequent low, if any, toxicity [16–18]. Molecular studies support the epidemiology, mineralogic and animal experimental findings. Short fibers have diminished capacity in inducing chromosomal aberrations, morphologic abnormalities, cell proliferation, oncogene activation, and reactive oxygen species compared with long fibers.

Assessment of 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 suspected occupationally related 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 (see Appendix for an example of questionnaire). The duration of asbestos exposure and precise job duties are important. The reliability of the history of asbestos exposure varies considerably across differently exposed populations. Brief, light, and intermittent exposures to asbestos are more subject to significant recall bias particularly given the inherent latency associated with all asbestos-related diseases. Exposure details decades prior to the clinical

manifestation of disease are often difficult to determine. Such temporally remote short-term exposures to commercial forms of amphibole asbestos (which may be biologically important to that individual case) may not be recognized by clinical enquiry of the exposed subject, family member, or coworker. In this setting, mineralogic fiber burden analysis of lung tissue may be useful to determine the retained amphibole asbestos fiber count and this is discussed below.

When subjects with malignant mesothelioma have no determined significant or substantiated occupational asbestos exposure history, it is then important to consider the occupational activities of other household and parental family members. It is also important to consider a life-long enquiry of potentially relevant neighborhood/environmental asbestos exposures and proximity to known heavy industry.

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 commercial amphibole asbestos exposures.

The conventional chest X-ray is the standard method for the recognition of asbestos-related lung and pleural abnormalities [94]. The most common manifestation is calcified and non-calcified parietal pleural plaques. These imaging abnormalities correspond to benign areas of paucicellular collagenous fibrosis which typically arise on the parietal pleura. The vast majority of individuals with pleural plaques alone have no symptoms. Pleural plaques may occur after low-level exposures to amphibole asbestos. Pleural plaques tend to occur 20–30 years after exposure. They are classically distributed in the posterolateral chest wall between the seventh and tenth ribs, lateral chest wall between the sixth and ninth ribs, and over the diaphragmatic domes and mediastinal pleura. The number and size of plaques is highly variable, and there is some correlation between extent of plaques and cumulative dose of amphibole asbestos. 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 amphibole asbestos exposure and do not indicate an increased risk of malignancy. When observed with pleural 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 effusions. 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 rare nowadays. Subclinical (occult) asbestosis is now more common than clinical asbestosis and may be determined by pathological examination in a resected lung cancer specimen, this is discussed below. There exist no specific clinical or radiologic features which allow a clinician to distinguish asbestosis from other forms of diffuse interstitial lung fibrosis. The exposure history is essential and as discussed difficult to characterize accurately. There is typically a history of heavy asbestos exposure, occupational based and protracted over many years. Asbestosis is a dose–response disease with disease extent correlating with cumulative asbestos exposures, mineralogically the correlation is with retained amphibole asbestos fibers not chrysotile.

It is important to emphasize that while the presence of asbestos-related disease may support an asbestos causation in pleural mesothelioma cases, the absence of asbestosis or other asbestos-related changes cannot overrule the occupational history of asbestos exposure [95].

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 risk assessment or retrospective dose assessment in personal injury claims.

Determining an individual's cumulative asbestos exposure (in fibers/mL-years) requires reconstructing a case-specific occupational, domestic, and environmental asbestos exposure history. This requires a comprehensive knowledge of likely industrial and professional workplace duties. In some asbestos-exposed industries, there have been detailed workplace airborne asbestos measurements based on static

(area) monitoring, personal monitoring, short-term (30–60 min) assessment, long-term (full shift, 8 h) assessment, or peak levels. The established most useful arbiter of cumulative exposure is made by obtaining mean weighted average exposures (usually collected over an 8-h period). The average airborne asbestos fiber levels for a person working 8 h per day, 5 days per week, 50 weeks per year (representing 2000 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 [96]. A standardized approach was advocated counting only structures with a length : width aspect ratio of 3 or more. This aspect ratio was an arbitrary figure accepted by the Asbestosis Research Council. Fibers greater than 5 μm in length were determined as reproducibly countable, and respirable fibers were those less than 3 μm in fiber diameter. The limit of optical microscopy is a fiber width of 0.25 μm. 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 [97].

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 asbestos 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 [98].

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 specific 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 was that it was introduced to regulate workplace dust levels but not one to specifically detect the biologically active respirable fraction of asbestos.

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. These assessments seek to determine what exposures an 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

In general, from a pathologist's perspective, for a causal attribution of malignant pleural mesothelioma to asbestos, there is a requirement to consider the following [7]:

1. Confirmation of diagnosis—it is recognized that the diagnosis of malignant mesothelioma is problematic and the one which necessitates considerable diagnostic expertise. Malignant mesothelioma is a morphologically diverse cancer with mimicry of a number of non-mesothelial tumors as well as benign processes in certain settings. The role of immunohistochemistry is now of paramount importance in optimizing diagnostic accuracy. Recommendations of the International Mesothelioma Panel are that a standard panel incorporating a broad-spectrum cytokeratin plus two mesothelial and two epithelial markers be used to effectively separate most mesotheliomas from other mimics. The choice of markers is laboratory dependent although it is recognized that some markers have better application than others in specific anatomic and gender-related settings [99].
2. Consideration of a substantiated and significant exposure history is important in evaluating disease causation. There may be information from subjects, family, coworkers, witness statements, and legal reports.
3. Consideration of an appropriate latency (on average 30–40 years, after occupational exposures). There is evidence that the latent period is inversely correlated with cumulative commercial amphibole asbestos dose in asbestos-related disease, i.e., latency is protracted following lower asbestos exposures observed in settings such as domestic/environmental exposures, whereas latent periods are shorter in subjects following heavy industrial exposures such as insulators, shipyard workers, and

asbestos miners. A short latent period less than 20 years is now regarded as exceptional.

4. Consideration of the presence of concurrent asbestos-related pathology such as pleural plaques or the identification of asbestos bodies in lung tissue. The finding of either plaques or asbestos bodies has significance beyond diagnosis alone as they allow for causal attribution to amphibole asbestos in pleural mesothelioma cases, on a balance of probabilities. However, in some cases of asbestos-related mesothelioma, pleural plaques and asbestos bodies are not seen. In this circumstance, mineral analysis may be used to support prior exposure to asbestos or exposure to other mineral fibers (identified in specific geographic locations) such as erionite, fluoroedenite, and Libby amphibole.

In all cases of malignant mesothelioma, there should be careful consideration of all potential causative agents which may be at play in the individual case. For example, while detailing an occupational exposure history may be commonplace, there should also be consideration of any prior ionizing radiation and other relevant factors, e.g., concomitant cancers which may suggest and prompt genetic testing, or chronic inflammatory diatheses.

In some individuals with malignant mesothelioma, there will be no clear asbestos exposure history, no biomarkers of exposure, and no mineral fibers determined on fiber burden analysis. It is reasonable to conclude that these mesotheliomas are not-asbestos-related. This proportion of mesotheliomas not asbestos-related is higher in young subjects, in women and in extra-pleural locations.

For those subjects with mesothelioma with no known external causative agents such as prior radiation, specific mineral fibers (e.g, erionite), or known specific genetic mutations, the case is concluded as a naturally occurring, spontaneous or sporadic mesothelioma. Nowadays, most mesotheliomas in women and in extra-pleural sites are naturally-occurring cancers.

In autopsy cases, the role of the pathologist is more extensive, namely:

1. To describe and diagnose all occupational/industrial disease manifestations.
2. To determine the etiology of the disease(s) present.
3. To determine the extent and severity of any other disease present (that would have potentially impacted life expectancy or quality) had the individual not died of other disease.

Accurate diagnosis may be problematic so multiple tissue blocks of tumor are required and good practice necessitates the use of immunohistochemical panels. It is not sufficient to simply rely on the macroscopic appearance of the tumor encasing the thorax or abdomen. It is well recognized that pseudomesotheliomatous cancers exist in which there is diffuse pleurotropic or other serosal membrane involvement [100]. Only pathologic examination can attain an accurate tumor diagnosis.

The College of American Pathologists and Pulmonary Pathology Society (CAP-PPS) asbestosis guidelines committee report [101] represents the state-of-the-art diagnostic criteria for asbestosis. In heavily exposed subject with mesothelioma, asbestosis may be present but not necessarily so, and the absence of asbestosis cannot rule out an association with asbestos in mesothelioma subjects.

In asbestos-exposed persons with malignant mesothelioma, the presence of benign pleural disease (pleural plaque formation/diffuse pleural fibrosis) is significant. Pleural plaques, particularly when multiple and bilateral, are typically associated with amphibole asbestos exposure, most often commercial amphiboles. It has been concluded that it is questionable if chrysotile absent amphibole asbestos exposures can induce the lesion [102].

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.

When an individual with pleural mesothelioma has pleural plaques or diffuse pleural thickening, it renders far more likely that there is a significant causative exposure to amphibole asbestos, typically commercial amphibole asbestos, even if there is no clear history that would suggest such an exposure.

When an individual with pleural mesothelioma does not have concomitant benign pleural disease, one cannot at this point alone rule out a prior significant causative asbestos exposure. However, it is emphasized that pleural plaques are associated with malignant mesothelioma in a high proportion of cases.

Routine light microscopy allows for a basic assessment of the retained dust. By light microscopy, multiple lung sections of background non-tumor-containing lung should be examined to identify for the presence of asbestos bodies. These are histological hallmarks of prior amphibole 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. 20.7). The vast majority of asbestos bodies form on long >20 μm commercial amphibole asbestos fibers. An analysis of asbestos bodies found in lung noted that 96% coated fibers are commercial amphiboles (amosite and crocidolite), 2% noncommercial amphibole asbestos,

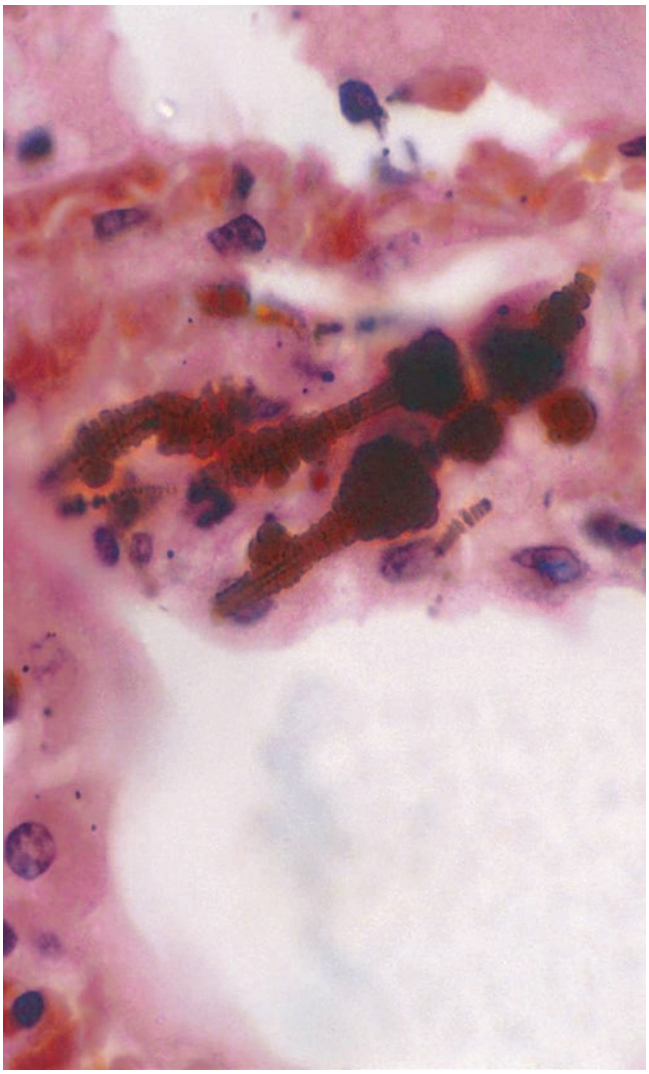

Fig. 20.7 Light microscopic image of asbestos bodies (H&E)

and 2% chrysotile serpentine asbestos [103]. Asbestos bodies represent only a small proportion of the total retained asbestos fiber content within the lung, and this is dependent on the asbestos fiber type present (amosite > crocidolite > chrysotile) and to host factors. It is now very rare to identify asbestos bodies in persons with no known occupational/para-occupation/neighborhood amphibole asbestos exposure, i.e., simply from ambient exposure. Consequently, if a subject with malignant mesothelioma has asbestos bodies identified by routine light microscopy, then on a balance of probabilitiesm amphibole asbestos, typically commercial 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.

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 20.2.

Table 20.2 Types of ferruginous bodies

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)

In a proportion of persons with malignant mesothelioma, asbestos bodies are not seen and suitable material (lung or lymph nodes) is not available to evaluate for asbestos bodies. In these cases, it is important to consider the role of mineral fiber analysis.

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 [104].

The main applications of mineral/elemental analysis in pulmonary disease are:

1. To verify the 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 fiber burden 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 mineral analysis cannot determine the timing of the exposure or the source of any mineral. A negative fiber burden cannot overrule a clear exposure history, especially where exposure is to chrysotile asbestos. Persons with heavy exposures to commercial chrysotile may have detectable tremolite amphiboles in their lungs following cessation of exposure but these historic heavy exposures are now rare and

typically observed in chrysotile miners/millers, textile manufacturers, and insulators.

Phase contrast light microscopy—This is a simple method for detecting elongate mineral particles. It is the method used by some hygienists to detect fibers in air. Airborne measurements and lung fiber studies performed by light microscopy and phase contrast light microscopy under current regulatory standards of fiber measurement are insensitive at identifying asbestos fibers and separating them from non-asbestiform cleavage fragments or indeed asbestos from non-asbestos fibers. Light microscopic analysis has limited resolution and cannot detect fibers less than 0.25 μm diameter (irrespective of fiber length). In a comparative transmission electron microscopic evaluation, it was reported that phase contrast light microscopy was able to visualize only 5% crocidolite, 26.5% amosite, and 0.14% chrysotile present in lung tissue [105].

It is evident that electron microscopic analytic techniques are more sensitive and may be performed in either scanning or transmission mode. Transmission electron microscopy has the capabilities to record selected area electron diffraction spectra and perform energy dispersive X-ray analysis which are necessary to distinguish the crystalline mineral habit of structures observed and their elemental composition. Analytic 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 [106]. This will vary with fiber type, geologic source of fiber and industry as well as individual test detection limits.

Mineral fibers may be detected in almost all populations. Therefore, laboratories have to define control (non-occupationally exposed) populations and establish reference values for certain diseases, for example, the asbestosis range value [7].

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 fiber count results—as a practical guide, tissue from the apical areas of upper and lower lobes and lung bases are suitable, around 8 cm^3 in volume. Care should be taken not to include tissue containing tumor and preferably not severely infected or severely fibrotic [7].

A high fiber burden indicates exposure but is not necessarily proof of disease so fiber counts must be contextualized against controls and in light of known pathology. There should be consideration of fiber type and size together with the context of exposure, i.e., consideration should be made of whether there exists an appropriate latent period. A negative result is not necessarily proof of the absence of exposure, 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, interstitial fibrosis (asbestosis), and peritoneal mesothelioma requires higher levels of fiber counts (within the asbestosis range) than is necessary to causally attribute a pleural mesothelioma to prior amphibole asbestos exposure.

Conclusion

Malignant mesothelioma has an increasingly complex relationship with its most etiologically important cause. Presently most pleural mesotheliomas in men remain asbestos-related cancers, whereas a significant proportion of pleural mesotheliomas in women are not [107]. Most malignant mesotheliomas arising extrapleurally and in young subjects (<50 years) are also likely unrelated to asbestos. It is important to be mindful of this when handling suspected cases. In a small but significant number of subjects with mesotheliomas (~12%) there exist a variety of inherited germline mutations which when present significantly increase the risk of cancer. Genetic testing is especially merited in young subjects, in extra-pleural disease cases and in those persons with mesothelioma and second cancers or a family history of cancers. For most subjects in which mesothelioma is not clearly asbestos-related, the tumor is most likely naturally-occurring or spontaneous, an important risk factor for these tumors is subject age secondary to endogenous DNA replication errors [108].

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Epidemiology of Mesothelioma

21

Paolo Boffetta and Francesca Donato

Introduction

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 [1].

Since the late 1950s, cases of pleural mesothelioma have been reported in miners from South Africa and American workers exposed to asbestos [2–4]. As early as 1964, the causal link between exposure to asbestos and development of mesothelioma in humans was recognized by international panels [5]. 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 [6]).

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Asbestos

An increased risk of mesothelioma has been demonstrated 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 oil refining [7], textile production [8], pulp and paper production [9], cigarette filter manufacture [10], and railroad industry [11]. In many high-income countries, the classic circumstances of high exposure to asbestos are of reduced importance because of the ban of most if not all uses of asbestos and precautions are taken when exposure is known; the greatest exposure is likely to occur among maintenance and construction workers [12]. In low- and medium-income countries, on the other hand, high levels of exposure might still occur [13, 14].

Industry-Based Studies

Table 21.1 reports the results of selected cohort studies of workers exposed to asbestos. Given the large body of evidence available, only studies of occupational groups primarily exposed to asbestos were included in the table. In the case of studies with multiple reports (e.g., subsequent follow-ups, inclusion in pooled analyses), only the most recent report was used. In order to reduce the random variability of the results, only studies with at least 50 total deaths or 15 lung cancer deaths/cases were 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 standardized mortality ratios (SMR) or the standardized incidence ratio (SIR) of pleural neoplasms or similar measures can suffer from a number of biases, as discussed in Table 21.2. Although some of these biases are common to studies of other

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Table 21.1 Results of selected cohort studies of mesothelioma in workers exposed to asbestos[a]

Reference	Industry	Asbestos type	Country	Period of employment [b]	Diagnostic evidence	Sex	Number of workers	Total deaths	Lung cancer deaths	Lung cancer SMR	PlM deaths	PeM deaths
McDonald and McDonald [15]	Gas mask manufacture	Cr	Canada	1939–1942	DC	MF	199	56	7	2.92	3	6
Jones et al. [16]	Gas mask manufacture	P Cr	UK	1938–1945	MR	F	578	166	12	1.94	13	4
Rossiter and Coles [17]	Shipyard	NA	UK	1947	BE	M	6292	1043	84	0.7	31	
Acheson et al. [18]	Gas mask manufacture. Blackburn	Ch	UK	1939	DC	F	570	177	6	1.25	1	0
		Cr	UK	1939	DC	F	757	219	13	2.1	3	2
McDonald et al. [19]	Textile product manufacture	P Ch	USA	1938–1958	DC	M	4137	1392			10	4
Thomas et al. [20]	Cement workers	P Ch	UK	1936–1977	DC	M	1592	351	30	0.93	2	0
Finkelstein [21]	Cement workers	Mix	Canada	1955–1959	DC	M	535	108	26	4.9	11	8
McDonald et al. [22]	Friction product manufacture	Ch	USA	1939–1958	DC	M	3641	1267	73	1.49	0	0
Acheson et al. [23]	Insulation manufacture	Am	UK	1945–1978	DC	M	4820	333	57	1.96	4	1
Ohlson et al. [11]	Railroad repair work	Mix	Sweden	1939–1980	DC	M	3442	925	37	1.16	5	0
Peto et al. [24]	Textile product manufacture	P Ch	UK	1933–1974	DC	M	3211	1113	132	1.31	10	1
Ohlson and Hogstedt [25]	Cement workers	P Ch	Sweden	1943–1976	DC	M	1216	220	11	1.23	0	0
Kolonel et al. [26]	Shipyard	Mix	USA	1950–1969	CR	M	5191	668	61	1.09	8	0
Alies-Patin and Valleron [27]	Cement workers	Mix	France	1940–1977	DC	M	1506	206	12	2.17	3	1
Newhouse et al. [28]	Mixed	Mix	UK	1933–1964	DC	M	4695	818	158	2.5	31	
						F	932	274	37	7.4	14	
Szeszenia-Dabrowska et al. [29]	Mixed	P Ch	Poland	1945–1985	DC	M	2403	527	35	1.41	1	0
Woitowitz et al. [30]	Mixed	Mix	Germany	1930–1974	DC	PM	3070	185	22	1.44	6	0
Seidman et al. [31]	Mixed	Am	USA	1941–1945	BE	M	820	593	102	4.97	8	9
Gardner et al. [32]	Cement workers	Ch	UK	1941–1983	DC	MF	2167	486	41	0.97	1	0
Hodgson and Jones [33]	Mixed	Mix	UK	1969–1981	DC	M	31,565	1128	186	1.26	35	
Hughes et al. [34]	Cement workers	P Ch	USA	1937–1970	BE	M	6931	2143			9	1
Amandus and Wheeler [35]	Vermiculite miners	Tre, Act	USA	1970–1981	DC	M	569	161	20	2.23	2	0
Enterline et al. [36]	Mixed	Mix	USA	1941–1967	DC	M	1074	617	77	2.71	6	2
Raffn et al. [37]	Cement workers	Mix	Denmark	1928–1984	CR	M	7996	1305	162	1.8	10	
Albin et al. [38]	Cement workers	P Ch	Sweden	1907–1977	CR	M	1465	592	27		12	
Neuberger and Kundi [39]	Cement workers	P Ch	Austria	1950–1981	DC	NA	2816	540	50	1.7	7	3
Hilt et al. [40]	Electrochemical	NA	Norway	NA	CR	NA	287	186	18	3.16	6	
Selikoff and Seidman [41]	Insulation workers	Mix	USA	1967	BE	M	17,800	4951	1008	3.75	173	285
Sanden et al. [42]	Shipyard	P Ch	Sweden	1977–1979	DC	M	3893		22	0.85	11	0

Sluis-Cremer et al. [43]	Miners	Am, Cr	S Africa	1945–1981	BE	M	7317	1225	63	1.72	22	6
Menegozzo et al. [44]	Railroad constr. work	Mix	Italy	1978–1989	DC	M	1543	194	28	1.45	3	2
Giaroli et al. [45]	Cement workers	P Ch	Italy	1952–1987	DC	NA	3341	274	33	1.24	5	
Berry [46]	Friction product manufacture	Ch, Cr	UK	1941–1986	DC	M	9104	2055	88	1.07	9	
						F	4346	522	4	0.89	1	
Zhu and Wang [47]	Mixed	Mix	China	1972–1981	DC	M	NA	260	34		1	
	Miners	Ch	China	1972–1981	DC	M	NA	240	24		3	
Liddell et al. [48]	Miners	Ch	Canada	1902–1971	DC	M	10,918	8009	646	1.37	38	
Oksa et al. [49]	Sprayers, asbestosis patients	Mix	Finland	1955–1976	CR	PM	247		43	11	8	
Szeszenia-Dabrowska et al. [50]	Cement workers	Mix	Poland	1945–1980	CR	M	3405	473	41	0.97	5	
Germani et al. [51]	Asbestosis patients	Mix	Italy	1979	DC	F	631	277	16	4.83	14	12
Tulchinsky et al. [52]	Cement workers	Mix	Israel	1953–1992	BE	M	3057		28	1.35	20	1
Karjalainen et al. [53]	Asbestosis patients	Mix	Finland	1964–1995	CR	M	1376		133	6.9	10	0
Battista et al. [54]	Railway carriage construction and repair	Cr	Italy	1945–1969		NA	734	199	26	1.24	5	
Puntoni et al. [55]	Shipyard	NA	Italy	1960–1981	DC	M	3984	2376	298	1.77	60	
Szeszenia-Dabrowska et al. [56]	Asbestosis patients	Mix	Poland	1970–1997	DC	M	907	300	39	1.68	3	0
Ulvestad et al. [57]	Cement workers	P Ch	Norway	1942–1976	CR	M	541		33	3.1	18	0
Smailyte et al. [58]	Cement workers	Ch	Lithuania	1956–1985	CR	MF	2787	473	30	0.9	1	0
Sullivan [59]	Miners	Tr	USA	1935–1981	DC	M	1672	767	89	1.7	14	1
Hein et al. [60]	Textile product manufacture	Ch	USA	1940–1965	DC	M	1807	1252	137	1.84	3	0
						F	1265	709	61	2.22	0	0
Harding et al. [61]	Mixed	Mix	UK	1983–1987[c]	DC	PM	98,117	15,496	1882	1.87	137	85
Sichletidis et al. [62]	Asbestos cement plant	P Ch	Greece	1968–2005	DC	M	317	52	16	1.71	0	0
Loomis et al. [63]	Textile product manufacture	P Ch	USA	1950–1973	DC	PM	5770	2583	277	1.96	4	0
Tomioka et al. [64]	Ship insulators	Ch, Am	Japan	1947–1979	DC	M	90	63	7	2.64	0	0
	Ship boiler repairers						159	95	8	1.61	1	1
Chen et al. [65]	Asbestosis patients	Mix	Hong Kong	1981–2008	DC	M	124	86	14	7.91	17	0
Lin et al. [66]	Mixed	Ch	China	1972	DC	M	577	259	53	4.08	1	1
Wang et al. [67]	Textile workers	Ch	China	1958–1972	DC	M	586	259	53	4.08	1	1
Lin et al. [68]	Mixed	Mix	Taiwan	1950–1989	CR	M	121,883		758	0.62	17	
						F	38,757		123	0.85	1	
Wu et al. [69]	Shipbreaking workers	Mix	Taiwan	1975–1989	CR	PM	4427	940	61	2.71	2	0
Levin et al. [70]	Manufacture of insulation materials	Am	USA	1954–1972	DC	PM	1130	569	89	2.44	16	7
Pira et al. [71]	Textile product manufacture	Mix	Italy	1946–1984	DC	M	894	618	101	2.51	24	12
						F	1083	401	42	5.29	36	36

(continued)

Table 21.1 (continued)

Reference	Industry	Asbestos type	Country	Period of employment [b]	Diagnostic evidence	Sex	Number of workers	Total deaths	Lung cancer deaths	Lung cancer SMR	PlM deaths	PeM deaths
Ferrante et al. [72]	Mixed	Mix	Italy	1907–2010	DC	M	46,060	19,394	2415	1.26	611	136
						F	5741	2651	78	1.43	134	35
Pira et al. [73]	Miners	Ch	Italy	1930–1990	DC	M	1056	722	53	1.16	7	1
Reid et al. [74]	Crocidolite miners	Cr	Australia	1943–1966	DC	M	3465	1876	213	1.58	152	23
			Italy				1031	563	70	1.8	62	17
Nynäs et al. [75]	Anthophyllite miners	Antho	Finland	1953–1967	CR	PM	734		78	2.46	8	
	Asbestosis patients	Mix		1977–1985			128		41	8.19	5	
	Asbestos sprayers	Mix		1987			133		22	11.3	11	
	Surveillance program	Mix		1990–1992			24,214		994	1.23	84	
Rusiecki et al. [76]	Shipyard workers	Mix	USA	1950–1964	DC	PM	4069	2669	253	1.07	6	

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

[a]When multiple reports have been published for the same cohort, only the most recent one is reported in the table

[b]Period of diagnosis for cohort of asbestosis patients

[c]Period of enrolment in the survey

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 (or SIR), allowing calculating the proportion of mesothelioma deaths over total deaths and the ratio of mesothelioma to excess lung cancer deaths/cases (the latter can be derived from the table as $[N - N/R]$, where N is the number of lung cancer deaths/cases and R is the SMR/SIR for lung cancer). In some of the studies listed in Table 21.1, the study population was defined according to the presence of asbestosis rather than employment in a given industry; by definition these individuals primarily developed the disease as a consequence of occupational exposure to asbestos.

Table 21.2 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)

One or more deaths from pleural mesothelioma have been reported in all but five of the 76 populations listed in Table 21.1. The proportion of pleural mesothelioma over total deaths was 1% or more in 37 out of 65 populations in which this ratio could be measured (57%). In eight cohorts ([16, 21, 41, 51, 65, 71] [female cohort]; [74] [Australian cohort]; [74] [Italian cohort]), more than 7.5% 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 0.59, p-value <0.0001, based on 60 studies Fig. 21.1).

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 21.3). 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 ($p = 0.7$). However, the difference between studies of pure or predominant chrysotile vs. amphiboles/mixed/unknown exposure was significant ($p = 0.01$). It is a matter of debate 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 [77–79].

Studies of lung fiber burden have shown that crocidolite and amosite persist for a longer period in the lung than chrysotile [80]. This finding might contribute to explain the lower risk of mesothelioma following inhalation of chrysotile as compared to amphiboles. Given the contamination of most

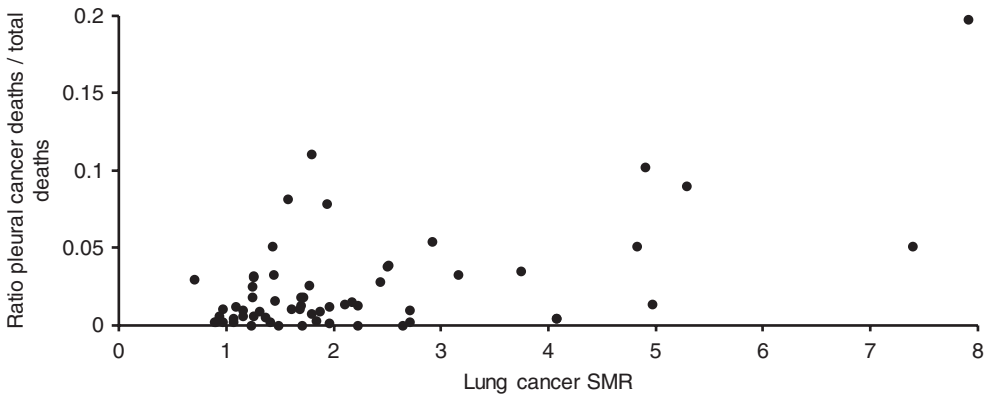

Fig. 21.1 Scatterplot of ratio of pleural cancer deaths over total deaths and lung cancer SMR ($N = 60$, from Table 21.1)

Table 21.3 Proportion of pleural mesotheliomas over total death (%) by type of asbestos fibers

	Pleural mesothelioma over total			Total mesothelioma over total		
Type of asbestos	*N* studies[a]	Mean	Standard deviation	*N* studies[a]	Mean	Standard deviation
Pure chrysotile	11	0.4	0.1	9	0.4	0.1
Predominantly chrysotile	11	0.7	0.2	10	0.5	0.1
Amphiboles[b]	16	3.0	0.8	13	5.2	1.5
Mixed, unknown	27	3.5	0.8	25	4.1	1.2

[a]Studies listed in Table 21.1
[b]Pure/predominant amphiboles or mixed chrysotile and amphiboles

commercially available chrysotile by amphiboles, and notably that of Canadian chrysotile by tremolite fibers [79], 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 [24, 81], 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 beginning of exposure. This has also been shown empirically [61, 82]. 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 beginning of the first exposure, and the contribution of recent periods of exposure is negligible 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 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 appear to modify the subsequent risk of mesothelioma, at least until 30–40 years after cessation [82]. Results of selected studies are summarized in Table 21.4. There are, however, relatively few 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 investigation 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 21.5 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 60–80%. In two studies, a detailed assessment of employment circumstances has led to a quantitative estimate of the risk following asbestos exposure [89, 92]. 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

Table 21.4 Risk of mesothelioma by time since cessation of asbestos exposure in selected studies

Reference	Study population[a]	Outcome	Years since cessation	*N* deaths	Measure of association		95% CI
Magnani et al. [83]	3434; Italy; no minimal duration; 1950–1986; cement; 1965–2003	Pleura	<3 3–15 15–30 >30	13 55 55 16	RR[b]	0.67 1.00 0.90 0.65	0.32, 1.40 – 0.53, 1.43 0.26, 1.63
Harding et al. [61]; Harding and Darnton [84]	98,912; UK; no minimal duration; 1971–2005, mixed; 1971–2005	Pleura and peritoneum	<10 10–19 20–29 30+	334 225 89 1	RR[c]	1.00 0.90 0.99 0.99	– 0.76, 1.08 0.78, 1.26 0.14, 7.02
Pira et al. [71]	1977; Italy; 1 month; 1946–1984; textile; 1946–2013	Pleura	<15 15–29 30+	7 27 26	RR[d]	1.00 3.56 3.10	– 1.53–8.31 1.26–7.67
		Peritoneum	<15 15–29 30+	5 24 19		1.00 3.58 2.08	– 1.34–9.54 0.73–5.89
Pira et al. [73]	1056; Italy; 1 year; 1930–1990; miners; 1946–2014	Pleura	<1 1–9 10–29 30+	1 1 2 3	SMR	16.85 6.75 3.32 6.59	0.43–93.9 0.17–37.61 0.40–12.0 1.36–19.3

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
[d]Relative risk adjusted for sex and age; reference category: <15 years since cessation

Table 21.5 Proportion of cases of mesothelioma with occupational exposure to asbestos in community-based studies[a]

Reference	Country, years of diagnosis	Design	Exposure assessment	*N* cases	% exposed cases	Comments
Cicioni et al. [85]	California, USA, 1972–1988	PCC	EE	101	36	Low sensitivity of exposure assessment
Chellini et al. [86]	Italy, 1970–1988	CS	JEM	100	72	
Muscat and Wynder [87]	New York, USA, 1981–1990	HCC	JEM	124	79	
Howel et al. [88]	England, 1979–1991	PCC	JEM	185	81	
Iwatsubo et al. [89]	France, 1987–1993	HCC	EE	405	71	
Rees et al. [90]	South Africa, 1988–1990	HCC	EE	123	96[b]	Area of crocidolite mining
Agudo et al. [91]	Spain, 1993–1996	PCC	EE	132	61	
Rodelsperger et al. [92]	Germany, 1988–1991	PCC	EE	125	91	
Pan et al. [93]	California, USA, 1988–1997	PCC	EE	2354 M 554 W	66 45	
Rake et al. [94]	Great Britain, 2001–2006	PCC	JEM	512M 110 W	93 34	Employment in high-risk jobs
Lacourt et al. [95]	France, 1998–2002	PCC	EE	334 M 34 W	92 45	
Offermans et al. [96]	Netherlands, 1986–2003	PCC	JEM	132	50	Use of a second JEM produced similar results

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]Only studies with at least 100 cases of mesothelioma and assessment of occupational exposure to asbestos based on the whole occupational history
[b]Including environmental exposure

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 [97].

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 [61, 84]: 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) [84]. 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) [94]. 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 non-metallic mineral product makers and manufacturers of asbestos products [98]. 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 lesion 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 [99], an increased risk of mesothelioma has been shown in several series of carriers. In an early study of shipyard workers from UK followed up between 1961 and 1970, the cumulative incidence of mesothelioma was 3/408 carriers of plaques and 0/404 non-carriers ($p = 0.08$) [100]. In an autopsy-based study from Italy, Bianchi et al. [101] 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 1596 Swedish pleural plaque carriers and the national population, resulting in a standardized incidence ratio of 11.3 (95% CI 5.13–21.3) [102].

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 [103].

Risk of Peritoneal Mesothelioma

Results on peritoneal mesothelioma were reported for 52 of the occupationally exposed populations listed in Table 21.1. In 22 of them, no cases were reported; peritoneal mesotheliomas represented more than 1% of total deaths in 14 populations. A strong correlation is present between percentage of deaths from pleural and peritoneal mesothelioma (correlation coefficient 0.48, $p = 0.0006$). Studies of workers exposed only or predominantly to chrysotile resulted in lower mean percentage of total deaths from peritoneal mesothelioma than other studies (means 0.10% ± 0.04 vs. 1.9% ± 0.5, $p = 0.01$). In all studies with adequate number of cases, a strong association has been found between occupational exposure to asbestos and risk of peritoneal mesothelioma [16, 21, 31, 36, 39, 41, 43, 51, 104]. In a study based on deaths certificates from 24 of the United States during 1984–1992, 657 deaths from peritoneal neoplasms were identified [105]. 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. A review of the association between asbestos exposure and risk of peritoneal mesothelioma has been published [106].

Risk of Mesothelioma in Other Organs

Albeit rare, cases of mesothelioma have been reported in the pericardium and the tunica vaginalis of the testis [107, 108]. 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.

Other Occupational Agents

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

Table 21.6 Mesothelioma deaths in cohorts of synthetic mineral fiber production workers

Study	Country	Total number of deaths	*N* mesothelioma deaths	Comments
Glass wool				
Marsh et al. [109]	USA	9060	0	
Boffetta et al. [110]	Europe	1281	1	
Moulin et al. [111]	France	N/A	0	
Continuous filament				
Boffetta et al. [110]	Europe	191	0	
Chiazze et al. [112]	USA	437	0	
Watkins et al. [113]	USA	161	0	
Rock/slag wool				
Marsh et al. [109]	USA	1011	1	Case not confirmed during pathology review
Boffetta et al. [110]	Europe	1679	4	Two cases with heavy asbestos exposure
Refractory ceramic fibers				
LeMasters et al. [114]	USA	87	0	

workers included in the available cohorts, only six were from mesothelioma (Table 21.6). 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 United States [87], and 3.1 (95% CI 1.2–8.1) in a study from Germany [92]. 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 21.5): the strong excess of mesothelioma among hamsters exposed by inhalation to this type of fibers [115], however, suggests prudence before concluding that refractory ceramic fibers do not pose a risk to humans.

An increased risk of mesothelioma has been reported sugar refinery workers from Sweden and Italy, which was attributed to exposure to organic fibers [116, 117]. These findings however have not been confirmed studies conducted in Hawaii [118] and Florida [119] and might be due to concomitant exposure to asbestos. While some cases of mesothelioma have been reported among miners and millers of talc contaminated with asbestos fibers [120], no cases have been reported in multiple cohorts of workers exposed to uncontaminated talc [121].

Conclusions

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 [122–124]. A fraction of mesotheliomas, however, originates in patients without apparent occupational exposure to asbestos (Table 21.5). 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 [125]) is ionizing radiation, which however is responsible for a very small number of cases [126]. 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 in fact 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 [127]: it is unclear to which extent this reflects under-diagnosis of the disease. Use of asbestos has greatly increased in many of these countries 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 [128–132].

Specific surveillance programs on mesothelioma have been implemented in several countries such as France [133]. 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.

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Soft Tissue and Bone Sarcomas

22

Alessandro Comandone, Giacomo Garzaro, Enrico Pira, and Paolo Boffetta

Introduction

Sarcomas represent a diverse group of malignant neoplasms of mesenchymal origin. They represent less than 1% of all adult neoplasms and 12% of childhood cancers [1]. They can be classified into two main categories: soft tissue sarcomas (STS) that represent approximately 80% of the total, and sarcomas of the bone. As classified by the World Health Organization, there are more than 100 different subtypes of sarcomas [2]. The rarity of the disease, combined with the high number of subtypes, make sarcomas a group of neoplasms difficult to diagnose and to study.

Soft Tissue Sarcomas

Epidemiology

Worldwide incidence rate of STS is estimated to be in the order of 3–4 cases/100,000 person-years [3]. The absolute number of cases in each country is not clearly defined, mainly because these types of neoplasms have challenging diagnostic procedures and complex classifications [2, 4]. The estimated incidence in the USA is in the order of 7000 new cases per year, and in the UK, Italy, and France of 2800–3000 cases per year [4]. The incidence of STS shows three peaks, before age 10, around age 20–30 years, and over age 60, most cases being diagnosed at old age [2]. Adult types of STS are different from those arising in childhood [5]. In childhood, round cell sarcomas and rhadbomyosarcoma are the most common types, while in adults and elderly people fusocellular or undifferentiated forms are most common [5].

Embryologically, STS is derived from mesenchymal tissues, including muscles, tendons, synovia, vessels, adipose tissue, and Schwann cells; however, the exact cell of origin of individual cases is often difficult to identify. As a consequence, there is a wide discordance in the diagnostic process of STS, especially in adults [2, 5].

Benign tumors of the soft tissue occur in superficial tissues and are usually less than 5 cm in diameter. Malignant neoplasms are rare, with a proportion of 1:200 to the benign lesions, but they can reach a diameter as large as 10 cm [6]. STS can occur everywhere in the body; they are mostly located in thorax and extremities, especially in the thighs, the buttocks, and the inguinal region (46%); a truncal localization is relatively common (18%), while less usual sites are the upper limbs (13%), the retroperitoneal space (13%), and the head and neck (6%) [7].

No screening approaches are currently available for STS, but an active educational program aiming at early diagnosis of soft tissue mass may be useful [2, 7]. Nine percent of STS are superficial, and the mean volume at diagnosis is 5 cm; 60% are deep-seated with a mean diameter of 9 cm, while the retroperitoneum hosts STS of large volume (up to 15 cm) with multifocality and invasion of surrounding organs [2]. Ten percent of STS are metastatic at the time of diagnosis, with metastases mostly to the lungs. Rhabdomyosarcomas, clear cell sarcomas, and peripheral nerve sheath tumors can metastasize to local nodes, and alveolar soft-part sarcomas can determine brain metastasis [2, 4, 6, 7]. The 5-year survival rate of STS patients in a large European study was 53% [8].

Ionizing radiation and alkylating agents used in chemotherapy are the best-characterized risk factors of STS. Several cohort studies have been carried out on long-term survivors of adult cancers, namely tumors of the female breast, cervix, endometrium, ovary, prostate, lung, colorectum, and

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lymphoma [9–16]. Most of these studies were based on linkage of American (e.g., SEER) and European cancer registries, and have a sufficient power to assess incidence of STS as second primary neoplasms. Rates were consistently increased among patients who underwent radio- or chemotherapy, and especially among those who received both treatments. Similar findings have been reported in studies of survivors of childhood cancer who received radio- or chemotherapy [17–19].

Clinical Characteristics

More than 50 different subtypes of STS have been described, but the most common forms are liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor (MPNST), undifferentiated pleomorphic sarcoma (UPS), and synovial sarcoma. Rarer forms are extra-skeletal chondrosarcoma, epithelioid sarcoma, clear cell sarcoma, and malignant perivascular epithelioid cells sarcoma (PEComa) [2, 4, 7, 20]. The 2013 World Health Organization (WHO) classification had updated some definitions, identified new entities such as myxofibrosarcoma and UPS, which were previously combined in the group of malignant hystiocytic tumors, and regrouped emangioendothelioma and pericytoma into the group of solitary fibrous tumors [2].

The etiology of the vast majority of STS is unknown. Some forms have a FAMILIAR or inherited component: neurofibromatosis NF-1 and NF-2 are associated with benign schwannomas, neurofibromas, MPNST (1% of cases), and gastrointestinal stromal tumors (GIST) [21]. In addition, aggressive fibromatosis or desmoid tumors can occur in familial adenomatous polyposis, especially in the Gardner's syndrome subtype [2]. Germline mutation of *TP53* can predispose to STS in the context of Li–Fraumeni syndrome, as *RB1* germline mutation can do in retinoblastoma syndrome [22].

STS typically presents as a soft tissue lump or mass. While it is challenging to foresee the behavior of the mass, and to distinguish a benign from a malignant tumor, all superficial masses larger than 5 cm and all deep nodules larger than 3 cm in diameter should be considered with suspect. Pain is rarely an early symptom (except for retroperitoneal STS); sometimes, the mass can present as a hematoma [4]. Retroperitoneal sarcomas are generally diagnosed as large masses found at imaging; either generic discomfort or abdominal pain are common symptoms [4]. When the mass is located in the extremities, an ultrasound scan is useful to confirm the clinical suspect. Plain X-ray can define the possible involvement of bones [4, 23].

Biopsy can be obtained with core needle or with an incisional technique in order to obtain a sufficient sample; it must be performed to establish the malignancy grade and histological nature of the neoplasms [4, 24]. Fine needle cytology is best performed in the suspect of local relapse of previous operated sarcoma; as a first diagnostic technique, it could be insufficient due to the scarcity of the material collected [7, 24]. In retroperitoneal sarcomas, percutaneous biopsy is recommended to define the histology of the mass [4, 7].

Histological diagnosis should be based on the current WHO classification and should be confirmed in a reference center or highly qualified network [2, 4, 7]. The grading system follows either the French (FNCLCC; 3 grades) or the American classification (4 grades) [25, 26].

If the diagnosis of STS is confirmed, a complete staging must be performed, in order to exclude metastatic disease and to properly define the neoplasm. A CT scan of the chest is compulsory, and in case of STS of the thigh and groin a CT scan of the abdomen is requested too. Staging should be scored following the American Joint Committee classification [4, 7].

Occupational Risk Factors

Dioxins, Phenoxy Acids, Chlorophenols

An association between exposure to dioxins, phenoxy acid herbicides, and chlorophenols and risk of STS was reported in case-control studies from Sweden [27–30]. These studies suffered from potential recall bias, and their results were not replicated in case-control studies from other countries, including New Zealand [31–34], the USA [35–37], Australia [38], and Italy [39, 40]. Studies of Vietnam veterans with potential exposure to Agent Orange also yielded negative results [41–43].

A series of cohort studies of phenoxy herbicide manufacturers and sprayers were conducted in several countries and eventually combined in a study coordinated by the International Agency for Research on Cancer (IARC) [44]. The mortality of almost 22,000 exposed and more than 4000 unexposed workers was studied in relation to exposure to phenoxy herbicides, chlorophenols, and tetrachloro-dibenzo-dioxin (TCDD) or higher polychlorinated dioxins (PCDD). Based on 9 (exposure to phenoxy herbicides or chlorophenols) and 6 (exposure to TCDD or higher PCDDs) deaths, the risk of STS was increased, even if confidence interval included unity. A nested case-control analysis of cases of STS from this cohort resulted in an increased risk associated with exposure to phenoxy herbicides and of a significantly increasing trend according to categories of TCDD exposure, with odds ratios (OR) of 2.8, 6.6, and 10.6, respectively, for low, medium, and high exposure [45]. Subsequent reports from individuals studies included in the IARC study did not provide additional support to the hypothesis of an association with phenoxy herbicides or TCDD [46–54], with two exceptions [55, 56].

Other studies of workers with potential exposure to phenoxy herbicides or chlorophenols include those conducted on leather workers [57–61], farmers, gardeners, and sawmill and forestry workers [62–71], and pulp and paper workers [72–74]. In addition, exposure to these agents was assessed in a few studies across multiple jobs and industries [63, 64, 75–82]. In general, these studies did not provide evidence of an association with risk of STS: however, many of them had low power to detect such an association.

Several studies address non-occupational exposure to dioxin and related compounds. The two most informative are a study from Finland that analyzed fat concentrations of 17 dioxins and furans in STS cases and hospital controls [81, 82], and the follow-up studies of the population exposed to an industrial accident in Seveso, Italy [83, 84]. In the Finnish study, a decrease in risk was found for increasing concentration of dioxins and furans, while in the Seveso study, no excess of STS incidence or mortality was observed.

In conclusion, despite extensive research, the hypothesis of an association between exposure to TCDD, PCDD, phenoxy acid herbicides, and chlorophenols and risk of STS, which was suggested in some early studies, has not been confirmed by those published during the last two decades. The results of the IARC multicenter cohort, which provide the strongest evidence in favor of such hypothesis, may be explained by chance or residual confounding.

Vinyl Chloride

High exposure to vinyl chloride, an agent used in the chemical industry, is causally associated with development of liver angiosarcoma, a rare form of liver cancer, leading to the hypothesis of a possible association with other types of sarcoma. The most informative studies on cancer risk among workers exposed to vinyl chloride are two multicenter cohorts from North America and Europe. The North American cohort includes more than 10,000 workers employed between 1942 and 1972 in 37 US and Canadian plants producing the monomer and the polymer [85]. Twelve deaths from STS were observed, with a significantly increased mortality ratio. The European cohort included more than 12,000 workers from 19 plants in Italy, Norway, Sweden, and the UK, producing the monomer and the polymer, and one plant processing the polymer [86]. Six deaths from STS were reported, with a non-significantly increased mortality ratio. During the review of the clinical evidence, three out of six deaths from STS turned out to be due to liver angiosarcoma.

Other smaller studies reported one death from STS, without providing risk estimates [87], or mortality from bone and STS combined [88, 89].

A meta-analysis of these studies resulted in a summary standardized mortality ratio of 2.4 (95% confidence interval [CI] 1.5–4.0) [90]. The authors however warned that this apparent increased risk might be due to misclassification on death certificate of cases of liver angiosarcoma, a neoplasm known to be associated with high-level exposure to vinyl chloride, as STS. In conclusion, it remains unclear whether exposure vinyl chloride may cause STS in addition to liver angiosarcoma.

Ionizing Radiation

The observation of an increased risk of STS among patients treated with radiotherapy (see above) generated the hypothesis of a similar effect among workers with low-level exposure to ionizing radiation. However, no increased risk of STS was detected in large cohorts of such workers, including uranium miners [91–93] and nuclear power plant workers [94].

Conclusions

In conclusion, there is no conclusive evidence for an effect of any occupational exposure on risk of STS.

Bone Sarcoma

Epidemiology, Pathology, and Clinical Aspects

Bone sarcomas are an uncommon group of neoplasms: they represent 0.2% of all new cancer cases registered in the USA [3]. They can affect any bone in the body, but the most common areas are the extremities, in particular the thighs. There are four histologic subtypes of bone sarcoma [2]: osteosarcoma, chondrosarcoma, Ewing's sarcoma, and chordoma.

Osteosarcoma is an osteogenic sarcoma; it is the most common malignant bone cancer in young age, due to the fact that it often occurs in growing bones. Most osteosarcomas occur in the metaphyseal region of skeletally immature long bones, which have the greatest growth potential. A biphasic pattern of incidence is observed: peaks have been noted before 19 years of age and in patients over 60 years.

Chondrosarcoma originates from cartilage cells and is a kind of neoplasm that usually occurs between age 30 and 60. It accounts for 20–27% of bones sarcomas.

Ewing's Sarcoma typically grows in bones, but can also grow in other tissues and muscles. It is more common in children and adolescents, but it can be diagnosed also in adults. In the USA, it is responsible for 3.5% of cancers in American children 10–14 years old, and for 2.3% of cancers arising among 15–19 years old [95, 96]. Peak incidence is in children between 10 and 15 years of age.

Chordoma affects bones in the spine and in the base of the skull. It occurs most frequently in adults 30 years old or older, in particular in men. It is a very rare neoplasm, with an incidence of 0.5/1,000,000. The peak of incidence is between 50 and 60 years of age.

Bone sarcomas tend to have symptoms as localized mass, swelling with or without erythema, warmth, and pain. Pain can be insidious and transient (particularly occurring at night), progressively becoming more severe and unremitting. Restricted movements in joints and pathologic fractures may also be presenting signs.

Little is known about etiology of bone sarcoma: a few predisposing factors have been identified, including genetics, ionizing radiation, trauma, and orthopedic implants [97]. From a genetic point of view, tumor suppressor gene mutations are involved: Li–Fraumeni syndrome (*TP53*), Retinoblastoma (*RB-1*), Bloom's syndrome (*BLM*), Werner's syndrome (*WRN*), Rothmund-Thomson Syndrome (*RECQ4*). Ionizing radiation, in particular from radiotherapy, is the strongest environmental factor leading to subsequent bone sarcoma development.

Occupational Risk Factors

Ionizing Radiation

High-level exposure to ionizing radiation is an occupational risk factor of bone cancer. However, because of strict protection measures implemented since the beginning of the twentieth century, the role of this agent as occupational carcinogen for the bone is mainly of historical interest.

A high incidence of bone cancer was reported among radiologists and other medical personnel who experienced high exposures to X-rays in the early years of radiology [98–101]. No such excess persisted among radiologist and other medical staff who were employed after 1920 in the USA and the UK [98–102]. An association between radium exposure and bone cancer was first reported by Martland [103]. An increased risk of bone cancer was observed in a cohort of 1250 women exposed to radium while working in the luminous watch-dial industry between 1913 and 1929, among whom 36 cases of bone cancer were observed [104]. The lowest radium intake dose associated with bone cancer, among 751 women whose dose was determined, was 202.5 μCi. The latency period to develop bone sarcoma declined with increasing dose level. Bone cancer incidence rates were higher in a group with intake dose of 750 or more μCi compared to a group with intake dose of 200–749 μCi.

Other Agents and Exposures

Results on exposure to agents other than ionizing radiation as risk of bone sarcoma are based on a small number of community-based studies.

Hoppin et al. [76] conducted a case-control study of 51 male cases of bone sarcoma and 1910 controls recruited during 1984–1988 in eight areas of the USA covered by cancer registration. Exposure to 13 agents or jobs was reported by study subjects during a telephone interview. For none of the agent, there was a significant association with risk of skeletal sarcoma although the ORs for exposure to wood or saw-dust and employment in saw mill were increased (OR 1.75; 95% CI 0.90–3.37, and OR 2.45; 95% CI 0.80–6.26).

Merletti et al. [97] conducted a multicenter study in nine European countries, which comprised 96 cases of bone sarcoma and 2632 controls. A full occupational history and detailed information on pesticide exposure were obtained from cases and controls; results were reported for 24 job titles and 25 industries with at least 5 exposed cases. An increased risk of was detected among blacksmiths, toolmakers, machine-tool operators (OR 2.14, 95% CI 1.08, 4.26), bricklayers (OR 2.93, 95% CI 1.55, 5.53), carpenters (OR 4.25, 95% CI 1.71, 10.50), and workers in the manufacturing of wood, cork products, and straw (OR 2.02, 95% CI 1.00, 4.08). The OR for exposure to pesticides was 2.33 (95% CI 1.31–4.13), it was reduced to 1.63 (95% CI 0.77–3.45) when the analysis was restricted to population-based cases and controls. No relationship was found between duration of pesticide exposure and sarcoma risk. Because of the large number of comparisons carried out in this study, results that are significant at 5% should be interpreted with caution.

Pukkala et al. [105] conducted an analysis of the Nordic Occupational Cancer Study (NOCCA) cohort. The NOCCA cohort consists of 14.9 million individuals from Finland, Iceland, Norway, Denmark, and Sweden who participated in population censuses in 1960, 1970, 1980/1981, and 1990. Occupational information was obtained from computerized census records from 1960 and later censuses in Sweden and Norway, from 1970 and later censuses in Finland, from 1971 census in Denmark and from 1981 census in Iceland, and classified into 53 job titles. Personal identity codes were used to link census records with the data from cancer registries and national population registries for information on cancer, death, and emigration. Each person was followed-up until the date of emigration, death or 31 December 2005 in Finland and Sweden, 2004 in Iceland, and 2003 in Denmark and Norway. A total of 2051 cases of bone cancer were observed among men and 1618 cases among women. An increased incidence of bone cancer among men was observed for "other health workers," which may comprise radiology technicians (SIR 2.25; 95% CI 1.29–3.66), seamen (SIR 1.64; 955 CI 1.15–2.26), drivers (SIR 1.24; 95% CI 1.05–1.48), public safety workers (SIR 1.49; 95% CI 1.07–2.01), and military personnel (SIR 1.57; 955 CI 1.02–2.32). No categories were at increased risk among women, but the numbers of exposed cases were small. As in the multicenter

European case-control study, the large number of comparisons suggests caution in the interpretation of results that were significant at the 5% level.

Conclusions

In conclusion, a part from the effect of high-level exposure to ionizing radiation detected in historical studies of radiologists and radium, no occupational risk factors have been identified for bone sarcoma.

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Malignant Neoplasms of the Skin

23

Malcolm R. Sim, Stephanie S. H. Tan, Sarah Kelly, and Rosemary L. Nixon

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 recognised 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 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 better able to do this work than older workers 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 occupational diseases 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].

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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 skin neoplasms and the current state of evidence for the effectiveness of workplace preventive measures, with a focus on new and emerging risks for skin neoplasms.

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), squamous cell carcinoma (SCC), a precursor form of SCC (actinic keratosis) and malignant melanoma (MM). Skin neoplasms apart from MM are often given the umbrella term of non-melanotic 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 tumour very rarely metastasises, 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

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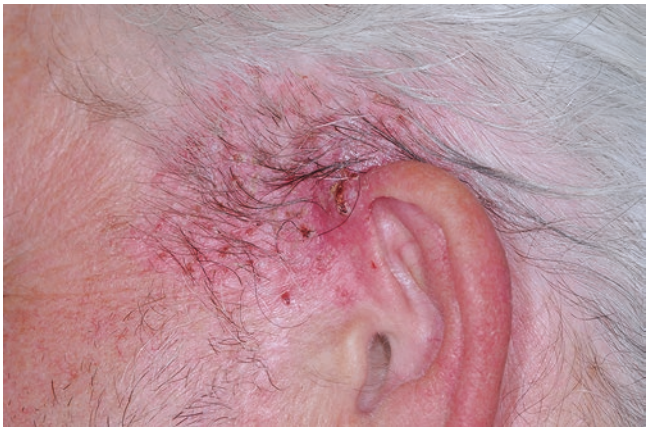

Fig. 23.1 Basal cell carcinoma on the ear

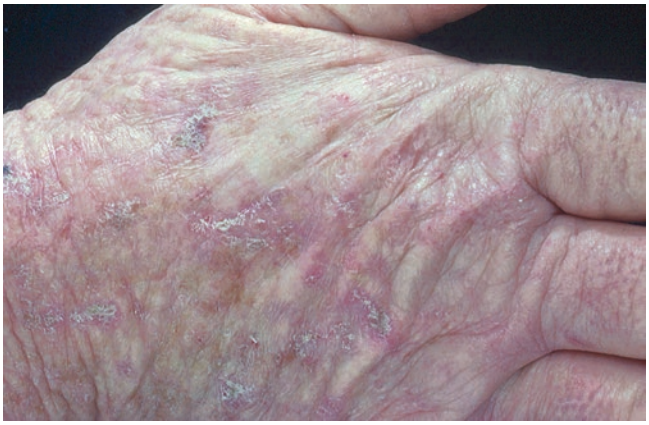

Fig. 23.2 Actinic keratosis on the dorsum of the hand

(Fig. 23.1), while approximately 15% of tumours occur on 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 colour, 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. Ethnicity 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].

BCCs may arise in 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. Tumour size can vary from a few millimetres to several centimetres in diameter. Characteristics vary for different clinical sub-types, 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 tumours. 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 white to yellow 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-looking 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 sub-type of nodular BCC that exhibits increased melanisation. Clinically, the lesions are fairly well-defined papules or plaques with a translucent or pearly appearance and range in colour from pink to dark brown or black.

Actinic Keratosis

Actinic keratosis (AK), also termed solar keratosis, represent 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 very sunny areas such as Queensland, Australia. Patient who are immunocompromised following organ transplantation are 250 times more likely to develop AK [10].

An AK may follow one of the 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 unclear, 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. 23.2). 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 disorganised keratinization and with a variable degree of inflammation. 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 often 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 ionising 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 derived 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 tumour acquires the ability to invade locally into fat, muscle, bone or cartilage. Approximately 2% of all SCCs metastasise, 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, as demonstrated by 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. 23.3). They also commonly occur on the dorsum of hands and forearms. SCCs present clinically as scaly nodules or papules and less commonly as plaques that are skin-coloured, pink or red. The tumour surface may be smooth, keratotic or ulcerated, and lesions may be exophytic or indurated. SCC must be excluded in any non-healing erosion, ulcer or skin lesion that repeatedly bleeds with minor trauma.

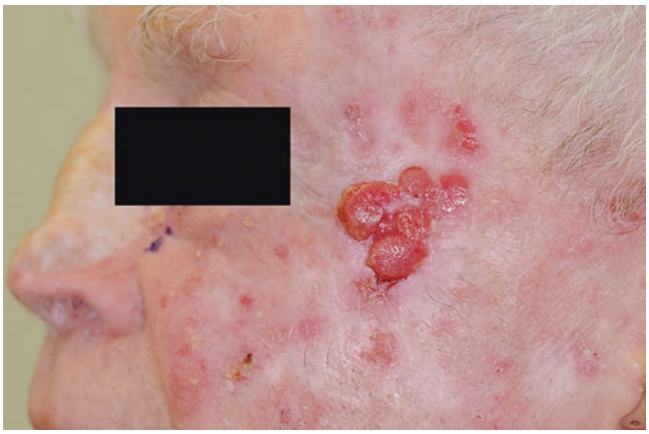

Fig. 23.3 Squamous cell carcinoma on the forehead

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. After non-melanoma skin cancer, malignant melanoma is the fifth most common cancer in Australia, behind NMSC, prostate, bowel and breast cancer [13]. Australians have a 1 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 phototype 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 pre-malignant lesions. Since there is an inverse relationship between the depth of invasion of MM and survival, it is important to recognise the early 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 (colour variegation), D (diameter > 6 mm), 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 colour over time (Fig. 23.4). Variegation in colour is a key feature of melanoma, and SSMs may become striking, with various hues of tan, brown, black, red, grey 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.

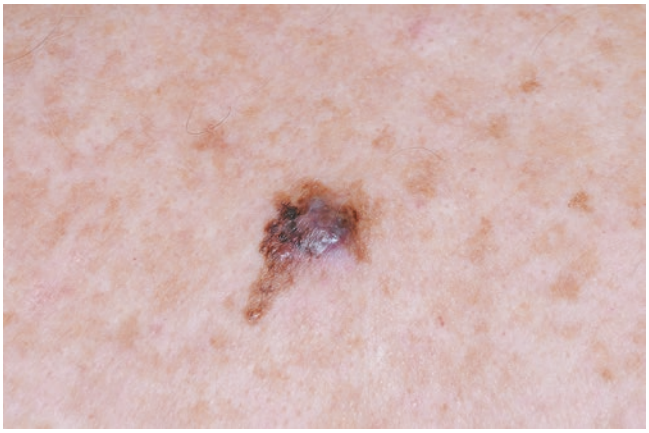

Fig. 23.4 Malignant melanoma on the trunk

Nodular melanoma (NM) is the second most common sub-type and more commonly arises de novo than in a pre-existing nevus. NM lacks the conventional criteria (ABCDE) that are helpful in clinical diagnosis of melanoma, and it often presents as a symmetric papule or nodule with regular borders. The colour is often uniform and is usually blue black or bluish red, but 5% are 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 nailfold is suspicious of melanoma and termed Hutchinson's sign. Lentigo maligna melanoma typically occurs on chronically sun-exposed and photodamaged skin, particularly on the head and neck. The tumour 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 unrecognised by treating clinicians, unless a careful occupational history is taken.

Epidemiology and Surveillance

The Global Burden of Disease study has estimated based on 2016 data that there are 282,000 incident cases of cutaneous MM, 635,000 cases of squamous cell carcinoma and 886,000 cases of basal cell carcinoma annually [19]. Due to under-reporting of NMSC, this likely underestimates the burden [20]. It is also estimated that there are 61,700 deaths due to MM and 53,000 deaths due to non-melanoma skin cancers annually [21]. For MM, it is estimated that there is a disease burden of 1.5 million disability-adjusted life years (DALYs) in 2016, an increase of 19.6% from 2006 and 63.7% from 1990. For SCCs, approximately one million DALYs were lost and for BCC about 1100 lost, increases of 18.3% and 23.8%, respectively, from 2006 to 2016. Deaths from BCC are rare and therefore total disease burden is less than for SCC or melanoma [22].

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 [23]. In the USA, the rising incidence of MM has been well documented, more than tripling in US men from about 7.5/110,000 in 1973 to 25.5/100,000 in 2004 [24]. 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.

Occupational Epidemiology

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 4415 work-related cancers in Australian males in that year [25]. In addition, it was estimated that 28,000 NMSCs in males were caused by occupation. Such estimates have acknowledged limitations, such as uncertainties in the numbers of exposed workers and levels of work exposure, as well as uncertainties in the PARs themselves, but these findings do help to identify skin neoplasm and work factors as an important problem to address.

A more recent estimate of the contribution of occupation to cancer in the UK has been undertaken, based on attributable fractions for the IARC Group 1 and Group 2A carcinogens and using data from the CARcinogen EXposure (CAREX) database [26]. This study estimated that 2928

NMSC registrations in 2004 were attributable to occupation, with almost all of the cases estimated to occur from three exposures; 1541 from UV light, 902 from mineral oils and 545 from polycyclic aromatic hydrocarbons (PAHs). The number of NMSCs attributable to occupation 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 the UK.

This method was subsequently used to estimate the burden of occupationally related cutaneous malignant melanoma due to solar radiation at work in the UK in 2011. The study estimated that 2% of all MM in the UK was attributable to occupational exposure to solar radiation. The construction industry had the largest burden (44% of deaths and 42% of registrations) [27]. The long latency of occupational cancers was highlighted in this study, as >50% of these melanomas occurred in those over 65 years of age.

Another approach is to try to obtain empirical data about the extent and risk factors for skin neoplasms by establishing disease notification programmes. Such programmes 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 programme involving physician-notified occupational skin diseases, found that about 12% of cases (n = 1468) were skin neoplasms for the period 1995–2006 [28]. More recent analysis of the THOR data for skin cancer notifications from 1996 until 2012 showed that in 99% of cases the suspected causal agent was sun/sunlight/ultraviolet light [29]. The most frequently reported occupations were outdoors, such as armed forces, agriculture and construction. Sixty-two percent of case reports were aged over 65 at the time of reporting, which reflects the findings of other studies including Rushton et al. [27]. The median duration of exposure was shortest for melanoma. Furthermore, duration of exposure was found to be longer for UK exposures than those with non-UK exposures, irrespective of type of skin neoplasm, which is in keeping with other studies showing an inverse relationship with latitude.

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. (2010) study [26] and the spectrum of work-related exposures and occupations is also very different from those estimates. 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 [30]. This may be due, in part, to the itinerant and seasonal nature of such work, leading to less regular contact with the health care system, and may be an important factor in the known underestimate of the extent of the occupational skin neoplasm burden.

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 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 industrialising 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 ionising radiation, while the main chemical exposures of interest are metals (e.g. arsenic), metalworking fluids and 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 [31]. Tables 23.1 and 23.2 present the cohort and case-control studies, respectively, which investigate the association between occupational exposures and malignant skin neoplasms and the findings for each exposure are summarised in the following sections.

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 [50].

Despite the large number of occupations involving PAH exposure, one review found few studies which investigated a link between PAH and skin neoplasms, but that the studies which included skin cancer found small, but statistically significant, increased risks with ORs ranging from 1.1 to 1.5 for different types of PAH exposure scenarios [51]. A more recent cohort study of workers exposed to bitumen found no

Table 23.1 Cohort 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 [32]	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 sulphite) 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 [33]	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 [34]	2101 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 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 standardised	Small number of MM cases (8), so limited power for subgroup analyses
Randem et al. (2004), four Nordic countries [35]	22,362 male asphalt workers; employed >1 season; cancer incidence via linkage with national cancer registries	Assessment of job histories into five 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 [36]	65,304 US white radiologic technologists; SCC and BCC ascertained by questionnaire and physician confirmation	Ionising 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 colour, lifetime UV exposure, total years worked	No association between year first worked and SCC
Sorahan 2007, UK [37]	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 cancer: 117 (110–124) 113 (104–123)	Age	No association with longer period from first employment. Refinery operators, craftsmen and administrative staff significant excess of mortality from MM

Dennis et al. (2010), North Carolina, USA [38]	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
Costello et al. (2011), USA [39]	14,139 white male autoworkers, mortality and cancer incidence until 2004	Exposure groups based on work history and air monitoring data	Straight >4.62 mg/m^3-years Soluble >10.41 mg/m^3-years	MM HR (incidence) 1.99 (1.00–3.96) 1.72 (0.69–4.27)	Year of birth, year of hire, type of fluid	Linear dose response for straight oils No associations with synthetic oils
Schernhammer et al. (2011), USA, Nurses' Health Study [40]	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* Never 1–2 years 3–5 years 6–9 years ≥10 years	HR for all skin cancers 1.0 1.02 (0.97–1.07) 0.99 (0.94–1.05) 0.91 (0.84–0.99) 0.84 (0.78–0.89)	Age No effect modification by history of UV light exposure	Similar pattern for BCC, SCC and MM when analysed separately. Little difference when further adjusted by personal factors Dark hair colour had lowest risk
Dos Santos Silva et al. (2013), UK [41]	16,329 flight crew and 3165 (ATCOs) employed between 1989 and 1999; follow-up to 2008 for cancer incidence	Occupational and lifestyle exposures by questionnaire and access to medical records	*Flight crew* *ATCOs* *Internal analysis*	SIR for MM 1.87 (1.45–2.38) 2.66 (1.55–4.25) HR for MM of flight crew vs ATCOs 0.78 (0.37–1.66)	Internal analysis adjusted for host and recreational exposures	Mutual adjustment for occupational and lifestyle exposures found skin that burns easily and sunbathing to get a tan were the strongest predictors of melanoma
Rajaraman et al. (2016), USA [42]	90,957 radiologic technologists who responded to a 1994–1998 survey were followed until 2003–2005 for cancer incidence and 2008 for cancer mortality	Number of years worked performing fluoroscopically guided IR procedures and cancer diagnosis recorded via survey	*Ever worked with*	HR MM 1.30 (1.02–1.32) BCC 0.98 (0.89–1.09) SCC 0.98 (0.80–1.19)	Age, smoking, BMI, alcohol, gender, skin tone, hair and eye colour	No information on radiation doses. No adjustment for non-occupational UV exposure

(continued)

Table 23.1 (continued)

Author, year, country	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Stenehjem et al. (2017), Norway [43]	24,917 male offshore petroleum workers employed between 1965 and 1998; Follow-up for an average of 13.5 years for incident cases of NMSC and melanoma	Industrial hygienist developed job-time-exposure matrices (JEMs) for skin contact with crude oil, benzene, mineral oil and ionising radiation	*Cumulative exposure to Benzene* *≤median* *Duration of exposure to benzene* *≥median*	HR for all skin cancers of forearm and hand 4.76 (1.10–21) 6.84 (1.10–21)	Age, sunburn frequency, education	Results unable to clarify the effect of UVR combined with PAH exposure as no cases unexposed to both (small numbers) Significant cumulative and duration p-trends found for benzene and crude oil
Heckmann et al. (2017), USA, Nurses' Health Study 11 [44]	74,323 female rotating night shift nurses; excluding those of African-American, Asian or Hispanic ethnicity; follow-up 1989–2001	No. of years on rotating shift work, average sleep duration, skin cancer diagnosis collected by questionnaire;	*Rotating night shift* *Never* *<2 years* *2–5.9 years* *6–6.9 years* *≥10 years* *Hours per night of sleep (per 5 years) duration* *<6* *7* *8* *≥9* *<6* *7* *8* *≥9*	Multivariable model HR BCC 1.00 0.93 (0.86–1.01) 0.95 (0.88–1.04) 0.83 (0.75–0.93) 0.83 (0.74–0.94) BCC 0.93 (0.86–1.00) 1.00 1.03 (0.95–1.11) 0.95 (0.82–1.09) MM 0.68 (0.46–0.98) 1.00 1.12 (0.80–1.56) 0.64 (0.31–1.34)	Age, SMI, alcohol, smoking, hair/eye/skin type, hours spent in sun, episodes of sunburn, artificial tanning However no effect modification so not included in main model	Long duration of rotating night shifts and short sleep time is associated with a lower risk of some skin cancers; mechanism remains unclear

Table 23.2 Case-control studies of occupational exposures and malignant skin neoplasms

Author, year, country	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Kenborg et al. (2010), Denmark [45]	42,542 cases of NMSC, 7690 cases of MM and 2341 cases of lip cancer from the Danish Cancer Registry	Population controls matched on age and sex chosen at random from the Danish Cancer Registry	Outdoor workers were identified from the Danish job-exposure matrix	Outdoor work >10 years	OR NMSC 0.83 (0.77–0.88) MM 0.97 (0.84–1.11)	Social class, place of birth, skin colour	Low levels of UV exposure in Denmark
Surdu et al. (2013), Hungary, Romania and Slovakia [46]	618 incident cases of NMSC in hospital setting	527 hospital-based controls	Experts judgement of occupational exposures based on self-reported lifetime occupational history; Questionnaire assessed host and lifestyle factors	Ever exposed to arsenic Ever exposed to arsenic and sunlight at work	OR for NMSC 1.21 (0.81–1.82) Female 8.73 (2.18–34.99) Male 0.99 (0.34–2.91)	Age, sex, family history of cancer, skin type, lifetime average of arsenic in drinking water	Small number of incident cases ($n = 21$) of NMSC in women exposed to both sunlight and arsenic
Vuong et al. (2014), The Australian Melanoma Family Study (AMFS) and the Genes, Environment and Melanoma study (GEM); Multi-national [47]	588 population-based cases of melanoma in the AMFS study and 1079 population-based cases of melanoma in the GEM study	472 controls in the AMFS study and 2181 controls in the GEM study	Self-reported weekday sun exposure used to estimate occupational sun exposure	GEM Study Total weekday sun exposure	OR for MM Head and neck 0.56 (0.36–0.86)	Age, sex, education, family history of melanoma, skin type	Inverse association for head and neck melanoma and occupational skin cancer. No association observed in the AMFS study
Trakatelli et al. (2016), EPI-DERM project [48]	360 histologically confirmed hospital-based cases of melanoma, 602 cases of BCC and 409 cases of SCC	1550 control persons	Questionnaires were used to assess occupational history, lifestyle habits, skin type and skin behaviours	Indoor Other outdoor Farmer/ construction	OR AK/BCC/SCC 1 AK 1.55 (1.09–2.18) BCC 1.53 (1.39–2.41) AK 2.58 (1.93–3.44) BCC 1.83 (1.80–2.96) SCC 2.77 (1.97–3.88)	Age, gender, phototype, smoking, sunscreen use in own country, outdoor hobbies	No significant associations for melanoma Also a significant risk of all skin cancers including AK in workers with ≥5 years of outdoor work
Fortes et al. (2016), Pooled analysis (Italy and Brazil) [49]	399 incident cases of melanoma in hospital setting	401 controls from other medical specialties	Interview and skin check to assess occupational history, lifestyle habits, skin type, eye and hair colour, sunburn episodes	Any pesticide Unexposed Exposed Occupational sun exposure + any pesticide Unexposed Exposed	OR for MM 1 2.58 (1.18–5.65) 1 4.68 (1.29–17.0)	Age, sex, education, phototype, sunburn episodes, family history of skin cancer	Suggests those occupationally exposed to sun and pesticides at increased risk of melanoma, Possible synergistic effect

convincing evidence of an increased risk of MM or NMSC by PAH exposure or by duration of employment, but numbers were small [35]. Coal tar, which has high levels of PAHs, is recognised by IARC as a Group 1 human carcinogen. A recent review of occupational exposure to coal tar found the majority of studies indicated the main metric for skin neoplasm development is chronic exposure [52].

Other organic compounds in the workplace have also been implicated as a cause of skin neoplasms. A meta-analysis of mortality from skin neoplasms 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) [53]. Most of the mortality data related to MM, as mortality is low from other types of skin neoplasms. 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 found small, but significant, excesses for both MM and NMSC mortality among refinery workers [37]. The most recent update of the Australian petroleum worker cancer incidence cohort study (Health Watch) has also found an excess of MM incidence (SIR 1.37, 1.19–1.58) although no clear work factors could be identified [54]. PAH exposure and outdoor work are exposures of prime interest in these workers. A cohort study from Norway examined skin cancer risk according to exposure to crude oil, mineral oil, benzene and ionising radiation and adjusted for UV exposure. For skin cancers of the forearm and hand, associations with skin cancer were found for cumulative and duration of exposure to crude oil and benzene. Dermal absorption of PAHs and benzene may explain this, although the number of incident cases of skin cancer on the upper limbs was small and exposure could only be assessed as ever/never [43].

Inorganic Arsenic

Another established skin carcinogen is inorganic arsenic, with exposure occurring both occupationally and environmentally, the latter usually through arsenic contaminated drinking water in countries such as Bangladesh and Taiwan [55]. Chronic exposure to inorganic 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 neoplasm. Arsenic exposure in workplaces usually occurs in the presence of other chemical substances and its carcinogenic effect on 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, involving UV exposure [56].

A more recent European case-control study of 618 incident cases of NMSC found no significant association between arsenic exposure in the workplace and NMSC, but did find an association between women exposed to both sunlight and arsenic at work (OR 8.73, 95% CI 2.18–34.99). However, this was based on a small number of incident cases and controls and was not replicated in men [46].

Metalworking Fluids

A further chemical hazard which has received attention in the literature is exposure to metalworking fluids among metal workers 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) [57]. This review suggested that the excess risk is more likely to be related to straight metal working fluids than soluble fluids.

A more recent study of metalworking fluids and MM has also demonstrated the strongest evidence for straight metal fluids, which have higher oil content than either soluble or synthetic metal fluids [39]. 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 Skinners' Disease. However, the bodily distribution of the MM cases in the Costello et al. [39] 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. 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 [32], 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 [34]. 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 [38].

A case-control study in Brazil of 95 incident cases of MM found those exposed to pesticides in the workplace had approximately twice the risk of MM (OR 2.06, 95% CI 1.03–6.89) [58]. A more recent pooled analysis (including the above Brazilian study and another in Italy) of 399 incident cases of MM found an association between ever use of pesticides and melanoma (OR 2.58, 95% CI 1.18–5.65) after controlling for confounders. Furthermore, subjects exposed occupationally to both sun and pesticides had an even greater risk of MM (OR4.68, 95% CI 1.28–17.0) [49].

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 outdoors [6]. The wavelengths for UV radiation range between 100 and 400 nm and are broadly categorised 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 [59].

While some studies have not shown a role for occupational UV light exposure as a cause of MM, such as studies by Hakansson et al. (2001) [33] and Vuong et al. (2014) [47], the studies in Tables 23.1 and 23.2 clearly document 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 [60]. The meta-estimate OR was 1.77 (1.40–2.30) and was of similar magnitude when the cohort and case-control studies were analysed separately. The same research group has also published a systematic review of occupational UV exposure and BCC [61]. 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 non-occupational 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 standardised metrics for this type of workplace exposure, especially when the relevant pattern of exposure is thought to be different between BCCs and SCCs. A case-control study in Demark found no association between outdoor work and MM or NMSC, although UV intensity was low, which suggests that the strength of the association between outdoor work and NMSC is likely to vary geographically [45]. 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 countries such as Australia or southern USA, and other high UV 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 [62].

A more recent multi-centre European case-control study, based on data from the EPIDERM project, found a significantly increased risk of outdoor vs. indoor work for AK, BCC and SCC. Of note, skin phototype was equally distributed by type of work, although outdoor workers were less likely to use sunscreen in their own country, had more outdoor hobbies and felt less confident in understanding medical information. As has been found in other studies, no associations were found for melanoma [48].

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 [63]. 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 [64]. Other occupations, such as cooks and metal workers, also showed elevated risks for ocular melanoma 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 [64], but there is no published research so far on the risk of skin cancer in workers at these salons.

Ionising 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) [65]. However, it is not clear in this

study whether ionising 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 cancers [66]. The highest risk for both types of cancer 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).

Consistent with the above review, a more recent meta-analysis found airline pilots and cabin crew to have twice the incidence of melanoma compared to the general population (SIR melanoma 2.21, 95% CI 1.76–2.77). However, again this does not adjust for confounders, most importantly skin phototype and recreational UV exposure [67]. A cohort study of 16,329 flight crew and 3165 Air Traffic Control Officers (ATCOs) found statistically significant increases in melanoma in both groups. However, when they adjusted for occupational and lifestyle confounders, they found no difference in melanoma rates between flight crew and ATCOs and identified skin that burns easily when exposed to sunlight and sunbathing to get a tan as the strongest risk predictors [41].

There has been longstanding 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 [65, 66]. In addition to these reviews, the findings of the Yoshinaga et al. (2005) study indicate that long-term exposure to low to moderate ionising 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 [36]. The strength of this study was the ability to adjust for UV exposure and personal characteristics, such as skin colour.

A more recent cohort study of 90,957 radiation technologists performing fluoroscopically guided interventional procedures in the USA observed increased incidence in of melanoma (HR 1.30, 1.05–1.61) but not for BCC or SCC. This study lacked detailed information on radiation doses and did not adjust for non-occupational UV exposure [42].

A review of occupations with ionising 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 [68]. 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 [32]. 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. [69] pointed 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, and results of studies to date have been mixed. The US Nurses' Health Study, a large longitudinal study has investigated the association for a range of cancers and Schernhammer et al. in 2011 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 tumours combined [40]. The most recent update to the US Nurses' Health Study adjusted for additional skin cancer risk factors and sleep-related variables. It found a longer duration of shift work to be associated with a significantly lower risk of BCC in women, strongest in those with brown or black hair. A similar non-significant lower risk of SCC was found and there was also no association with MM. A short sleep duration was associated with lower risk of melanoma and BCC but not SCC. The mechanism underlying these associations remains unclear [44].

Measures to Prevent Skin Neoplasms in Workers

There is evidence that the pattern of sun exposure related to skin neoplasms is different for the different types of skin neoplasms. 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 [70], 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 [71].

This indicates a strong need for sun protection programmes, 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 feasible options, so the main focus needs to be on measures lower in the hier-

archy 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 [72]. 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 [73]. 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 gender differences are considered in designing sun protection and information programmes in workplaces.

A 2013 systematic review assessed outdoor workers' sun-related knowledge, attitudes and protective behaviours. Studies published up to April 2012 were reviewed and the authors concluded that published findings regarding outdoor workers' sun-related knowledge and attitudes to be scarce. Overall, sun-protective behaviours were inadequate and variable across different countries, occupations and genders. As found in the previous review, men were found to be more likely to wear hats and women more likely to use sunscreens [74].

Interventions to Reduce Work Exposures

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 risk factors have received lesser attention. A 2007 systematic review by Glanz et al. concluded that there were too few well-designed studies to determine the effectiveness of skin protection programmes to reduce the impact of UV light exposure in the occupational setting [72].

In the last decade, some well-designed studies have been published on this topic and two systematic reviews have been published providing evidence for occupational sun safety education. Reinau et al. in 2012 analysed 16 interventional studies and concluded that there is now sufficient evidence that sun safety programmes in the workplace can foster favourable sun protection behaviours among outdoor workers [74].

Horsham et al. in 2014 updated a previous 2007 systematic review and included six studies [75]. The reviewers found evidence for the effectiveness of studies involving educational and multi-component interventions in increasing sun protection behaviours and less evidence for the effectiveness of policy or specific intervention components. Few studies measured the effect of individual interventions, which makes it difficult to determine their effectiveness.

Three of the randomised trials provided evidence for the long-term efficacy of workplace-based interventions involving education and awareness about skin protection. In the first study, using a health belief model, they found that the use of skin cancer videos and photos of sun damage in their own faces were associated with a significant increase in sun protection behaviours and a significant decrease in skin colour measured by a spectrophotometer in 148 male highway workers which persisted for 1 year after the intervention. Two large-scale interventions also found long-term efficacy; the first being the Go Sun Smart (GSS) programme, a worksite sun safety programme of employees in high altitude ski areas, largely based on the diffusion-of-innovations theory [76]. Education and training on wearing sun protection was delivered via posters, newsletters, magnets, articles and websites as well as training programmes for managers. The GSS programme was evaluated in a pair-matched, group-randomised, pre-test/post-test controlled design enrolling employees at 26 ski areas in Western North America. At 6-month follow-up, a slightly lower proportion of workers at ski areas that received GSS reported sunburn over the past summer (50%) compared to those at the control areas (53%, $p = 0.01$) [77].

A further two-group randomised study assessed a sun safety intervention promoting the wearing of wide-brim hats and sunscreen use among US postal workers [78]. This study involved 2662 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.

Another study looked at sun protection policies and found that a mandatory policy increased some protective behaviours, but not others. In addition, it found those workers who reported increased use of sun protections while at work reported low sun protection during leisure time, highlighting the need for all types of exposures to be considered in the development of sun protection policies at work [79]. Walkosz et al. published an update to the GSS programme in 2015 which assessed the sustainability of an Occupational Skin Cancer Prevention Programme. They surveyed 2940 employees in ski areas used in the previous study. Employees who had 'ever heard' of the GSS programme were assessed for their sunburning and sun protection behaviours. They found no significant difference in the prevalence of sunburn, but differences were identified for all sun safety behaviours. Overall, 23.9% of those who had heard of the GSS programme engaged in sun protection behaviours compared to 21.86% of those who had not heard of the programme [80].

Summary

Occupational neoplasms of the skin have been recognised 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 skin neoplasms. UV light has been shown to be the most important current cause of occupational skin neoplasms, particularly for SCC and in particular related to outdoor work. There are also some well-established chemical exposures in the workplace, such as PAH exposure and some other possible emerging hazards, such as shift work, which require further research to investigate their relationship with skin neoplasms and possible mechanisms. 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 [81]. The development of effective skin protection programmes in the occupational setting is clearly an urgent priority and while there is some evidence of effectiveness, this needs to be an important focus of future research.

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Breast Cancer

24

France Labrèche, Mark S. Goldberg, Dana Hashim, and Elisabete Weiderpass

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, in more developed and less developed countries. In 2018, 2.09 million new cases were reported in the world, corresponding to 24.2% of all cancers occurring in women that year. The incidence rates of female breast cancer vary greatly, being highest among women in North America, Southern, Western, and Northern Europe, and Australia and New Zealand (greater than 80 new cases annually per 100,000 women). Incidence is lowest in South-Central Asia, and in Eastern and Middle Africa (incidence below 30 new cases annually 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 more developed countries as compared to less developed countries (Fig. 24.1) [1].

Incidence rates have been decreasing in North America, a few European countries and Australia and New Zealand, but are currently increasing in less developed countries. In the United States, the decrease in incidence rates over the last few years has been attributed 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 and have, in fact, decreased particularly in more developed countries [4].

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 24.1.

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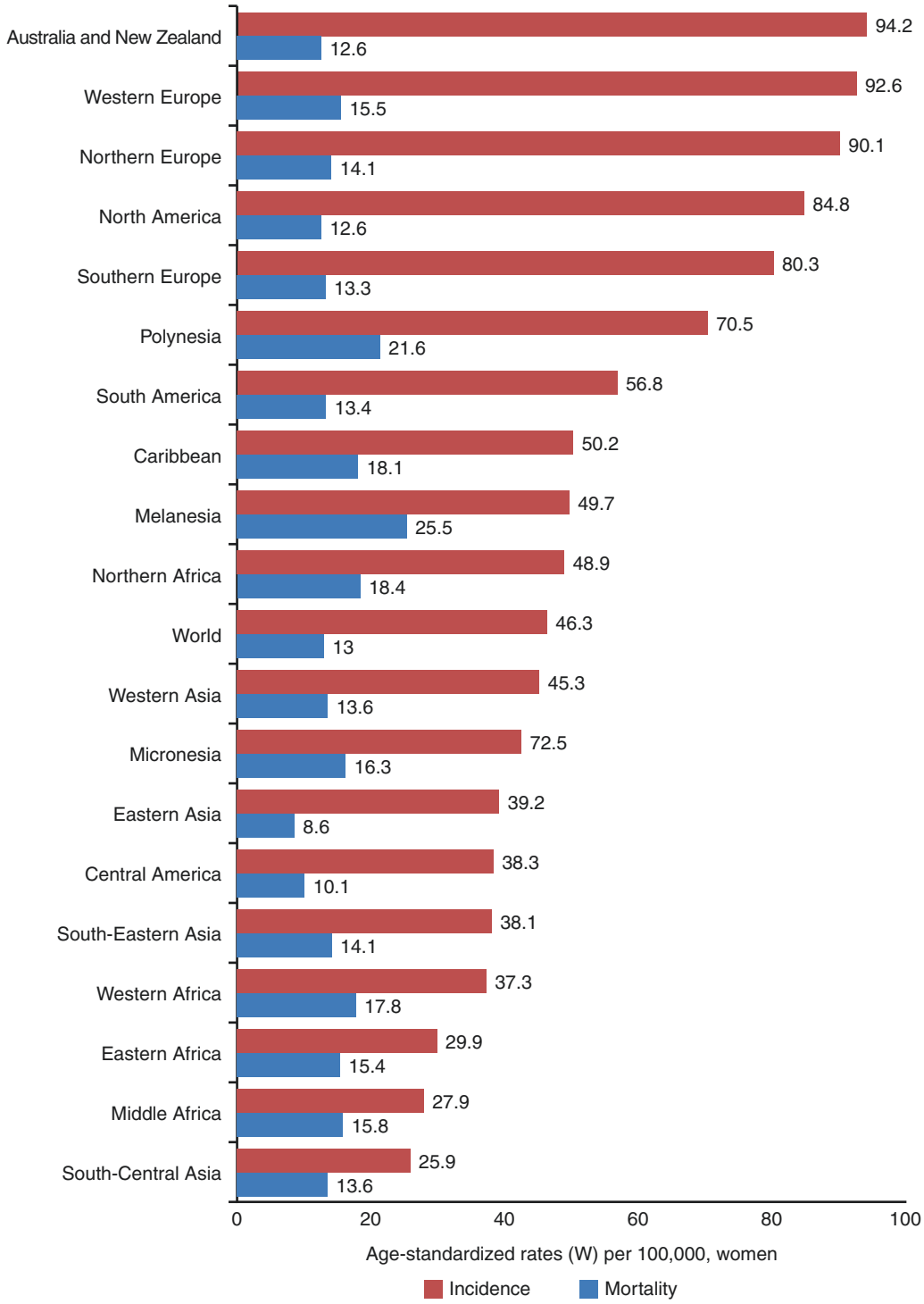

Fig. 24.1 Age-standardized incidence and mortality rates of female breast cancer in different world regions. GLOBOCAN 2018 (W: Standardization done according to the average-age structure of the world) (Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [16 March 2019])

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 <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 [14, 19]; 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].

Table 24.1 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, 13]
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, 13]
Lifestyle and personal risk factors				
Height (as a marker of factors affecting growth)	Per 5 cm increase	Increase of 2–11% in risk	Any	[14]
High body fat	Exposure–response relationship	Decrease in risk	Premenopausal	[11, 15]
High body fat	Exposure–response relationship	Increase in risk	Postmenopausal	[14, 16]
Physical activity	Per 7 MET h/week	Decrease of 3% in risk	Any	[14–16]
Alcohol consumption	Per 10 g ethanol consumed daily	Increase of 10% in risk	Any	[14, 17]
Total fat consumption		Increased risk	Postmenopausal	[7, 14]
Other exposures				
Chest irradiation (X- and γ-radiation)	High doses vs. minimal (irradiation from puberty to childbearing years)	2–4	Any	[7, 18]

METs describe the energy cost of physical activity relative to a person's resting metabolic rate

Use of Exogenous Hormones

According to the International Agency for Research on Cancer (IARC), diethylstilbestrol may cause breast cancer in women exposed during pregnancy [13]. 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 [13]; 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, 13]. 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, 15].

Diet, Body Size, and Physical Activity

The World Cancer Research Fund [14] evaluated the available evidence on the risk of cancer and several aspects of diet, physical activity, and body size. The *IARC Handbooks of Cancer Prevention* series also included similar evaluations [16, 17]. The results from the World Cancer Research Fund and 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, but the relationship has not been clearly established [14]. Regarding body fatness, an international panel of experts judged the evidence that supports an exposure–response relationship convincing for postmenopausal women, whereas the same group judged probable a protective effect among premenopausal women [11, 16]. There is robust evidence for a mechanistic explanation indicating that greater body adiposity after menopause is associated with tissue inflammation, which may play a part in initiation or promotion of cancer [14, 17]. 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) [14].

With respect to height, prospective epidemiological studies show a clear exposure–response relationship, and there is some 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 [14].

Evidence from prospective studies on physical activity suggests a protective effect against both pre- and postmenopausal breast cancer for high levels of physical activity, including occupational active employment [20] but no evidence that breast cancer risk is increased with inactivity, except in relation to occupational sedentariness for which increased risks of about 20% has been reported [21]. The evidence is stronger for postmenopausal breast cancer than for premenopausal breast cancer. There are little data regarding frequency, duration, or intensity of activity, but the evidence is robust for mechanisms operating in humans [14, 16].

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 the evidence as "convincing" 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). 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) [14].

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 risk appears to increase when smoking starts early and before a woman's first full-term pregnancy (before the breast tissue matures) and if it 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, 18, 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 24.1) [18, 23, 24]. In addition, α-radiation and neutrons have been classified as carcinogenic agents for several cancer sites, but the evidence is deemed insufficient for female breast [18].

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 woman. 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 24.2) [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].

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 24.2) [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 24.2) [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

Table 24.2 Accepted breast cancer susceptibility alleles

Susceptibility alleles	Frequency in European populations	% of familial relative risk explained
High risk		
BRCA1, BRCA2, TP53, PTEN, STK11/LKB1, CDH1	Rare–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

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 to identify carcinogenic agents and circumstances. Agents are classified into one of the five groups: Group 1 agents are deemed to be 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 if there is 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 24.3 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 is derived from personal use, and not from exposures in occupational settings. The rationale presented for X-radiation and γ-radiation is derived 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) although a few occupational studies have also shown increased risks among exposed workers [18]. The evidence for polychlorinated biphenyls (PCBs) comes from both nonoccupational and occupational exposures [47]. Only one Group 1 agent, ethylene oxide, is an occupational exposure. However, evidence for carcinogenicity to the human breast is *limited* for this exposure. It is important to appreciate that few studies of occupational risk factors for breast cancer have been carried out, so the paucity of well-established 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

Ethylene oxide (Group 1 agent) [48] and night shift work (Group 2A agent) [49] are considered to be related to occupation (see Table 24.4).

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 [65]. Less than 1% is used as a sterilizing agent, a fumigant, or a pesticide by different healthcare facilities, spice manufacturers, or sterilization contractors [65]. In the early 2000s, the approximate estimates of the number of exposed workers in the United States were in the order of 48,000 [66]. In the European Union in the early 1990s, the corresponding estimate was around 47,000 workers [67].

The data used by the IARC to classify ethylene oxide [48] is derived mainly from four occupational cohort studies [50–54]. Because mortality from breast cancer is highly misclassified, one must rely on incidence rates, as reported in three of the four aforementioned cohort studies [50–52, 54]. A US National Institute for Occupational Safety and Health cohort study of 7500 women [52], which had accounted for several important potential confounding variables, showed a clear exposure–response relationship between exposure to ethylene oxide and the incidence of breast cancer, with a relative risk of 1.87 among women in the highest quintile of cumulative exposure as compared to the lowest quintile. A smaller study from the United

Table 24.3 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 1–123

Agent	IARC classification[a]	Weight of evidence[b] for causation in breast cancer		
		In humans	In animals	From occupational exposure studies
Lifestyle factors				
Alcoholic beverages	1	S	S	N/A
Tobacco smoking	1	L	L	N/A
Pharmaceuticals				
Diethylstilbestrol	1	S	S	N/A
Digoxin	2B	L	I	N/A
Estrogen menopausal therapy	1	L	S	N/A
Estrogen-progestogen contraceptives	1	S	S	N/A
Estrogen-progestogen menopausal therapy	1	S	S	N/A
Mixed exposures (*environmental and occupational*)				
Dieldrin	2A	L	L	I
PCBs	1	L	L	I
Tobacco smoke (second hand)	1	I	I	I
X-radiation, γ-radiation	1	S	S	L
Occupational exposures				
Benzene	1	I	L	I
ELF-EMF	2B	I	L, I	L, I
Ethylene oxide	1	L	L	L
Organic solvents				
Mixtures	1, 2A, 2B, 3	I	L	I
Tetrachloroethylene	2A	I	L	I
Trichloroethylene	1	I	L	I
Other pesticides	1, 2A, 2B, 3	I	S, L, I	L, I
PAHs	1, 2A, 2B, 3	I	L	I
Pharmaceuticals				
Estrogens	1	S, L	S	I
Antineoplastics	1, 2A, 2B, 3	I	S	I
Night shift work	2A	L	S	L

This table does not include risk factors not covered in *IARC Monographs* Volumes 1–123, notably reproductive and other hormonal factors, diet and nutritional factors, and genetic susceptibility traits

Abbreviations: *PAHs* polycyclic aromatic hydrocarbons, *ELF-EMF* Extremely-Low-Frequency Electric and Magnetic Fields, *PCBs* 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

States also showed increased risks (standardized morbidity ratios 1.57–1.72) among women from a sterilization company [51]. In a Swedish study, no increase in risk was initially found [50], but an internal analysis after a longer follow-up revealed significantly increased risks for women in the two upper quartiles of exposure compared to the lower half of exposure (rate ratios of 2.76 and 3.55) [54]. A few animal studies showed 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].

Night Shift Work

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]. Shift work disrupts biological rhythms and the most important factor 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].

Table 24.4 Occupational[a] exposures with limited evidence for carcinogenicity to the female breast, and their major industries or occupations (*IARC Monographs* Volumes 1–120)

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	[50–54]
	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.)		
Night shift work	Healthcare sector	Cohort studies	[55–58]
	Transportation	Any duration: ~1.0	
	Accommodation and food services	≥20–30 years (nurses): 1.4–1.8	
	Agriculture	Nested case-control studies	[59–61]
	Manufacturing industry	Any duration: 1.0–1.5	
		≥7–30 years: 1.7–2.2	
		Case-control studies	[62–64]
		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

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 less than twofold) among women who worked night shifts for a long period of time, or who did rotating work including night shifts as compared to women who worked daytime hours. Several definitions of shift work were used as well as different designs: two prospective cohort studies among nurses [55, 56]; three nested case-control studies [59–61]; and one retrospective case-control study [62]. Two studies showed negative results, a census-based cohort study [57] with important design limitations, and a case-control study initially designed to study the relationship between electromagnetic fields and breast cancer [63]. These studies included mainly white women and women with postmenopausal breast cancer. In some of the studies, not all potential confounding variables were accounted for. Misclassification of exposure may have biased the results toward the null. Studies of aircraft personnel were considered by the IARC Working group to support the association between shift work and breast cancer although these workers had concomitant exposures that could have confounded the association (such as cosmic radiation and electromagnetic fields) [49].

Since the IARC evaluation, several additional studies, including five cohort studies [58, 75–78] and eleven case-control studies [64, 79–89] have been published on shift work in relation to breast cancer risk. Most of these studies have been reviewed in 2016 by an expert working group of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES). The working group concluded that these recent epidemiological studies provide more evidence on the increased risk of breast cancer among night shift workers; however, this evidence is still limited and it is not yet possible to rule out, with certainty, the existence of residual confounding factors that could explain some of the observed associations [90, 91].

Seven recent meta-analyses [92–98] reported at least one meta-risk estimate of breast cancer in association with night shift work based on slightly different sets of studies. Overall, meta-risk estimates ranged from 0.99 (ten prospective studies [98]) to 1.40 (nine high-quality studies [93]) for ever/never night shift work exposure. These meta-analyses were not conclusive on other metrics of night shift work exposure or other study characteristics.

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. This disruption might increase cancer risk through several pathways [99], including a decrease of melatonin's possible oncostatic and free radical scavenging properties, as well as perturbations 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 the incidence of breast cancer [100]; levels of 6-sulphatoxymelatonin decreased with increasing number of nights worked in the 2 weeks prior to

urine collection [101]. However, another cohort study in the general population did not find such a relationship [102]. In classifying shift work that involves circadian disruption as probably carcinogenic to humans, IARC concluded that there was *sufficient* evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night) [49].

Clearly, more studies in humans are needed to allow a thorough understanding of the relationship between shift work and the incidence of breast cancer. A working group convened by the IARC 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], and although a few studies already addressed these issues, more evidence needs to be gathered [90].

Occupational Circumstances with Insufficient Evidence for Carcinogenicity to the Human Breast

A few additional agents have been found to be associated with an increased breast cancer risk in women, but the weight of evidence in these studies was not deemed sufficient to support their classification as carcinogenic to the human breast (see Table 24.5).

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 [18], 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 cosmic rays that are 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 [18]. 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 [152]. The doses were relatively low: 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 [152].

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 [18]. 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 [103]. A small case-control study nested in the same Chinese cohort showed a non-significant exposure–response relation with increasing cumulative dose [153]. This pattern of higher risks among women born before 1940 and 1930 was also confirmed in a study of radiology technicians in the United States [104] and in a follow-up of that same cohort until 2008 [154]. Indeed, most recent cohort studies have not shown evidence of increased risks at current exposure levels [24, 105, 155]. A recent review of epidemiological studies of medical radiation workers concluded that information on average annual exposure to occupational radiation, time trends in radiation 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 [156].

The available cohort studies of uranium production and of nuclear energy workers have very small numbers of female workers, and consequently very low power to detect increased risks of breast cancer. Cohort studies of workers at a few uranium mines or production facilities in the United States (primarily α-radiation from dusts) did not show any increased incidence or mortality rates of breast cancer among exposed workers, and a small increase was observed among nonexposed workers [106, 157]. 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) [107], whereas a study of French uranium fuel cycle workers showed a higher but still non-significant increased risk (standardized mortality ratio 1.53, 95% CI 0.94–2.37) [158]. One 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

Table 24.5 Agents or exposure circumstances that have been associated with female breast cancer, but with insufficient evidence

Agents and circumstances with some, but insufficient, evidence in humans			
Agents	Examples of industries/occupations	Range of risk ratios	References
X- and γ-radiation	Diagnostic radiology	0.9–5.3 (depending on cumulative exposure)	[103–112]
	Nuclear medicine		
	Industrial radiology		
	Nuclear workers		
	Uranium workers		
PCBs	Capacitor manufacture	0.8–1.3	[113, 114]
Dieldrin	Spouses of men who had used dieldrin	0.8–1.6 (not statistically significant)	[115]
	Farm spouses who used dieldrin	3.5 for ER-PR-tumors	[116]
Organic solvents (including halogenated solvents), other chemicals	Painting	0.5–2.4 (depending on type of solvent and cumulative exposure)	[108, 117–130]
	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		
ELF-EMFs	Telephone and telegraph operators	1.0–4.6 (depending on cumulative exposure, age at first exposure, and tumor hormonal status)	[122, 131–135]
	Electronic data processing operators		
	Sewing machine operators, textile workers		
	Denturists		
	Machinists		
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)	[120, 128]
Pharmaceutical drugs	Pharmaceutical workers	0.3–4.1	[122, 130, 136–138]
Several chemicals	Laboratory technicians, chemical workers	1.1–2.3	[129, 130, 139–141]
Pesticides and agrochemicals, solvents, etc.	Farmers and farm workers	0.7–2.8	[129, 130, 133, 142]
EMFs, solvents, pigments, textile fibers	Working in textile and clothing	0.5–4.1	[108, 122, 129, 130, 143]
EMFs, cosmic radiations, shift work	Flight personnel	0.8–3.3	[144–148]
Organic solvents, EMFs, metals, welding fumes	Semiconductor and computer manufacturing industries	0.7–1.3	[125, 130, 149]
PAHs, EMFs, cleaning chemicals	Chefs and cooks	0.7–1.6	[122, 129, 130, 150]
Organic solvents, glues, etc.	Cosmetologists and manicurists	0.7–1.2	[108, 130, 151]

Abbreviations: *ELF-EMF* Extremely-Low-Frequency Electric and Magnetic Fields, *PAH* polycyclic aromatic hydrocarbons, *ER-PR-tumors* Estrogen-Receptor and Progestogen-Receptor-negative tumors

exposure assessment methods (expert assessment based on occupational history) [108]. Another case-control study estimated occupational exposure to ionizing radiation using automatic assignments to occupational histories; it showed an increased risk of human epidermal growth factor receptor 2-positive (HER2+) breast cancer with occupational exposure in premenopausal women (OR = 2.57; 95% confidence interval, 1.09–6.03) [159]. 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 [160]. As exposure decreases over the years, risks are presumably being reduced and very large studies will be needed to detect excess risks.

Polychlorinated Biphenyls (PCBs)

PCBs are a group of 209 aromatic hydrocarbons that were widely used because of several interesting properties (non-flammability, chemical stability, high boiling point, and high dielectric constant). Although their production and use was banned worldwide (dates vary from the 1970s in the United States to 2006 in Korea), they can still be found in numerous products manufactured before the ban. Workers are therefore mainly exposed during abatement in construction, in waste incineration, and recycling of electronic equipment and fluorescent lights [47]. PCBs were classified as carcinogenic to humans, with sufficient evidence for malignant melanoma, and limited evidence for breast cancer [47].

The available evidence for breast cancer comes from case-control studies based on levels of PCBs measured in serum and adipose tissues of women, without certainty on the source of exposure [47]. The occupational data comes mainly from mortality studies of capacitor manufacturing cohorts with small numbers of female workers; these mortality studies were negative [114, 161], and only one suggested a relatively small increased risk of breast cancer incidence following occupational exposure to PCBs [113]. Thus, the extent to which occupational exposures to PCBs can be linked to increased incidence of breast cancer is still debated.

Dieldrin

Dieldrin (and aldrin, which is metabolized into dieldrin) is an organochlorine pesticide that has been banned since the 1970s in several countries because of environmental concerns on its environmental persistence [162]. Dieldrin is still measurable in the air, soil, ground water, and food in several developing [163, 164] and developed countries [165, 166]. Dieldrin was classified as probably carcinogenic to humans, with limited evidence for breast cancer [162].

As for PCBs, most of the evidence for breast cancer comes from studies based on serum levels of dieldrin. A prospective Danish study found a significant dose–response relationship between the risk of breast cancer and increasing serum dieldrin levels [167, 168], whereas a similar study in Norway was negative [169]. Positive associations with breast cancer were also reported in spouses of men who had used dieldrin in the US Agricultural Health Study, regardless of their own direct exposure to the pesticide [115, 116]. Hence, there appears to be an association between dieldrin burden and the incidence of breast cancer, but the importance of the contribution of occupational exposure to the increased risk will probably not be elucidated given the ban of organochlorine pesticides.

Occupational Exposure to Hormones, Antineoplastic Drugs, or Other Pharmaceuticals

So far, a few pharmaceutical drugs have been classified as carcinogenic or probably carcinogenic to the female breast of treated patients. Among these, diethylstilbestrol used during pregnancy, oral contraceptives or hormone replacement therapy containing estrogens only or estrogen-progestogen combinations [13] and digoxin [170] have been classified as carcinogenic (Group 1 agents) by the IARC. However, occupational exposures to these pharmaceuticals were not addressed in the corresponding issues of the IARC Monographs, other than to report on chromosomal aberrations in healthcare personnel handling antineoplastic drugs [13].

Several studies among pharmaceutical and healthcare workers reported evidence of elevated levels of urinary metabolites of antineoplastic drugs [171], or of effects linked to exposure to steroids (e.g., gynecomastia and loss of libido in men and menstrual problems in women) [172]. However, only a few epidemiological studies reported, more than 20 years ago, on the risk of cancer among pharmaceutical workers. Elevated risks of breast cancer in the order of 1.5–2.9 were reported in a Danish record-linkage study [136] and in two of four cohort studies of pharmaceutical workers [173, 174]. Another cohort study reported a small increase in incidence among women in the highest exposure groups [137], whereas in the fourth cohort study, only mortality was assessed and there were very few breast cancer deaths to draw conclusions [138]. Not enough data are available 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 15 years, few studies have been conducted on the role of other 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 [117–119] and solvents that metabolize into reactive oxygen species [120]. Industries and occupations that entail exposure to organic solvents have also been associated with increased breast cancer risk [121, 175]: laundry and dry cleaning occupations; working in the aircraft and automotive industries, including service attendants at gasoline stations [122]; electronic workers and those in semiconductor plants [118, 123, 124]; and printing machine operators and tenders [123]. However, in some studies the risks were very low [124, 125] or even nonexistent, such as for styrene [126]. Etiological factors for breast cancer appear to differ according to the hormonal receptor status of the tumor. For example, exposure to solvents appears to increase the risk of breast tumors with certain hormonal receptor status, such as estrogen receptor-positive tumors [120, 175] and some progesterone-negative tumors [119, 120]; younger age at first exposure appears to increase the risk [117, 118, 120, 175].

Aromatic hydrocarbons are a large family of molecules containing at least one benzene ring (i.e., a six-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) [176]. PAHs are derived from incomplete combustion of organic material, and their concentrations are influenced particularly by industrial and traffic-related sources [48, 176]. Some PAHs are carcinogenic in humans, while a few others are classified as probably or possibly carcinogenic to humans.

Exposure to benzene [128], to MAHs as a group [120], and to PAHs [129] has been associated with an increased incidence of about 30%, but not consistently [177]. The increased risk has been observed in both premenopausal [128] and postmenopausal women [120]. The effects of exposure to PAHs appear to be influenced by genetic susceptibility [178]. 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 [179], and with risk patterns that may differ according to the hormonal receptor status of the tumor [180]. Finally, a small risk has also been reported for exposure to soluble metalworking fluids [181].

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 [182]. 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 [183]. 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 [184].

More recent studies, including meta-analyses, have not found that exposure to EMFs increases the risk of female breast cancer [131, 185–187]. Specifically, a large population-based case-control study showed a slight increase in risk [132], whereas another case-control study showed a fourfold increased risk among telephone and telegraph operators [133]. 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 [134], and premenopausal women with estrogen receptor-positive breast cancer were associated with a long duration of high occupational exposures [135].

Other Pesticides and Other Organochlorines

Results from most of the recent studies show either none or only a very small increased risk of breast cancer after exposure to pesticides [188] or other organochlorines [189]. 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 [190]. In a few recent papers, increased risks were linked to certain polymorphisms, notably of cytochrome P-450 1A1 [191] and GSTM1 [192]: it is possible that small increased risks of breast cancer do exist, but only in the presence of certain polymorphisms.

Specific Job Titles

The first published mention of an "occupational" increased risk of breast cancer occurred more than 300 years ago by

Bernardino Ramazzini, who reported on increased occurrence of breast cancer among nuns, which he attributed to celibacy, sensing a relationship with nulliparity [193]. 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 [129, 130, 133, 150, 194–198]. The increased risk presented by these professional occupations has been ascribed by most authors [129, 130, 150, 196, 197, 199] (but not all [198]) 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.

Increased risks have also been reported for farming occupations [133, 142], textile and clothing workers [108, 130, 200], leather and fur processors and glass-manufacturing workers [133], nurses [61], dentists [201], electricity power plant workers [202], semiconductor and computer manufacturing industries [125, 149], metalworking and automotive plastics manufacturing [203], rubber industry workers [179, 200], and scientists and laboratory workers [141, 150]. However, similar occupations have also been associated with absence of risk in other studies, for example, the occupation of farm worker [130, 204–206], garment worker [143], glass manufacturer [129], dentist [201], and cosmetologist and manicurist [151].

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 [207]. After adjusting for possible confounding by reproductive factors, a few studies still showed an increased risk [144, 145] although there were a few negative studies [146–148, 208, 209].

In summary, several high-quality studies have been conducted, but our understanding of how occupational and environmental agents affect female breast cancer risk is still limited partly because of inconsistencies and partly because only a handful of potentially hazardous agents have been investigated. In many studies on specific industries or occupations, other lifestyle factors known to be associated with breast cancer (such as alcohol consumption, lower parity, and late age at first full-term pregnancy) were often not taken into account, so confounding could not be ruled out. Subtleties of the mechanistic relationships are also difficult to capture in epidemiological analyses, due to difficulties in past exposure assessment, 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 [210], but little human data are available and the association with human breast cancer remains unclear [211].

Since the improvement and accessibility of traffic-related air pollution exposure assessments, a handful of studies on traffic-related air pollution exposure and breast cancer have been conducted. In a case-control study based in New York State, an association was found with increased volumes of vehicular traffic [212] and higher concentrations of total suspended particulates were associated positively with exposures to benzo[a]pyrene [213, 214]. In the Nurses' Health Study II, no associations were found for incident breast cancer and fine particulates, but increased rates were found among premenopausal and postmenopausal women living within 50 m of major roads [215]. In the Sister Cohort [216], increased risks for nitrogen dioxide (NO_2) exposure measured by fixed-site monitors were also found among cases with positive estrogen receptor and positive progesterone receptor status (hazard rate: 1.10; 95% CI: 1.02–1.19). A hospital-based case-control study by Crouse and colleagues [217] reported increased risks of postmenopausal breast cancer with exposure to traffic-related air pollution in Montreal, using ground-level concentrations of nitrogen dioxide, a reliable marker of traffic-related air pollution. A subsequent population-based case-control study of postmenopausal breast cancer from 2008 to 2011 was conducted by Goldberg and colleagues [218] in the same city. They found an increased breast cancer risk per increase in the interquartile range (IQR = 5.8 ppb) of NO_2: OR: 1.10; 95% CI: 1.02–1.19. The study was also the first to examine associations of breast cancer with ultrafine particles (<0.1 μm in aerodynamic diameter); however, there was little evidence of association in any of the models or sub-analyses and little variability in the ORs. In another population-based case-control study conducted in eight provinces of Canada from 1975 to 1994, positive associations between incident premenopausal breast cancer and ground-level concentrations of NO_2 were found: for a 10 part per billion (ppb) the ORs varied between 1.26 and 1.32 and the 95% confidence intervals excluded the null. Lower ORs were found for postmenopausal breast cancer, in the order of 1.10 [219].

Air pollution is a complex chemical and physical mixture, and many of the pollutants 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, carbon monoxide, and PAHs [119, 120, 127]. 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 [220]. These studies provide insights into mechanisms and can help to determine possible enzymes or proteins that can act on potential carcinogens [220]. 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 major issue in such studies is having sufficient statistical power, and only studies with thousands of subjects can produce reliable results, and many of the studies reported below may not have been large enough.

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 [221]. In a German study [222], urinary concentrations of metabolites of PAHs were associated with certain polymorphisms of CYP1A1 and GSTP1. Elevated relative risks of breast cancer were found for high levels of plasma PCBs and CYP1A1 variants in case-control studies [223, 224] and in the Nurses' Health Study [225], but in another case-control study no associations between occupation and CYP1A1∗2 polymorphisms [226] were found. Results between the risk of breast cancer and exposure to smoking or second hand tobacco smoke are inconsistent in relation to slow and rapid NAT2 acetylators [227–229], and with exposures to aromatic and heterocyclic amines [180]. Elevated risks of breast cancer were suggested for current alcohol consumption with certain glutathione *S*-transferase genotypes (null GSTM1, GSTT1, and GSTM3) [230–232], and there was an inverse association between breast cancer risk and frequency of alcohol consumption with alcohol dehydrogenase II polymorphism [233]. The Breast Cancer Association Consortium recently published an analysis of the interaction between 70 single-nucleotide polymorphisms (identified by genetic fine-scale mapping of susceptibility loci) and 11 breast cancer risk factors: they notably found interactions between CFLAR-rs7558475 and current smoking, and between 5q14-rs7707921 and alcohol consumption for estrogen-receptor-negative tumors [234].

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 [235]. 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 [236].

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

As of 2017, four groups of researchers had published estimates of the burden of breast cancer attributable to occupational exposures now or in the future. The first study included ionizing radiation and exposure to hair dyes among hairdressers and concluded that 1.7% of breast cancer in Finland could be attributed to occupational exposures [237]. The second study, considering shift work and flight personnel, estimated that 4.6% of female breast cancers in Great Britain could be attributed to occupational exposures [238]. The third study calculated that 5.7% of breast cancers in the United States could be attributed to shiftwork [239]. Finally, the last study predicted that 0.7% of breast cancers diagnosed among women at work in 2012, until they are 100 years of age, would be caused by exposure, as of 2012, to ionizing radiation, ethylene oxide, and shift work [240] (see Table 24.6).

Male Breast Cancer

Descriptive Epidemiology

Male breast cancer is a very rare disease, with incidence rates varying from 0.1 to 2 per 100,000 men worldwide [241]. Rates are higher in North America and Europe (estimated at 0.47 per 100,000 [242]) 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 all breast cancers worldwide [241]. 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

Table 24.6 Estimated proportions of female breast cancer attributable to occupation now or in the future

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	[237]
Great Britain	Shift work, flight personnel	4.6 (3.3–6.0)	Proportion of attributable deaths by breast cancer	[238]
United States	Shift work	5.7 (0.0–11.9)	Proportion of attributable deaths by breast cancer	[239]
Australia	Ionizing radiation, ethylene oxide, shift work	0.7	Future excess fraction (FEF)	[240]

much smaller scale. Conversely, in the Nordic countries and Switzerland, incidence has been stable over the last 40 years [243–245].

General Epidemiology and Lifestyle-Related Risk Factors

The etiology of male breast cancer is poorly understood. This may be due to the rarity of the disease 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) [246]. 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 [247].

Among the lifestyle 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 [247–251]. So far, the IARC has not identified any carcinogens specifically 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 [249] and X-radiation and γ-radiation [109, 252]. Some evidence of a relationship with occupational ionizing radiation exposure has also been reported [110], and a recent analysis of the Japanese Atomic Bomb Survivors data reported higher radiation-associated relative risk for male breast cancer compared to the risk in women [253].

Inconclusive Occupational Exposures

A few occupational exposures have been associated, albeit inconclusively, with male breast cancer [246, 247, 254].

Extremely-Low-Frequency Electric and Magnetic Fields

In its 2002 monograph, the IARC Working Group on non-ionizing 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 [183]. Since then very few studies and one meta-analysis have been published regarding male breast cancer risk. A modest increased risk of male breast cancer (OR of 1.31, 95% CI 0.94–1.81) has been reported in men exposed to ELF-EMFs above 0.12 microteslas (exposure attributed using a job-exposure matrix); 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 [255]. In a meta-analysis of 18 cohort and case-control studies, a pooled risk estimate of male breast cancer of 1.32 (95% CI 1.10–1.59) was estimated with any occupational exposure to EMF from seven studies that used job title or a job-exposure matrix to assess exposure [256]. In conclusion, 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 and PCBs

The few epidemiological studies investigating the relationship between exposure to PAHs and male breast cancer did not show consistent findings. In a record-linkage study, Hansen [257] 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 [257]. However, in an Italian case-control study, no association was found between male breast cancer and occupational exposure to PAHs [258]. Two recent studies of capacitor workers showed non-statistically significant increases in mortality and in incidence of male breast cancer based on very little numbers ([259], based on two deaths; [161], based on six cases).

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 [246, 247]. 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" [260–262], 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 [258]. 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 [248, 263–265]. 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 [266]. 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 [129]; the authors underscore a common characteristic of these occupations—they usually include shift work, which has been associated with increased breast cancer risk in women [49]. A significantly increased risk of dying from breast cancer has been reported in policemen [267] and in professional firefighters [268, 269], but the incidence of breast cancer was not increased in the same cohort [270]. More recent studies of firefighters showed non-significant increases of incidence [269, 271] or of both mortality and incidence [271]. A 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) [272]. One study reported a relationship between carrier status for BRCA1/2 mutations and the occupation of truck driver in male breast cancer risk [273].

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, although similarities between male and female breast cancers [274] suggest potential common causal factors. As the most common cancer among women, breast cancer represents an important global burden. 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 [272] means that continuous research on the relationship between occupational exposures and breast cancer is warranted.

Breast cancer risk is 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, particularly in women, 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 occupational hygiene field: anticipation of potential carcinogens, followed by their recognition, evaluation, communication, and control (elimination, substitution, and reduction of exposure) in the workplace.

Disclaimer Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization. Dr. Hashim was at IARC at the time of writing this chapter.

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Malignant Tumors of the Female Reproductive System

25

Elisabete Weiderpass, Dana Hashim, and France Labrèche

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. 25.1), while the other cancers of the female reproductive system are very rare.

Cervical cancer is the fourth most common cancer in women worldwide, behind breast, colorectal, and lung cancers, and the fifth most common cancer overall, with an estimated 569,847 new cases in 2018 (Table 25.1). More than 70% of the global burden occurs in less developed regions, where it accounts for 11% of all cancers in women. Cervical cancer remains the most common female cancer in Eastern Africa, Southern Africa (except South Africa and Namibia), a few countries in Southeast Asia (Nepal, Bhutan, Myanmar), and in Bolivia (South America) (Fig. 25.2). Incidence is high in Southern, Eastern, Western and Middle Africa (standardized incidence rates 43.1, 40.1, 29.6, and 26.8 new cases per 100,000 women, respectively), and Melanesia (27.7 per 100,000). Rates per 100,000 women are lowest in Western Asia (4.1), Australia/New Zealand (6.0), North America (6.4), and Western Europe (6.8). The overall mortality-to-incidence ratio of cervical cancer is 53%; it was responsible for 311,365 deaths in 2018.

Endometrial cancer is the sixth most common cancer in women, with an estimated 382,069 new cases in 2018, and a standardized incidence rate of 8.4 per 100,000 women (Table 25.1). Incidence rates are substantially higher in countries with very high and high HDI (Fig. 25.3). North America, Central/Eastern and Northern Europe as well as Polynesia are observed to have some of the highest standardized incidence rates (more than 15.6 new cases per 100,000 women), and the lowest rates are observed in Africa and South-Central Asia (less than 5 per 100,000) [2]. Overall, the mortality-to-incidence ratio of endometrial cancer is 21%, and it was responsible for 89,929 deaths in 2018. This low ratio is probably due to the fact that symptoms of endometrial cancer are overt (consisting of postmenopausal bleeding in the majority of cases) and have a high cure rate when surgical treatment is performed during the early disease stages.

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, with 295,414 incident cases (standardized incidence rate of 6.6 per 100,000 women) and 184,799 deaths (standardized mortality rate of 3.9 per 100,000 women) estimated to have occurred in 2018 (Fig. 25.1). Both more developed and less developed regions of the world are affected (Fig. 25.3), 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 59% (Table 25.1).

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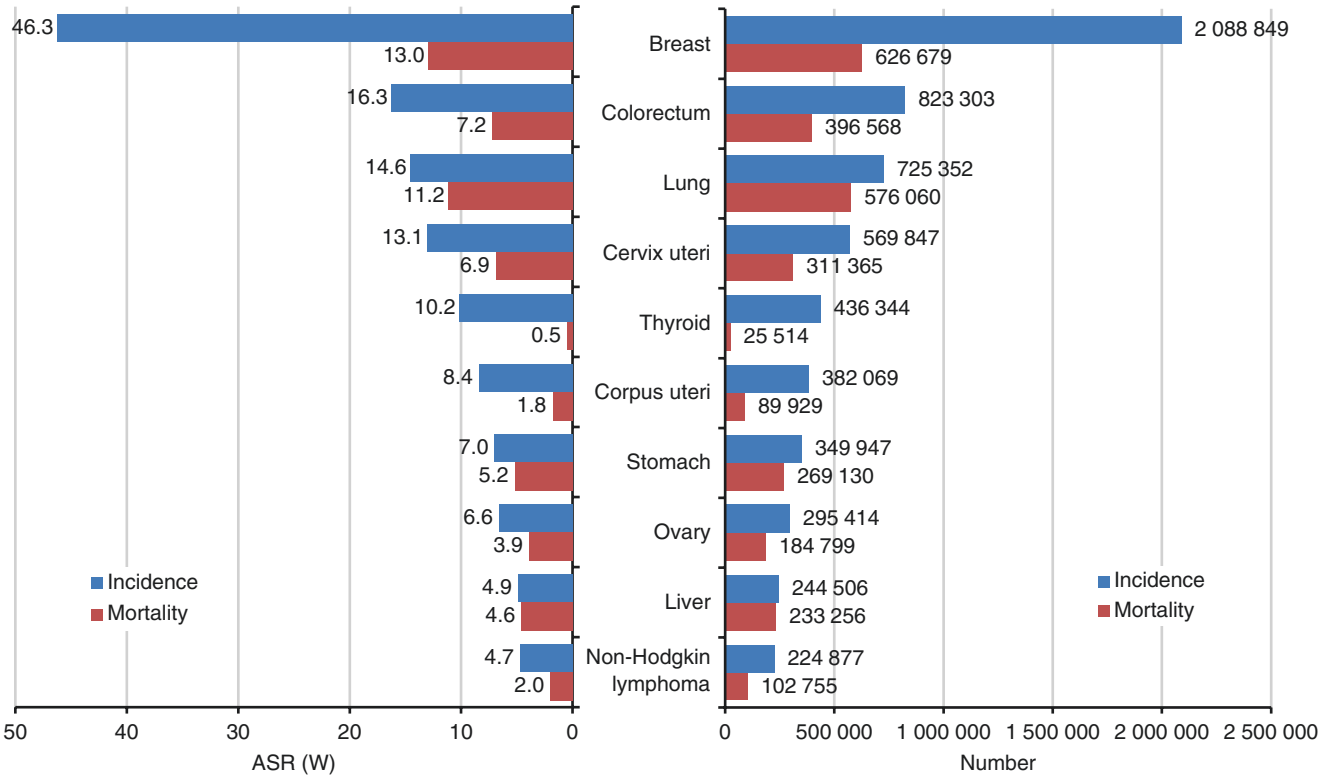

Fig. 25.1 World age-standardized cancer incidence and mortality rates, and number of cases and deaths among women. GLOBOCAN 2018. *ASR (W)* world age-standardized rate per 100,000 (Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [16 March 2019])

Table 25.1 Statistics on selected cancer sites among women worldwide, GLOBOCAN 2018 [1]

	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[a]	8,218,216	182.6	18.3	4,142,577	83.1	8.7
Breast	2,088,849	46.3	5.03	626,679	13.0	1.41
Cervix uteri	569,847	13.1	1.36	311,365	6.9	0.77
Corpus uteri	382,069	8.4	1.01	89,929	1.8	0.21
Ovary	295,414	6.6	0.72	184,799	3.9	0.45
Vulva	44,235	0.88	0.09	15,222	0.27	0.03
Vagina	17,600	0.37	0.04	8062	0.16	0.02

[a]Including non-melanoma skin cancer

The number of new cancers of other female genital organs worldwide that includes the vulva, vagina, uterus (unspecified), fallopian tubes, and placenta is not well known for most countries. Taken individually, they are also relatively rare. However, the case number can be extrapolated from incidence rates in countries where information is available [3]. From 2003 to 2007, the estimated number of new cancers of the female genitalia across all registries worldwide was 428,122 although this number must be interpreted with caution as not all countries have the same percentage of microscopically verified cases and some countries base incident cases on death certificates only, rather than institutional-based case reports [3]. The age-standardized incidence rates of these cancers worldwide are estimated to vary between 0.2 and 12.5 new cases per 100,000 women by registry [3]. However, human papilloma

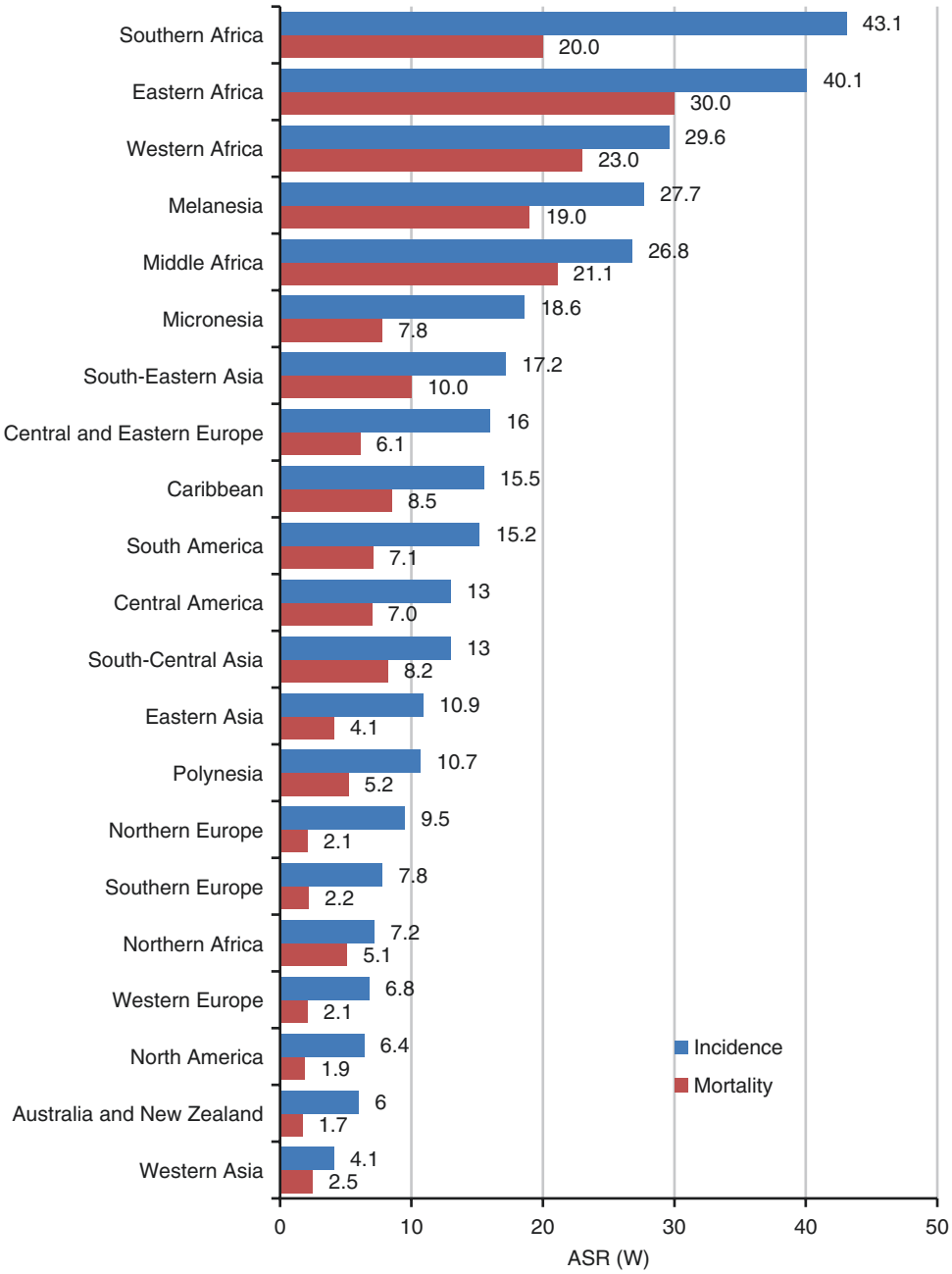

Fig. 25.2 World age-standardized incidence and mortality rates of cervical cancer in different world regions. GLOBOCAN 2018. *ASR (W)* world age-standardized rate per 100,000 (Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [16 March 2019])

virus (HPV) contributes to a large number of these cancers. Standardized incidence rates of cancers of the vulva and vagina are higher in North America and Europe than the other continents [4, 5].

Choriocarcinomas constitute about 0.6% of all cancers of the female reproductive system. In 2002 there were about 5800 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].

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, prognosis is extremely poor, even in countries with standardized tertiary healthcare facilities available to all patients. The introduction of cervical cancer screening has dramatically

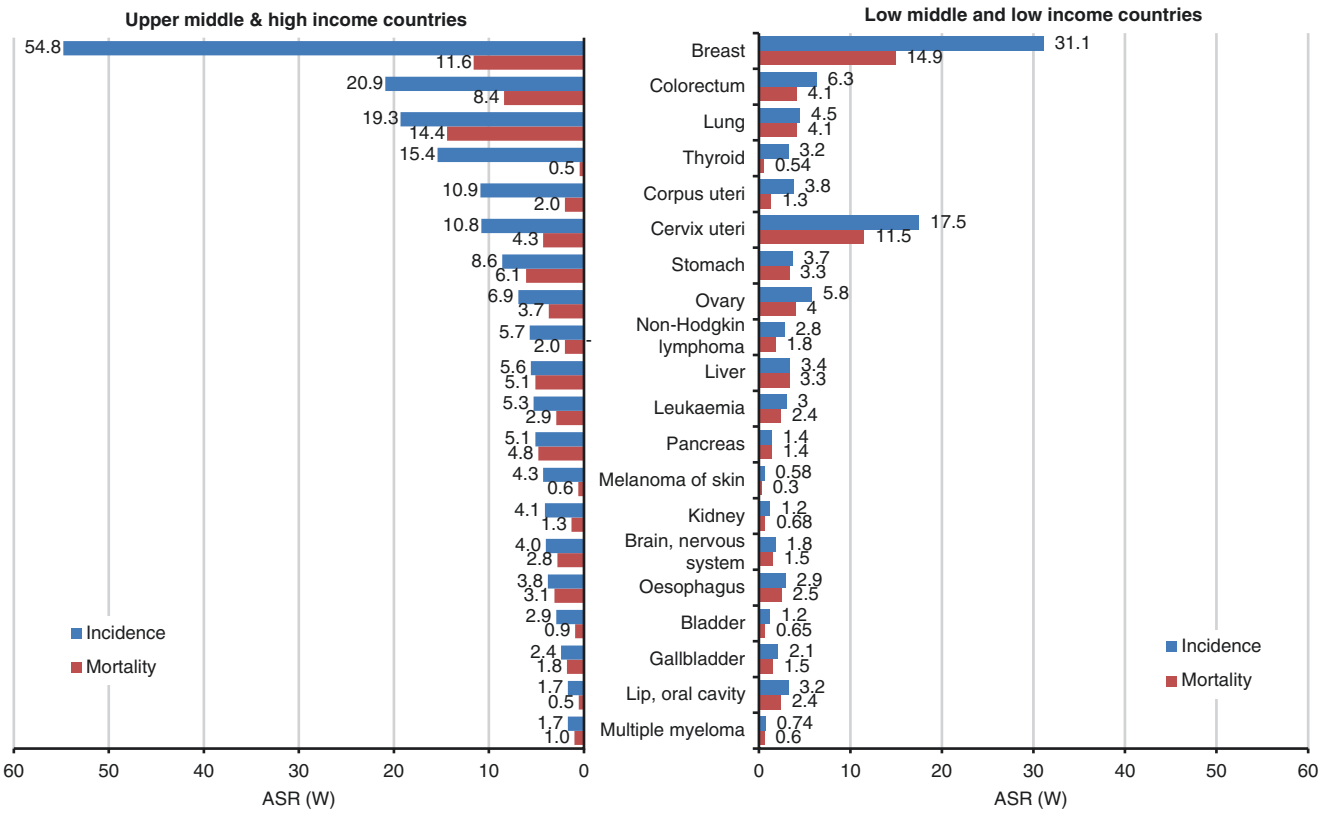

Fig. 25.3 World age-standardized cancer incidence and mortality rates by cancer type. Women in upper middle and high income countries compared to low middle and low income. GLOBOCAN 2018. *ASR (W)* world age-standardized rate per 100,000 (Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [16 March 2019])

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 in low middle and low income countries, cervical cancer is a major cause of cancer death among women [1].

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 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 adenocarcinomas of endometrioid type (75–80% of all endometrial cancers). The other 20–25% of endometrial cancers include serous, mucinous, and clear cell, mixed cell, and carcinosarcoma types [10]. Endometrioid types are usually hormone sensitive and occur in women exposed to estrogens unopposed by progesterone. These types are well differentiated with mild-to-moderate nuclear pleomorphism and have a low potential for invasion and metastasis [10]. Other types of endometrial cancer are not associated with estrogen or progestogen stimulation and have a high probability of myometrial invasion and metastasis and a very poor prognosis

[11–15]. Overall, 5-year survival for endometrial cancer 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 menopausal 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 regimen. 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. In addition, 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 menopausal 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 90–95%), stromal (5%), or germ cell (less than 5%) [32]. Epithelial ovarian cancer can be further classified into the histological subtypes of serous, mucinous, endometrioid, clear cell, and Brenner (transitional cell) tumors [33].

The IARC monograph working group experts found that there is sufficient human evidence that epithelial ovarian cancer is caused by estrogen menopausal 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), Asian ethnicity, 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 an expert-based critical resource to identify agents and circumstances that increase the risk of human cancer. 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 25.2 shows the known or suspected causes of cancers of the female reproductive system abstracted from a summary of the IARC Monographs [9] and completed by a review of the online monographs (Volumes 1–123) [38]. Only one of these agents or exposure circumstances can be directly related to occupational exposure: asbestos (Group 1 agent), which is considered to be carcinogenic to the human ovary [39] (Table 25.3). 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 viruses (HIV1 and several HPV types) [38].

Cervical Cancer

No occupational exposure has yet been associated with some certainty to cervical cancer in the IARC monographs. However, there is some evidence for a few occupational exposures that will be presented here.

Tetrachloroethylene

In 1995, the IARC Working Group had classified tetrachloroethylene as probably carcinogenic to the cervix uteri based on three cohort studies with statistically significant findings [44]. Two cohort studies of dry cleaners showed an excess risk of 60–70%, based on 8 [45] and 21 deaths [46], respectively, while a cohort of workers monitored for tetrachloroethylene exposure reported two cases of cervical cancer [47]. However, a recent review of the evidence gathered since then led the IARC to judge in 2012 that the evidence was considered insufficient to make an evaluation for cervical cancer specifically [48].

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) [49] and 95% (SMR 1.95, 95% CI 1.00–3.40) [50]. 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 [51]. A 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 [52]. These studies 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

Table 25.2 Known and suspected carcinogenic agents of the female reproductive system[a], as identified in the International Agency for Research on Cancer (IARC) Monographs, Volumes 1–123

Cancer site	Agent	Overall 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 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	1	X	
	Human papillomavirus type 68	2A		X
	Human papillomavirus types 26, 53, 66, 67, 70, 73, 82	2B		X
Endometrium	Estrogen menopausal therapy	1	X	
	Estrogen-progestogen menopausal therapy	1	X	
	Tamoxifen	1	X	
	Diethylstilbestrol	1		X
Ovary	Asbestos (all forms)	1	X	
	Estrogen menopausal therapy	1	X	
	Tobacco smoking	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 completed by the *IARC Monographs* Volumes 1–123 [38]. It does not include risk factors not covered in these volumes, notably reproductive and other hormonal factors, diet and nutritional factors, and genetic susceptibility traits

[a]As of the beginning of 2019, 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

Table 25.3 Known occupational cause of cancers of the female reproductive system, as identified in the International Agency for Research on Cancer Monographs

Agent with sufficient or limited evidence in humans				
Agent	Industries/occupations	Cancer site	Range of risk ratios	References
Asbestos	World war II gas mask manufacturing	Ovary	Compared to UK population: SMR 1.48–2.75	[40]
			Compared to local population: SMR 1.74–2.96	
	Manufacturing and use of asbestos products: asbestos cement, brake pads, roof tiles, etc.		SMR 1.2 SMR 2.3	[41] [42]
	Mining and milling of asbestos fibers.		SIR 1.0–1.3	[43]
	Construction workers in insulation work, building maintenance or demolition, asbestos abatement work			

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

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, drivers, and hairdressers [45, 46, 49, 50, 53–57]. Women working in agriculture also appear to be at increased risk [54–56, 58–60], as are women exposed to tobacco flakes dust in the beedi cigarette rolling industry in India [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, and defined as holding 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 pooled analysis of three Scandinavian cohorts exposed to trichloroethylene calculated a statistically significant increase of cervical cancer incidence (SIR 2.31, 95% CI 1.32–3.75) [65], whereas a French case–control study reported a 50% increase that did not reach statistical significance [66]. Another record-linkage study showed a 48% increased risk of cervical cancer among Swedish workers exposed to diesel exhaust fumes, with suggestion of a dose–response relationship [67]. 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 [54, 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 [68]. A cohort study of automobile 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) [69].

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 [70].

In conclusion for cervical cancer, all the occupational exposures for which there is some evidence of an association still 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 for that organ. The evidence thus far accumulated indicates 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 [54, 56, 71–73], have all been associated with increased risks of endometrial cancer. A recent follow-up study of a cohort of workers exposed to insoluble beryllium compounds reported an excess of deaths from uterine cancer (SMR 302.3, 95% CI 121.5–622.9) [74]. A mortality study update of a cohort of three electrical capacitor manufacturing plants found that uterine cancer mortality increased with estimated cumulative polychlorinated biphenyls (PCB) exposure [75]. 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 crude, 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 [76]. All of these occupations are sedentary, which is consistent with the idea that physical activity may be a protective factor for endometrial cancer [77]. A recent meta-analysis reported a statistically significant reduced risk with occupational physical activity [78]. Mechanisms that are associated with a sedentary lifestyle that are also associated with cancer include insulin-related metabolism differences and weight gain [77]. However, the evidence of an association between sedentary habits and endometrial cancer risk is still limited due to the possibility of confounding in currently available studies.

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) [59]. A case–control study within a cohort of Chinese textile workers found an increased risk of endometrial cancer among women who worked in silk production for 10 years or more (hazard ratio [HR] 3.8, 95% CI 1.2–11.8) [79]. 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 endometrial 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 [56]. 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 [80].

In conclusion for endometrial cancer, no particular occupational exposure appears to definitively convey an excess risk.

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 [40]. 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 [81]. 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 1.3 million in the United States and 1.2 million in the European Union [82].

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 [83], 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 [84, 85] and from studies suggesting that asbestos can accumulate in the ovaries of occupationally exposed women [83]. 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 [84]. A smaller cohort study of another group of United Kingdom gas mask workers also showed a borderline significant increased risk of 1.8 (95% CI 0.9–3.3) of dying from ovarian cancer [85]. 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) [43].

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 [86]. 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 [87].

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) [88]. 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 [89]. 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 [89].

The available human evidence of a relationship between ovarian cancer and exposure to X-radiation and γ-radiation has been classified as limited (Table 25.2) [9], and no mention

of increased ovarian cancer risk was suggested in relation to occupational exposures by the IARC Working Group [90].

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) [71]. However, a cohort study of radiologic technologists in the United States did not report any increased risk of incidence of [91], or mortality from [92] 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 [93]. A cohort study of US workers at a 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 [94]. 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 ninth revision codes 183 and 184, SMR 1.1, 90% CI 0.76–1.56) [95]. 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 [96, 97]. 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 [56, 86, 93, 98]. 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 due to aggregate-level data and possible misclassification of exposures and job titles [86].

Hormones, Antineoplastic Drugs, or Other Pharmaceuticals

Estrogen menopausal therapy has been classified as carcinogenic to the human ovary [99], 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) [100]. A retrospective cohort study among employees with possible exposure to chemical, pharmacological, or biological agents in a pharmaceutical company in Sweden observed two cases of ovarian cancer, which was expected given the subject enrollment number [101]. A few record-linkage studies reported small or nonexistent increased risks of incident ovarian cancer in pharmacy technicians or workers in the pharmaceutical industry [56, 98, 102, 103]. A death certificate study reported an increased risk of mortality among pharmacists (mortality OR 2.4, 95% CI 1.6–3.7) [71]. 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, Pesticides, 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) [86] or that solvent use among occupations associated with ovarian cancer suggests an etiologic role of aliphatic and aromatic hydrocarbons [98]. 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) [98]. Another record-linkage study found a small increased risk for printers [56]. 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 [87]. Results for dry cleaners were inconsistent: one study reported no increase in risk of ovarian cancer in Finland [86], whereas a small increased risk was found in a Swedish study [98] of similar design. A recent follow-up of a mortality study among styrene-exposed boat-builders found an increased risk of ovarian cancer mortality which was attributed by the authors to possible asbestos exposure among boat-builders [104]. 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.

A follow-up study of the female spouses of pesticide applicators in the prospective Agricultural Health Study (AHS) cohort reported a statistically significant increase of ovarian cancer in association with organophosphate pesticide use among premenopausal women [105].

Two Finnish record-linkage studies reported a two- to threefold increased risk of ovarian cancer associated with exposure to diesel engine exhaust fumes [86, 106]; the same studies also reported a 50–70% increased risk associ-

ated 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 [54, 56, 71–73, 103]. A case–control study reported significant excess risk among teaching occupations and among bookkeepers and accounting clerks; the same study also showed increased risks for workers in certain retail stores, educational service, and non-institutional health services (adjusted OR 2.54, 95% CI 1.13–6.52) [107]. 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.) [72, 73]. 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 [59], and a multicenter case–control study found similar results for cancer incidence [108], 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) [109].

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 [110]. 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% [111]. An excess risk of the same magnitude was also reported by a recent record-linkage study [56]. 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 [112]. A longitudinal occupational study of occupation and ovarian granulosa cell tumors in the Finnish, Norwegian, and Swedish populations found no occupations associated with ovarian granulosa cell tumors [113]. In addition, a few other occupational exposures have been associated to significant excess risk for ovarian cancer, including silica dust in textile workers [114], and shift work in several industrial sectors [115], however with sparse evidence.

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, there is little solid evidence that ovarian cancer is associated with other occupational exposures, although carefully designed studies adjusting for potential confounding factors are still needed for exposures to occupation-specific agents.

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 25.2). 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 as a group. A few earlier studies that could not adjust for non-occupational risk factors reported increased mortality risks of several of these rare cancers for seafarers [116].

The largest study on occupation and risk of primary fallopian tube carcinoma was done using census data in Denmark, Finland, Iceland, Norway, and Sweden. Significantly increased risks of primary fallopian tube carcinoma were observed for smelting workers (SIR 3.99, 95% confidence interval 1.46–8.68), artistic workers (2.64, 1.44–4.43), hairdressers (2.18, 1.41–3.22), packers (1.62, 1.11–2.29), nurses (1.49, 1.14–1.92), shop workers (1.25, 1.07–1.46), and clerical workers (1.20, 1.07–1.35), indicating a possible role for occupational exposures. Notably, this study was also able to adjust for reproductive and lifestyle risk factors [117]. One record-linkage cohort study of Swedish hairdressers reported no increased risk for cancers of the female reproductive system other than ovarian, cervical, and endometrial cancers [57].

An earlier record-linkage study reported elevated SIRs of less than 20% for cancer of the vulva among domestic assistants and building caretakers [56]. 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 = 2.19; $P < 0.05$) and workers in laundry, cleaning, and other garment services (OR = 4.65; $P < 0.05$) [118].

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 [56].

Using the same study design, Riska and colleagues reported two- to fourfold increased risks of fallopian tube cancer among smelting workers (based on six cases), artistic workers ($n = 14$), and hairdressers ($n = 25$) [117]. The authors stressed that their results must be validated by studies with individual information on confounding factors, such as socioeconomic status, reproductive history, and lifestyle factors [117].

Finally, an elevated risk of choriocarcinoma has been reported among nurses (based on four cases) and agricultural workers ($n = 2$) in a Finnish record-linkage study [119]. 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) [120].

In conclusion for the other cancers of the female reproductive system, there is no established evidence of increased risks from occupational exposures. However, conducting studies on these rare cancers is a challenge, considering the small case numbers and lack of available variables on potential confounding factors per individual.

Conclusion

A few studies suggest that some occupational exposures are associated with increased risks of female reproductive system cancers. Apart from the evidence for asbestos fibers on the risk of ovarian cancer, the link is not well established. As lifestyle habits are known to play a major role in the etiology of these cancers, most published case–control studies did not gather information on occupational history. Given the complex nature of female reproductive system cancers, it is imperative to conduct occupational studies that can adjust for individual confounding factors, in particular reproductive history, female hormone use, socioeconomic status, and lifestyle factors, including physical activity.

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Malignant Tumours of the Male Reproductive System

26

Fabrizio Giannandrea

Introduction

Prostate cancer and testicular cancer are the main tumours of the male reproductive system. For both cancers, their incidences have been rising worldwide in last decades. Interestingly, these two tumours appear to be specular in their reverse hormonal and epidemiologic characteristics. Prostate cancer is commonly diagnosed among the elderly and rare in younger ages and, by contrast, the incidence peak of testicular cancer is registered among young adults, which may suggest that causal factors for testicular cancer could play a role at an earlier stage of life than prostate tumour. With regard to ethnicity, the incidence of prostate cancer is the highest among native African populations and their African-American counterparts. Conversely, Africans have lower incidence of testicular cancer than the Nordic populations.

Several epidemiologic studies have suggested that prenatal exposure to oestrogens could enhance the risk of testicular cancer. Recently, other studies have investigated the association between a number of 'proxy' of endogenous androgen levels (i.e. baldness and severe acne) and the risk of testicular cancer, suggesting a role of androgens in lowering the risk of such tumour. In addition, findings of greater testosterone levels in black mothers led to the hypothesis that lower risk of testicular cancer in black men may be determined by higher maternal testosterone concentrations.

In contrast, androgens and androgen receptor polymorphism seem to have an opposite and causative role with regard to prostate cancer aetiology. In fact, Africans have fewer CAG repeats and a higher incidence of prostate cancer than Caucasians. One possible explanation could be that the average shorter length of the polymorphic polyglutamine stretch in the androgen receptor among Africans may be slightly more efficient in activating transcription. Further and indirect evidence that androgens are implicated in prostate carcinogenesis is obtained by large clinical trials on the ability of 5α-reductase inhibitor finasteride to reduce the risk of prostate cancer.

Notwithstanding these hypotheses on the role of non-modifiable risk factors for these tumours appear suggestive, their aetiology remains largely undetermined. Recent emerging evidence suggests that exposure to some modifiable risk factors might also promote prostate cancer and testicular cancer, including lifestyle-related factors and certain occupational exposures.

Prostate Cancer

Descriptive Epidemiology

Prostate cancer ranks second among cancer affecting men throughout the world, with an estimated 1.1 million new cases according to GLOBOCAN 2012, and it is the most commonly diagnosed tumour among men beyond middle age, with about 80% of the cases diagnosed at 65 years of age or older (Fig. 26.1) [1]. Almost 70% of the cases of prostate cancer have registered in more developed regions such as the USA and the Scandinavian countries [1, 2]. In South and Central Asia, the incidence rate for prostate cancer was reported as the lowest in the world (4.5 per 100,000). In GLOBOCAN 2012, prostate cancer resulted as the fifth most common cause of death worldwide (307,000 deaths, 6.6% of the total men deaths) [1]. Mortality rates are relatively high in North America, Northern Europe (i.e. ASR: 25 per 100,000), Australia, New Zealand, and African-American populations (i.e. sub-Saharan Africa ASR: 19–24 per 100,000), and very low in Asian populations (i.e. ASR: 2.9 per 100,000 in South-Central Asia) [1]. An estimation by Quon et al. (2011) projected that incidence rates will raise from 25,355 new cases in 2009 to 35,121 new cases by 2021 [3]. In recent decades, the introduction of prostate-specific antigen (PSA) testing has produced a massive detection of low-grade prostate tumours in asymptomatic men [4]. This has led to a worldwide substantial increase in the incidence of prostate cancer and significantly changed its epidemiologic

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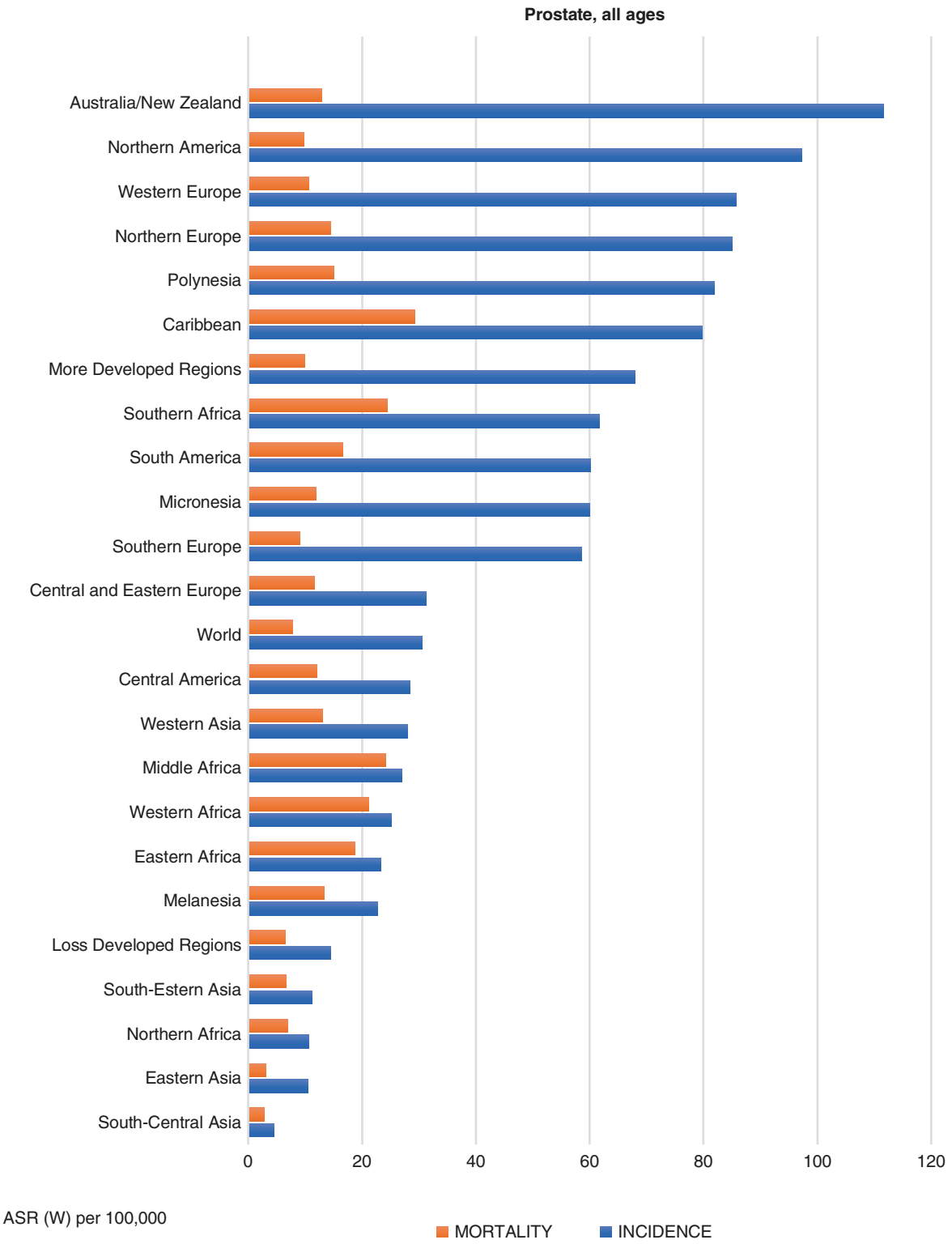

Fig. 26.1 World age-standardized incidence and mortality rates of prostate cancer in different world regions. GLOBOCAN 2012 [1]

portrayal. PSA screening which improved early diagnosis of the tumour has also conducted to a fall in prostate cancer-specific mortality and highly aggressive tumours [4]. In turn, the high sensitivity of PSA and the subsequent overdiagnosis of prostate cancer have led to overtreatment of cases that would not have produced clinical effects if untreated, causing needless side effects that could dramatically affect a man's quality of life [4]. Mortality rates are less influenced than incidence by the effects of early diagnosis weather through PSA-testing or by detection in tissue analysed during biopsy [4].

Non-modifiable Risk Factors for Prostate Cancer

It has hypothesized that the initiation of preneoplastic prostatic malignancies is significantly influenced by genetic–environmental interactions. Advanced age generally over 65 years, race particularly Black-African ethnicity and family history of prostate cancer are all non-modifiable risk factors that are strongly associated with the risk of prostate cancer. Racial factors are particularly manifest within the USA, where the Black-African population has incidence rates from 35 to 50% greater than Caucasians and approximately 60 times higher than the South-Central Asian population, where rates are lowest [5]. According to GLOBOCAN 2012, specific incidence rates worldwide ranged from 97.2 per 100,000 in North America, 85.0 per 100,000 in Northern Europe, 79.8 per 100,000 in the Caribbean, 61.7 per 100,000 in Southern Africa, and 4.5 per 100,000 in South-Central Asia [1]. Powell suggested in a review that prostate cancer is genetically more aggressive in African-American men compared to European-Americans [6].

Age is an established risk factor for prostate cancer. Approximately three-quarters of cases in the world are diagnosed in men aged ≥65 years, and diagnosis of prostate cancer is rather uncommon among men aged younger than 50 years [7]. In many developed countries, incidence rates increased exponentially with growing age. For example, the incidence rate of prostate cancer in the year 2008 in Canada was around 100 per 100,000 in men aged 50 to 54, 500 per 100,000 men aged 60 to 64 and 700 per 100,00 in men aged beyond 80 [8].

Another established and non-modifiable risk factor for prostate cancer is family history for such tumour. The number of relatives with prostate cancer and their age at diagnosis could significantly influence the early development of prostate cancer [9]. A number of studies have observed familial association, reporting two- to threefold statistically significant increased risk among men with first-degree male relatives (father, brother, son) who have a history of prostate cancer [9, 10]. Fradet et al. found a 20% enhanced risk of prostate cancer among men whose fathers had diagnosed prostate cancer before age 60 years compared with men without history [8–10].

The role of sex hormones, especially androgens, is significant on development, but the endocrine basis for carcinogenesis is still not well clarified and genetic polymorphism in the androgen receptor may be more significant than any difference of hormones [11]. Circulating insulin-like growth factor 1 (IGF-1) is a probable risk factor for prostate cancer and several systematic review and meta-analysis concluded that increased IGF-1 levels increase the risk of aggressive prostate cancer, in particular of aggressive disease [11].

Lifestyle-Related Factors for Prostate Cancer

Diet also play a significant role as suggested by studies showing association between the consumption of dairy products especially milk, processed meat and fat intake, and the increase in the risk of prostate cancer [12–14]. Diet can influence circulating hormone levels, by affecting steroid hormones status. High intake of fat has been associated with increased risk of prostate cancer. Armstrong and Doll (1975) found that international incidence rates of prostate cancer in 1960–1966 in the 35–65-year-old age group was associated significantly with intake of total fat [15]. A traditional western diet rich in fats and cholesterol levels raises the risk of prostate cancer [14]. Obesity and increased body mass index has been widely investigated in relation to prostate cancer in systematic reviews and meta-analyses resulting in a positive association with the risk of advanced grade of cancer [16, 17].

In turn, there is some evidence that foods containing the vitamins A, E, and D, selenium, and lycopene may exert a protective effect on cancer development [12–14].

Smoking as a risk factor for prostate cancer is still considered a controversial matter. However, prospective cohort studies of prostate cancer mortality reported a dose–response association with cigarette smoking, showing that heavy smokers (i.e. >40 cigarettes per day) had 51–61% increased risk of dying from prostate cancer [18–20].

Occupational Risk Factors for Prostate Cancer

Several studies have been conducted on occupational risk factors for prostate cancer. Of these, farmers received greater interest. A study reviewing 216 occupations and 88 industries of men died between 1950 and 1984 in British Columbia has found an excess mortality from prostate cancer among farmers [21]. A population-based case-control study conducted in South Carolina reported a 60% increase in risk for prostate cancer among farmers who mixed or applied pesticides [22–24]. In this study, farming was also associated with higher risk of prostate cancer among white Caucasians (OR = 1.8), but not among African-Americans. Overall, elevated risk for prostate cancer has been associated with occupational or leisure exposure to pesticides and higher incidence and mortality rates for such tumour have been reported in several cohort studies of pesticide applicators.

The majority of the recent evidence is emerging from the Agricultural Health Study [22–24]. One of such studies show that private pesticide applicators had raised the risk of prostate cancer (SIR = 1.26) while commercial applicators had a slightly higher risk (SIR = 1.37) [22–24]. A case-control study conducted in Canada found a ~ 100% increase in the risk of prostate cancer (95% CI = 1.3–4.2) for those exposed to pesticides or garden sprays during leisure [25]. Van der Gulden et al. (1996) reported an excess in risk in relation to frequent pesticide exposure [26]. A case-control study noted an increased risk of prostate cancer among farmers exposed to organochlorine insecticides and acaricides including DDT (OR = 2.5, 95% CI = 1.4–4.2) [27]. Although these studies show an association between pesticide exposure and prostate cancer, their conclusions are limited as mainly based on self-reported data and subjective assessment. In order to avoid the recall and misclassification bias of self-reported exposure assessment, serum levels of organochlorines has used in recent years as surrogate measures of long-term exposure to pesticides. Organochlorines comprise pesticides, such as DDT, DDE, and lindane. Many pesticide organochlorines are recognized endocrine disrupters and may control steroid sex hormones as agonists, antagonists, or as mutually agonist-antagonists, principally with regard to oestrogen or testosterone action. Ritchie et al. (2003) have evaluated the relationship between serum levels of pesticide organochlorines and risk of prostatic cancer, finding that pesticide oxychlordane (OR = 3.1, 95% CI = 1.3–7.6) was associated with an increased risk of prostate cancer [28]. A study evaluating adipose tissue levels of persistent pesticides found a significant increase in prostate cancer risk based on levels of trans-chlordane (OR = 3.49) and increased risk for several pesticides or their metabolites including HCB (OR = 2.39), p,p′ DDE (OR = 2.30), and a number of chlordane metabolites [28, 29].

Preliminary studies on Vietnam veterans occupationally exposed to Agent Orange, an herbicide contaminated with dioxins, have shown an increase in prostate cancer mortality [30]. However, recent data of the Air Force Health Study from the Ranch Hand veterans who were responsible for handling and spraying Agent Orange have not reported an overall increased risk of prostate cancer [30]. Conversely, the study reported a significant increased risk of prostate cancer among veterans who served prior to 1969 (RR = 2.37) and a significant dose–response trend in prostate cancer risk associated with increasing years of service in Southeast Asia [30].

A cohort study of workers in the sector of electrical capacitors manufacture showed a dose–response trend for prostate cancer mortality with increasing cumulative exposure to PCBs that were significant at 10-year and 20-year exposure lags [31]. In another study investigating adipose levels of persistent organic pollutants, levels of PCB 153 were related with prostate cancer (OR = 3.15) [32].

Several studies have explored the relationship between exposure to cadmium compounds and prostate cancer. Cadmium was found in relatively high concentrations in prostate tumour tissue and cadmium compounds have been reported to cause prostate cancer in rats in many animal studies [33].

However, results of case-control studies show somewhat inconsistencies among studies, except for a case-control study, which reported that the risk of prostate cancer was significantly associated with exposure to cadmium contained in toenails at the highest concentrations (OR = 4.7) [34]. A 2005 meta-analysis of cohort studies of nickel-cadmium battery plant workers produced an SMR of 1.26 (95% CI: 0.83–1.84) [33]. The following cohorts using quantitative estimates produced also inconsistent results.

Recent data significantly reinforces the evidence concerning the role of genetic polymorphism in the association between PAH exposure and prostate cancer [35]. No significant increased risk of prostate cancer was identified associated with cumulative PAH exposure from different occupational groups, although risk was slightly elevated based on PAH exposure via inhalation to petroleum (OR = 1.12), coal (OR = 1.29), and via percutaneous exposure to coal (1.48) [35]. However, in this same study, a gene–environment interaction was observed associated with a polymorphism in the GSTP1 gene such that men under age 60 who carried the GSTP1 Val variant and were exposed to high levels of PAHs were at a significant increased risk of prostate cancer (OR = 4.52) [35]. Exposure to PAHs among aerospace workers resulted in a slight non-significant increased risk of prostate cancer, but only among those highly exposed.

Additional studies examining specific occupations and/or exposures and risk of or mortality from prostate cancer found significant elevations among firefighters. Two meta-analyses of studies of firefighters and prostate cancer have been conducted [36]. The most recent meta-analysis included a great majority of the studies examined by the IARC Working in the Monograph on firefighters. The IARC Working Group performed a meta-analysis using 16 available studies and 1764 cases until 2007, which produced an estimated 30% excess in the risk of prostate cancer (1.30; 95% CI: 1.12–1.51) in this occupational population [36].

The IARC Monograph on shift work assessed studies on airline pilots and reported a significantly elevated incidence of prostate cancer in their earliest studies [36]. However, these results may be limited by the possible detection bias due to the diffusion of PSA-testing in this occupational group. A meta-analysis of cohort studies published by Ballard et al. in 2000 found evidence of an excess risk of 65% (1.65, 95% CI: 1.19–2.29) of prostate cancer among flight personnel [37]. Pukkala

et al.'s reported an SIR of prostate cancer of 1.21 (95% CI: 0.93–1.54) among 10,000 pilots in the Nordic countries [38].

Lastly, systematic reviews on prostate cancer risk in relation to metal working concluded that there was no evidence of an association [39]. Prostate cancer was modestly associated with exposure to metal fumes (RR = 1.11) in the Netherlands Cohort Study and also in a case-control study in Western Australia. The association between exposure to metalworking fluids/mineral oils and increased risk of prostate cancer was further evaluated in a study of workers in the auto industry. This study demonstrated an increase of prostate cancer risk occurring at the highest exposure level of 270 mg/m^3-years to straight fluids (RR = 3.41) [40]. A study using data from this same cohort of auto-industry workers, the risk of prostate cancer increased linearly with exposure to straight fluids from puberty to early adulthood (RR = 2.4 per 10 mg/m^3 years of cumulative exposure) showing that early adulthood exposures are critical to prostate cancer risk later in life [40].

Testicular Cancer

Descriptive Epidemiology

Testicular cancer is currently the most common diagnosed malignancy in men aged 15–40 years [41–44]. Its incidence has been increasing over the past 40 years in several western regions [41, 42]. Explanations for this rise are not completely understood although enhanced diagnostic measures may be only in part responsible. The incidence peak of testicular cancer among young adults may suggest that underlying factors could play a part at an early stage of life. Although it has been proposed for decades that rise in endogenous oestrogen levels in pregnancy and/or prenatal exposures to numerous occupational and environmental oestrogenic substances, such as endocrine-disrupting chemicals (EDCs), is mostly responsible for its onset; this notion is still argued [44]. Latest research has proposed that environmental exposures occurring in infancy and childhood may also contribute to the development of testicular cancer, and that factors related to child growth might be deeply involved in testicular cancer progression. Approximately 98% of all testicular malignancies are germ cell tumours. Although there are several histologic types of testicular cancer, around 55% may be classified as classic seminomas, 44% as non-seminomas (embryonal carcinomas, teratomas, yolk sac tumours, choriocarcinomas), and 1% as spermatocytic seminomas [43]. According to GLOBOCAN 2012, specific incidence rates worldwide ranged from 7.2 per 100,000 in Northern Europe, 5.0 per 100,000 in Northern America, 1.0 per 100,000 in the Caribbean, 0.9 per 100,000 in South-Central Asia, and 0.6 per 100,000 in Southern Africa (Fig. 26.2) [1]. While incidence rates have increased, the type of cancer has persisted, as no differences in rise have been described between seminoma and non-seminoma [43].

Non-modifiable Risk Factors for Testicular Cancer

As discussed for prostate cancer, there are a number of non-modifiable risk factors that are significantly associated also with the risk of testicular cancer.

The most consistently identified risk factor associated with testicular cancer is cryptorchidism, which increases a man's risk of testicular cancer development by nearly five-fold [44]. Familial testicular cancer is also an established risk factor for developing the disease. Studies have estimated that brothers of testicular cancer patients have an eight- to ten-fold increased risk of gaining testicular cancer, whereas the fathers/sons have a four- to sixfold increase in risk [44].

Several studies have reported that increased adult height may be a risk factor for testicular cancer, thus suggesting that factors related to tallness may also be related to the risk of this malignancy [45]. Dieckmann et al. (2008) found that very tall men (>195 cm) carried a testicular cancer risk of OR: 3.35 (95% confidence intervals, CI: 2.88–3.90; adjusted) [46]. In the STEED Study, there was a statistically significant increased risk of testicular cancer linked with greater height, and this association was principally evident in men with seminomas [44].

One height-related factor may be insulin-like growth factor (IGF) and the IGF pathway [45]. Increased serum IGF-1 concentrations were associated with increased height has also been described in several studies. However, the associations among height, IGFs, and the risk of testicular cancer are likely to be complex and not simply explained [47].

With regard to ethnicity, the incidence of testicular cancer in African-Americans resulted only one quarter of that reported among white Americans. Findings of greater testosterone levels in black mothers led to the hypothesis that lower risk for testicular cancer in black men may be determined by higher maternal testosterone concentrations [48]. Another possible explanation could be a difference in the length of the polymorphic polyglutamine stretch in the androgen receptor, which is on average shorter among Africans and possibly more effective in activating transcription [49]. The risk of native African populations has not changed by much with migration to a new environment. Differences in incidence persisting after migration argue in favour of genetic rather than exogenous risk factors.

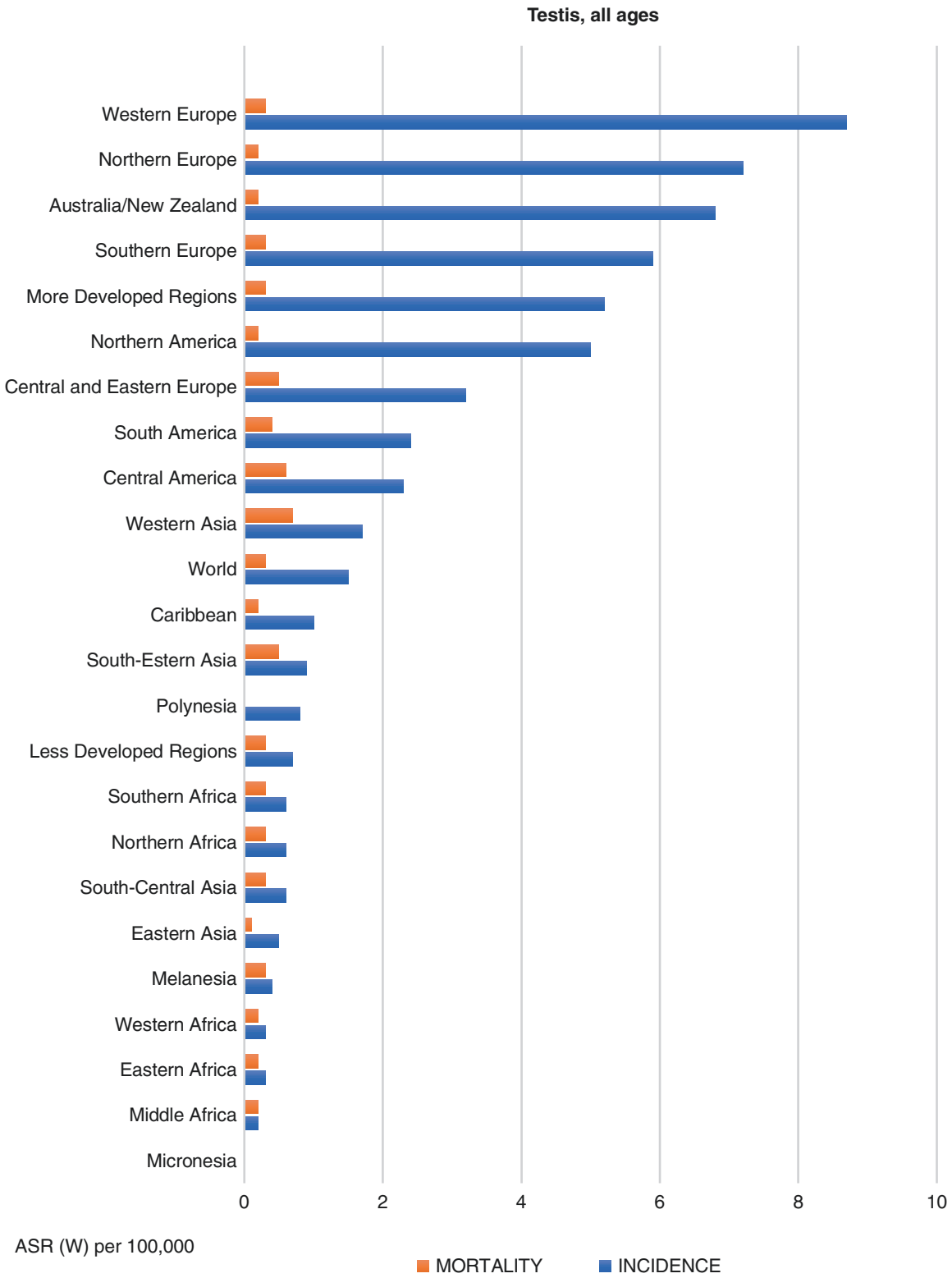

Fig. 26.2 World age-standardized incidence and mortality rates of testicular cancer in different world regions. GLOBOCAN 2012 [1]

Lifestyle-Related Factors for Testicular Cancer

Diet has received the greatest attention among lifestyle-related factors possibly related to testicular cancer [44]. High intake of fat has been associated with increased risk of testicular cancer, a result consistent with findings also concerning other hormone-related cancers such as breast, prostate, and ovary. In their ecological study, Armstrong and Doll (1975) found that international incidence rates of testicular cancer in 1960–1966 in the 35–65-year-old age group correlated strongly with consumption of total fat ($r = 0.76$) [15]. Other ecological studies found similar associations with dietary fat and high calorie intake. Sigurdson et al. (1999) found that high fat consumption 1 year before diagnosis of testicular cancer was associated with an increased risk of testicular cancer [50]. Testicular cancer was also associated with consumption of dairy products. Dairy products, particularly milk and cheese, contain the female sex hormones oestrogen and progesterone. Garner et al. (2003) found that high dairy product intake 2 years before interview was associated with an increased risk of testicular cancer [51]. Davies et al. (1996) also observed in a case-control study of diet and testicular cancer that the cases had consumed significantly more milk during adolescence than controls [52]. In Stang et al. [53] study, adolescent dairy product consumption (with the exception of yoghurt) and especially milk was a risk factor for testicular cancer, especially for seminoma. They found an increasing risk for seminoma with increasing milk fat intake and an even stronger association between galactose consumption and seminoma especially in the younger men (age 15–34 years). In an ecological study of testicular cancer rates in 42 countries and their dietary practices, Ganmaa et al. (2002) found that cheese, animal fats, and milk were highly correlated with the incidence of testicular cancer at ages 20–39 [54]. The correlation coefficient was highest when calculated for cheese consumed during the period 1961–1965 (maternal or prepubertal consumption). Furthermore, stepwise multiple regression analysis revealed that milk + cheese (1961–1965) were associated significantly with the incidence of testicular cancer [54]. The notion that the diet of children might be associated with testicular cancer risk originated from several epidemiological observations of constantly increasing incidence of testicular cancer since the beginning of the twentieth century with the only major interruption in this trend occurring for men born during World War II or immediately thereafter, when food availability had been dramatically reduced [55]; it is also well-known from both animal and human studies that dietary restriction during early life does in general reduce adult cancer risk; moreover, it has been proven that poor and nutritionally underprivileged populations such as African, including US blacks, and Asian populations experience a lower testicular cancer risk than more affluent people.

Occupational Risk Factors for Testicular Cancer

Testicular cancer has often viewed as a cancer of the youth due to both its prevalence in the younger age and the persistence of theories supposing its prenatal origin. Therefore, less attention was focused on risk factors occurring during adulthood, such as in particular occupational exposures. However, a number of jobs and occupational risk factors have recently been suggested as entailing significant increased risk of testicular cancer. In particular, reviews and meta-analyses have associated the risk of testicular cancer with employment as firefighter, farmer, soldier, and jobs involving occupational exposure to pesticides. In addition, there are a number of other jobs and industries that have been suggested to involve an increased risk of testicular cancer, including flight personnel, metal workers, and painters. However, findings for these jobs are still limited, and studies are often scarce.

The current findings available from the literature suggest that the increase in testicular cancer incidence in recent decades could, at least in part, be related to the accumulation of some pesticides in the environment. Several pesticides have been classified as endocrine disruptors since they may mimic the actions of oestrogens or have anti-androgenic effects. Exposure to these compounds has recently been suggested to elevate the risk of testicular cancer by interfering with the regular hormonal balance of the subject. Many occupational pesticide studies are designed to examine mortality rather than the incidence of testicular cancer and find conflicting results. Considering the recent improvements in therapy, mortality rates due to testicular cancer have declined sharply in developed countries, while its incidence has more than doubled over the past four decades. Therefore, the use of mortality rates should be considered suboptimal for the study of testicular cancer. Several incidence studies revealed that long periods of exposure to pesticides significantly increased the risk of testicular cancer. Guo et al. [56] found positive exposure–response relationships between testicular cancer and occupational exposure to pesticides, particularly for insecticides ($\geq$0.002 mg/m^3-years; relative risk (RR) = 3.26, 95% confidence interval (CI) = 1.20–8.83), with significantly elevated standardized incidence ratios (SIRs) after 10- and 20-year lag periods of exposure [56]. The incidence of testicular cancer was also significantly elevated among licenced pesticide applicators in Florida during follow-up in the period 1975–93 (SIR = 2.48, 95% CI = 1.57–3.72) (Table 26.1) [57]. The SIR for testicular cancer was significantly increased with ‘time since licence’ >10 years in pesticide applicators in Swedish agriculture (SIR = 2.54, 95% CI = 1.1–5.00) [58, 59]. The Agricultural Health Study showed a slight increase in the risk of testicular cancer (without statistical significance) among commercial applicators; but only 11% of this group had applied pesticides for periods >20 years [60, 61].

Table 26.1 Cohort incidence studies on pesticide users and applicators and testicular cancer

Reference, study location and period	Cohort description	Exposure assessment	Number of observed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Fleming et al. (1999), Florida, United States [57] 1975–1993	30,155 licensed private, commercial, or public pesticide applicators	Registered licensees	Private applicators: 15	2.48 (1.57–3.72)	Age, period	Herbicide use: 20% in the 1950s, 51% in the 1960s, 68% in 1970s
Ditch et al. (1995), Sweden [58, 59] 1965–1991	20,025 licensed pesticide applicators	Registered licensees	21	1.09 (0.68–1.67)	Age, period	Insecticide use: 15% in the 1950s, 34% in the 1960s, 46% in the 1970s
		268 applicators interviewed on the use of pesticides				Fungicide use: 7% in the 1950s, 16% in the 1960s, 31% in the 1970s
Koutros et al. (2010), Iowa and North Carolina, United States [60, 61] 1993–2006	Agricultural Health Study (AHS) cohort	Questionnaire at recruitment	Private applicators: 32	0.97 (0.67–1.37)	Age, period, race, country	Individual pesticides have been studied within the AHS cohort but power was too limited for testicular cancer
	Licensed private (51,035) and commercial (4712) male pesticide applicators		Commercial applicators: 6	1.21 (0.45–2.64)		
Frost et al. (2011) United Kingdom [62, 63] 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	
MacFarlane et al. (2009), New South Wales State, Australia [63] 1983–2002	1813 pest controllers using pesticides	Workers participating in a pesticide surveillance program offered by the state	6	1.98 (0.89–4.41)	Age, period	

RR relative risk, *CI* confidence interval

Recently, Frost et al. (2011) found significantly elevated incidence of testicular cancer in British users of pesticides followed up between 1987 and 2004 (SIR = 1.26, 95% CI = 1.04–1.53), with a non-significant increase in mortality (Table 26.1) [62, 63]. A recent review noted that increased serum levels of organochlorine pesticides were consistent with a positive association with testicular cancer, with the two studies that included pre-diagnostic serum samples providing the strongest evidence [64].

The possible causal relationship of testicular cancer with long-term pesticide exposure is also corroborated by the accumulation of these chemicals over time in the serum of subjects with testicular cancer. To date, six case-control studies have examined the association between serologic measures of organochlorine pesticides and testicular cancer. The results were indicative of a positive association in five of the six studies for p,p'-DDE (Dichloro-diphenyl-trichloroethylene), a metabolite of DDT which is a potent androgen receptor antagonist commonly used as a pesticide until it was banned in the 1970s–1980s, and chlordane and its derivatives (oxychlordane, trans-nonachlor, cis-nonachlor) [65–68]. None of these studies none have found evidence for an association with the fungicide, hexachlorobenzene (HCB). The case-control study (49 cases, 51 controls) nested within the Norwegian Janus Serum Bank cohort detected very high levels of p,p′-DDE and chlordane compounds using pre-diagnostic blood samples [65–68]. The U.S. Servicemen's Testicular Tumor Environmental and Endocrine Determinant (STEED) Study, a large case-control investigation of testicular cancer (754 cases, 928 controls) conducted among US servicemen, found elevated pre-diagnostic concentrations of p,p′-DDE and chlordane compounds among cases versus controls. In this study, the association for serum p,p′-DDE was statistically significant in the highest quartile of exposure (OR 1.71, 95% CI 1.23–2.38, p trend = 0.0002) [65–68]. In a Swedish hospital-based study of 58 cases and 61 controls, cases were found to have higher serum levels of p,p′-DDE, although the association was not statistically significant, and significantly higher serum concentrations of both trans-nonachlor (OR 4.1; 95% CI 1.5–11) and cis-

nonachlor (OR 3.1; 95% CI 1.2–7.8) among cases compared with controls [66, 68]. Biggs et al. (2008) found no evidence that the risk of testicular cancer was associated with serum DDE and HCB [67]. A hospital-based case-control study conducted in Italy found elevated concentrations of p,p′-DDE in testicular cancer diagnosed cases, compared with controls ($OR_{adjusted}$ = 3.34, 95% CI = 1.09–10.17) [69, 70].

A number of studies have focused on testicular cancer in firefighters. Bates (2007) investigated testicular cancer in firefighters for which the OR was reported as 1.54 (1.18–2,02) [36]. Four cohort studies that examined testicular cancer in firefighters produced risk estimates that ranged from 1.2 to 2.5. In the IARC Monograph on firefighters, the IARC Working Group provided a meta-analysis based on six studies published until 2007 and 409 cases, which resulted in an approximate 50% increased risk of testicular cancer (1.47; 95% CI: 1.20–1.80) in this occupational population [36].

A 2007 IARC Monograph evaluated the possible association of testicular cancer with painting activities, but no association was found for painters. In the same monograph was also investigated the role of shiftwork in relation to testicular cancer risk. Night shift work produces altered levels of melatonin and may interfere with the normal hormonal balance [36]. Except for a case-control study from the Czech Republic that showed an odds ratio of 1.48 (95% CI: 1.07–2.06) for testicular cancer among subjects who worked on night shift for at least 3 years before diagnosis, data so far at hand are somewhat scarce [36].

Several studies have focused on testicular cancer in military personnel with inconclusive results. A number of inconsistent findings were reported in studies on navy personnel and the US Navy. Tarone et al. (1991) observed an increase in the risk of non-seminoma tumours associated with service in the Vietnam War, but not with Agent Orange exposure during the Vietnam War [71]. US veterans serving at the Gulf War have been studied for testicular cancer risk, with no evidence of an increased risk of such tumour in comparison with non-Gulf War veterans and the general population.

Conclusion

Testicular cancer and prostate cancer are the most frequently occurring malignancies, respectively, among young men and the elderly in the western world, and substantial effort has been expended to link their differences in incidence rates with reproductive, genetic, endocrine, and environmental factors [44]. Firefighting, long-term use and exposure to pesticides, and exposure to specific organochlorine compounds as well are likely to be associated with testicular cancer (Table 26.2) [72]. Exposure to pesticides is the main occupational risk factor of interest also for prostate cancer although the evidence of an association is still debated. The last decades have witnessed an explosive growth in the research on prostate cancer and testicular cancer, and current scientific research shows a possible link between pesticides and other environmental exposures with endocrine-disrupting activity and the risk of these tumours which should be further investigated. Future epidemiologic studies need to improve their methods in exposure assessment and consider the synergistic effect of exposures from environmental xenoestrogens and sex hormones, assessing the possible additive role from androgen secretion acting in cancer development of both these tumours.

Table 26.2 Modifiable and non-modifiable risk factors for testicular cancer

	Non-modifiable risk factors	Modifiable risk factors (lifestyle-related and occupational risk factors)
Certain	Age	
	Cryptorchidism	
	Ethnic group	
	Family history	
	Contralateral testicular cancer	
Likely to be associated	Height	Firefighting
		Long-term pesticide exposure
		Some organochlorine compounds
Possibly to be associated	Low birth order/ sibship size	Aircraft maintenance
	Low birth weight	Diet
	Twinning	Ionizing radiation
	Age at puberty	Military service
	Subfertility	

Modified from McGlynn et al. [72]

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Kidney Cancer

27

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Introduction

Malignant tumors of the kidney account for approximately 2% of all new primary cancer cases diagnosed in the USA 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 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.

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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 27.1) [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) 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

Table 27.1 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)
Cohort studies					
Axelson et al. (1994) [52]	Cohort study of men ($N = 1670$) 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-7180; $N = 6$). 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 1670 total subjects 1727 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 2050 male and 1924 female workers from Finland	Cancer incidence follow-up from 1967 through 1992. Various cancers evaluated including kidney (ICD-7180; $N = 7$). 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 8974 total subjects 3089 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-9189; $N = 5$). 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, 4733 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 3814 male uranium processing workers in Ohio, USA	Cancer mortality follow-up from 1951 through 1989. Various cancers evaluated, including that of the kidney (ICD-8189; $N = 5$). 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 3814 total subjects, 2971 assumed to be exposed to TCE	Never/ever exposed to TCE	Ever exposed to TCE SMR = 0.65(0.21–1.51)

(continued)

Table 27.1 (continued)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95% CI)
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-9189.0–189.2; $N = 125$ 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, 2267 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)
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-7180; $N = 4$, 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-9180.0–189.2; $N = 17$). 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, 1111 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)

Table 27.1 (continued)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95% CI)
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-8189; $N = 15$). 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 7204 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 collect 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-8189.0) cases and 161 hospital-based controls	Questionnaires used to collect 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 3014 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)

(continued)

Table 27.1 (continued)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95% CI)
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 1202 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 collect 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 collect 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 antihypertension 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 4298 population-based controls	Questionnaire and interviews used to collect 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
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 collect 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)

Table 27.1 (continued)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95% CI)
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 collect 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 1097 RCC cases and 1476 hospital-based controls	Interviews and occupation-specific questionnaires used to collect 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 (<1080/1080+ 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

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 1097 RCC cases and 1476 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 27.2), and results have 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 1723 cases and 2309 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 1279 cases and 5370 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.

Table 27.2 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-9189.0; *N* = 489) and renal pelvis (ICD-9189.1; *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-9189.0; *N* = 1732) 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* = 2309) 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-9189.0; *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

(continued)

Table 27.2 (continued)

Reference (year)	Study type and location	Cases	Controls	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)	Adjustment
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* = 1279) cases from eight Canadian provinces identified from cancer registries	Population-based controls (*N* = 5380) 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 collect 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, 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
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* = 1097) cases, 20–88 years old, identified from local participating hospital centers	Hospital-based controls (*N* = 1476) 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, ≤1230 h, >1230 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 ≤1230 h OR = 1.43 (0.70–2.93), >1230 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

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 1100 cases and 1500 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 (*ALAD1*, *ALAD2)* [single nucleotide polymorphism (SNP) 1,800,436], 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 *ALAD2* 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 (K68 N) [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 die-

sel exhaust and kidney cancer in humans have produced mixed results [128–136]. A small but significant increase in kidney cancer risk (N = 2243, 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 2557 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 4008 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 and comorbidities). 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.

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Bladder Cancer

28

Manolis Kogevinas

Introduction

Tumors of the urinary bladder contribute significantly to the overall human cancer burden with approximately 550,000 new cases per year worldwide (http://gco.iarc.fr/today/home). Of those, around 425,000 occur in men, and about two-thirds occur in high income countries. Occupation has been identified, after smoking, as the second important risk factor for bladder cancer, and several exposures, occupations, and industries have been associated with increased bladder cancer risk. Aromatic amines (benzidine, 4-aminobiphenyl, b-naphthylamine, *ortho*-toluidine) in dyestuff manufacture and in the rubber and other industries are specific agents in the workplace which have been unequivocally associated with bladder cancer. Exposure to polycyclic aromatic hydrocarbons (PAHs) in aluminum process workers and other industries has also been clearly associated with bladder cancer. Excess risks have been observed among painters, machinists and other metal workers, workers in the textile industry, printers, hairdressers, dry cleaners, and transport workers. Exposures associated with the increased risk in these occupations/industries include PAHs, industrial oils/cutting fluids, diesel engine exhaust, paints, dyes, chlorinated hydrocarbon solvents, and metals.

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. An extensive review of the international evidence throughout the last decades was recently published [1]. A review of the evidence based on the IARC evaluations has been recently published [2]. 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 28.1.

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 [58]. 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 [14, 59] in the UK dyestuff manufacturing workers. Exposure to 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 [9]. Numerous other studies in dyestuff manufacture including auramine and magenta production have confirmed these findings [58] and provided, for example, exposure–response analyses [60]. In exceptional situations extremely high risks were described, with all 15

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Table 28.1 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) [3]; 100 F (2012) [4]	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 [5], 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 [6] 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 [7]. A recent follow-up of the Canadian cohort continued identifying an increased risk for bladder cancer incidence (197 cases, SIR = 1.8, 95% CI 1.6–2.1) [8]
4-Aminobiphenyl	99 (2010) [9]; 100 F (2012) [4]	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 [10]
Arsenic and inorganic arsenic compounds	84 (2004) [11]; 100 C (2012) [12]	Bladder cancer risk has been associated with exposure to arsenic through drinking water in Taiwan, Chile, and other countries. Occupational exposure to arsenic through inhalation has been evaluated in several cohort studies in smelters that identified an increased lung cancer risk [13] while there is no clear evidence for an increase in bladder cancer risk
Auramine production	99 (2010) [9]; 100 F (2012) [4]	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) [9]; 100 F (2012) [4]	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 [14], 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 [9]. 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 [15]
Magenta production	99 (2010) [9]; 100 F (2012) [4]	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 [14], the SMR was 23 (95% CI 5–67), and in the Italian study [16] 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) [9]; 100 F (2012) [4]	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. [14] 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 [17], 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) [18]; 100 F (2012) [4]	About 40 epidemiological studies have evaluated bladder cancer risk among painters. Two recent meta-analyses [19, 20] provided similar conclusions. The meta-analysis by Guha [19] 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). Small increased risks of around 5–15% were found in large record linkage studies in the Nordic countries and Canada

Table 28.1 (continued)

Chemical, industry, or occupation	IARC monograph	Main epidemiological evidence
Rubber production industry	Suppl 7 (1987) [21]; 100 F (2012) [4]	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. The IARC evaluated the evidence in 1982 [22] 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 [23] and identified moderately increased risks for bladder cancer. In cohort studies reporting results by calendar period, the risk was highest among workers employed before 1950. A similar conclusion was reached in a recent meta-analysis that identified 46 cohorts and 59 case-control studies in this industry. An increased risk was found for bladder cancer [standardized incidence ratio (SRR) = 1.36; 95% CI 1.18, 1.57], but in a stratified analysis, this risk was not increased for workers first employed after 1960 (SRR = 1.06; 95% CI 0.66, 1.71) [24]
Ortho-toluidine	99 (2010) [9]; 100 F (2012) [4]	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 reported an excess risk in bladder cancer [25–28]. In the US study of workers employed in the production of rubber additives from *ortho*-toluidine and aniline [26], risks were greatest for workers with the strongest likelihood of exposure (27 cases, SIR = 3.9, 95% CI 2.6–5.7) and for those exposed more than 10 years (17 cases, SIR = 6.2, 95% CI 3.6–9.9). Sorahan et al. [27, 28] reported an excess in bladder cancer risk in workers exposed to *ortho*-toluidine in the UK and found [28] increased risks with longer duration of employment in departments where *ortho*-toluidine was processed (0.1–4.9 years exposure, four cases, RR = 3.72, 1.21–11.4; ≥5.0 years exposure, two 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) [29]; 100D (2012) [30]	The Life Span Study (LSS) of atomic bomb survivors and three 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 [31]. 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) [9]	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. [32] 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. [33], 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) [3]; 100 F (2012) [4]	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 [34]). 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) [35]
Dry cleaning	63 (1995) [36]	Two US cohorts [37, 38] 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) [39]. 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 [40]. A European pooled analysis of 11 case-control studies [41] found an OR of 1.24 (95% CI 0.67–2.31) for launderers, dry cleaners, and pressers. In a recent meta-analysis, employment as a dry cleaner was associated with bladder cancer (meta-RR = 1.47 (95% CI: 1.16, 1.85); seven studies; 139 exposed cases), and for smoking-adjusted studies, the mRR was 1.50 (95% CI: 0.80, 2.84; four case-control studies) [42]

(continued)

Table 28.1 (continued)

Chemical, industry, or occupation	IARC monograph	Main epidemiological evidence
Diesel engine exhaust	105 (2014) [43]	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 [41], 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 [44]. A recent case/control study from the Canadian National Enhanced Cancer Surveillance System identified an increased risk for workers exposed to diesel engine exhaust (OR = 1.64, 0.87–3.08) that was higher among those exposed for more than 10 years (OR = 2.45, 1.04–5.74) [45]
Hairdressers and barbers (occupational exposure)	99 (2010) [9]	There are numerous cohort and case-control studies in hairdressers and barbers. A 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 [39]. An update of the Nordic countries pooled analysis confirmed the earlier findings [46]. 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) [41] or female [47] 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) [48]	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) [39]. In a large pooled analysis of European case-control studies [41], an increased OR was found for printers and related workers in men (OR = 1.45, 1.07–1.97)
Soot	92 (2010), [3]; 100F (2012) [4]	Soot was first noted as a cause of scrotal cancer in humans by Pott in 1775. A cohort study in Sweden [49] and a large record linkage study in the Nordic countries [39] have identified an increased risk of bladder cancer among chimney sweeps exposed to soot. An update of the Nordic countries pooled analysis confirmed the earlier findings [46]. In the Swedish study, there were 37 cases of bladder cancer with an RR of 2.53 for exposure to soot (95% CI 1.78–3.49). Increased risk was also observed after adjusting for smoking but no internal dose–response was observed for bladder cancer
Tetrachloroethylene	106 (2014) [50]	Tetrachloroethylene is one of the most widely used chlorinated solvents in dry cleaning and currently in chlorofluorocarbon production. The largest cohort studies were of dry cleaners in four Nordic countries [51] and in the USA [37, 38]. All three cohorts found an increased risk of bladder cancer and one study [38] reported an exposure–response relationship (Standardized Mortality Ratio = 4·08, 95% CI 2.1–7.1; workers exposed >5 years and first exposed >20 years). Several case-control studies showed positive associations after adjustment for smoking and other potential confounders. A recent meta-analysis among tetrachloroethylene-exposed workers did not identify an increased risk (meta-relative risk (mRR) = 1.08, 95% CI: 0.82, 1.42; three studies; 463 exposed cases) [42]
2-mercapto-benzothiazole	115 (2018) [52]	2-Mercaptobenzothiazole is a high production volumen chemical principally used as a reactant in the manufacture of rubber products. Studies on the carcinogenicity of 2-mercaptobenzothiazole were conducted in a plant that manufactured chemicals for the rubber industry in Wales, United Kingdom [27, 53], and a chemical manufacturing plant in West Virginia, USA [54]. Both found increased bladder cancer incidence (UK study) or mortality (US study). Internal comparisons adjusting for other occupational exposures but not for smoking showed increasing risk with cumulative exposure with a twofold risk in the highest exposure group in the UK study
Textile manufacturing	48 (1990) [55]	The most consistent results for an increased risk of bladder cancer when the IARC evaluated the evidence were for workers using dyes and possibly for weavers, with several studies reporting twofold or higher risks. In recent case-control study conducted in Spain [56] 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 [57] 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) [39]

workers in a plant distilling b-naphthylamine developing bladder cancer [14]. 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 [25, 32, 61, 62]. Findings for users of dyes are less consistent [40, 63, 64]. Increased risks in relation to aromatic amines are still found although these are not as extreme as in the past. For example, recent analyses in Europe and the USA on workers exposed to *o*-toluidine identified RRs for bladder cancer ranging from 2 to 6, depending on degree of exposure [26, 28].

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 [22]. Figure 28.1 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 [17]. 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 [65, 66] 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 studies of rubber workers published in the 1980s and 1990s although risks were highest in workers employed prior to the 1950s [23]. A large recent study conducted in Germany that, however, had a relatively short follow-up did not observe an increased risk of bladder cancer [67]. A similar conclusion was reached in a recent meta-analysis that identified 46 cohorts and 59 case-control studies in this industry for workers first employed after the mid-1970s (Fig. 28.2, from [68]). An increased risk was

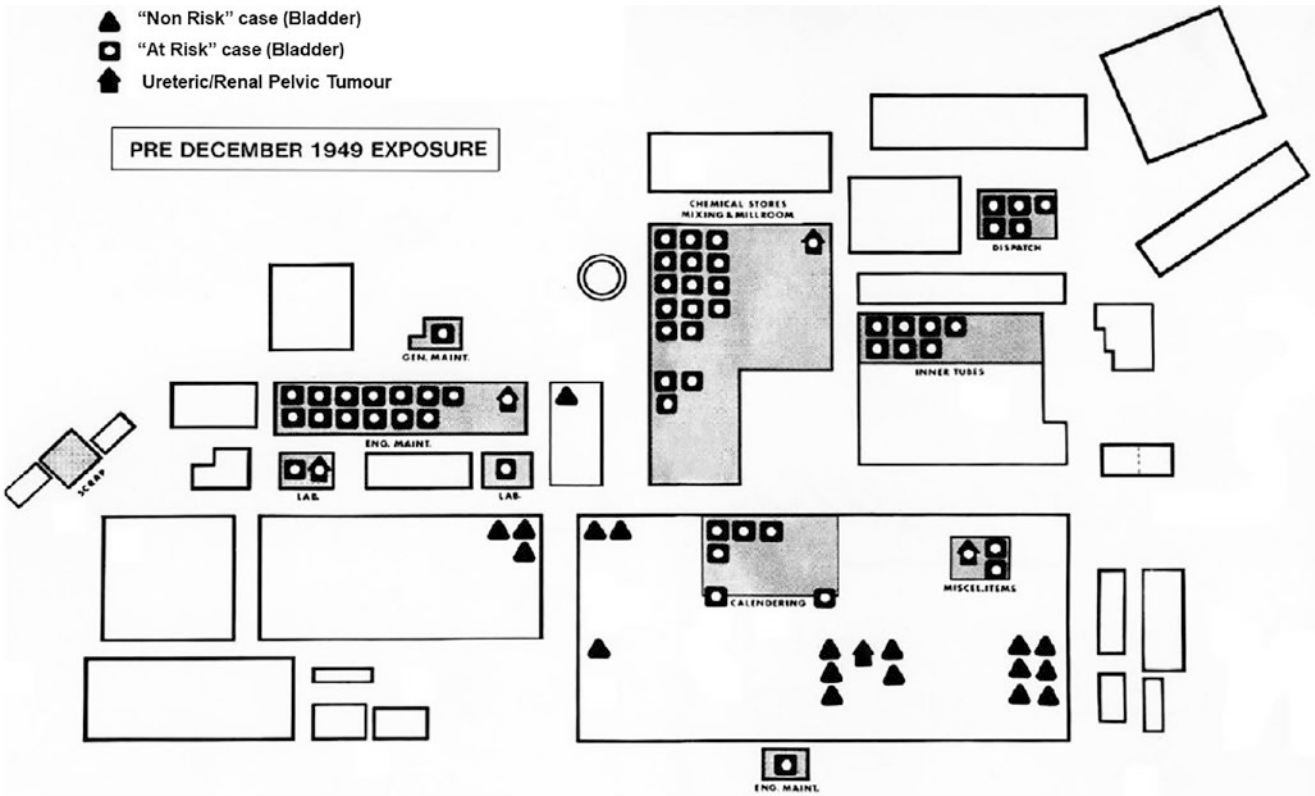

Fig. 28.1 Map of rubber tire production in a factory in England and deaths from bladder cancer (squares) for men employed before December 1949. *Shaded areas* indicate departments of the plant where 2-naphthylamine exposure occurred. (From Veys [17], by permission of Oxford University Press)

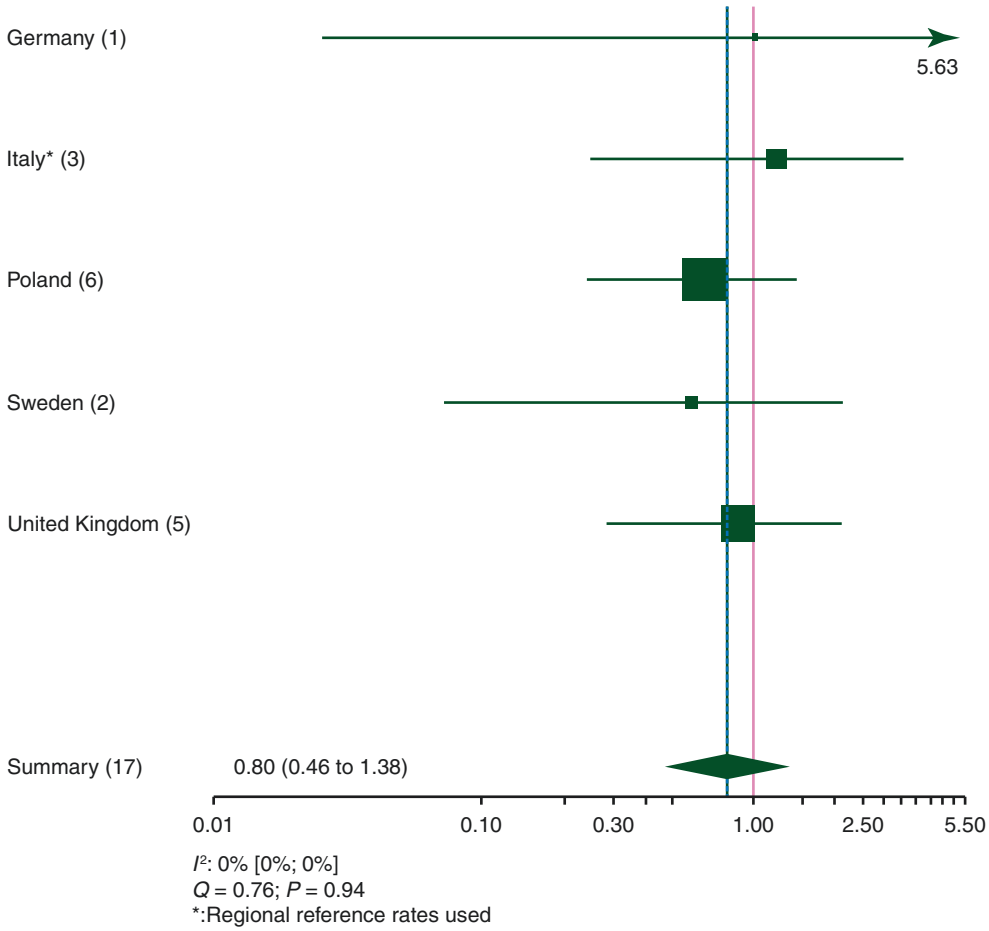

Fig. 28.2 Forest plot of the risk of bladder cancer mortality (men and women combined) from five cohorts of European rubber workers, first employed after the mid-1970s. Numbers of deaths are reported in brackets. The pink line corresponds to a standardized mortality ratio (SMR) of 1, i.e., no difference in mortality between the cohort and the general population. The blue line corresponds to the SMR for all-cause mortality. (From Boniol et al. [68])

found for bladder cancer [standardized incidence ratio (SRR) = 1.36; 95% CI 1.18, 1.57], but in a stratified analysis, this risk was not increased for workers first employed after 1960 (SRR = 1.06; 95% CI 0.66, 1.71) [24].

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 [69].

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 "involve metabolic activation, formation of DNA adducts, and induction of mutagenic and clastogenic effects" [4]. 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, 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). High levels of exposure to PAHs have been observed in aluminum production (Söderberg process) with midrange levels observed in roofing and paving. The IARC evaluated the evidence in 2005 published at [3] and again in 2009 published at [4]. 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

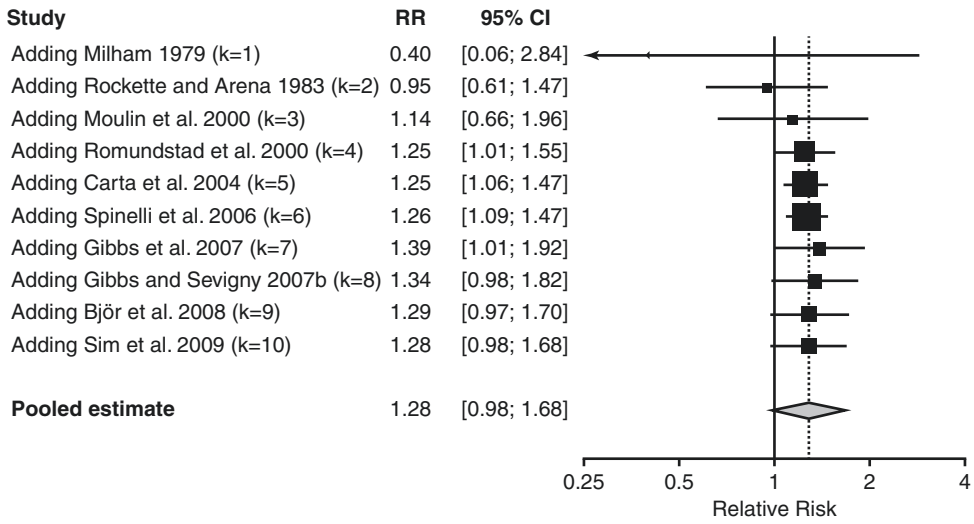

Fig. 28.3 Relative risks (*RR*) of bladder cancer among aluminum production workers and corresponding confidence intervals (*CI*), by year of publication of subsequent reports. The numbers of studies included in the cumulative meta-analysis for each year and overall. Meta-analysis of cohort studies

production for which the epidemiological evidence for bladder cancer was classified as sufficient, the strongest evidence for most other industries was for lung or skin cancer.

Early studies in the aluminum industry in Quebec, Canada associated exposure to PAHs with bladder cancer [5]. Subsequent studies in British Columbia, Canada, the USA, Norway, and France have also identified increased risks and a dose response with estimates of B[a]P-years. Adjustment for smoking was done in several of these studies and did not modify results substantially. In the Quebec studies, increased risks were only observed for workers exposed prior to the 1950s. More recent studies in Australia and Sweden have not identified an increased risk. A recent study in Spain identified increased bladder cancer risk in secondary aluminum production [70].

Roofing and paving of roads involve the use of bitumen and coal-tar pitch [71], although the latter has been phased out in many countries. IARC [4] evaluated exposure to coal-tar pitch in 2012 as Group 1 carcinogen based on the findings for lung cancer. IARC also mentioned a positive but less strong association with bladder cancer. Bladder cancer incidence was evaluated in paving cohorts from Denmark, Finland, Norway, and Israel by estimated benzo[a]pyrene exposure levels. In an internal comparison, there was an indication of a trend with average exposure to benzo[a]pyrene [35]. The overall incidence of bladder cancer in the large European asphalt workers cohort study was similar to that expected (SMR 1.05; [34]).

Soot was first noted as a cause of scrotal cancer in chimney sweeps by Pott in 1775. Soot is classified by IARC as a Group1 carcinogen based on the findings on skin (scrotum) cancer. A positive association has also been identified for bladder cancer. A cohort study in Sweden [49] and a large record linkage study in the Nordic countries [39] have identified an increased risk of bladder cancer among chimney sweeps exposed to soot. An update of the Nordic countries pooled analysis confirmed the earlier findings [46]. In the Swedish study, there were 37 cases of bladder cancer with an RR of 2.53 for exposure to soot (95% CI 1.78–3.49). Increased risk was also observed after adjusting for smoking but no internal dose–response was observed for bladder cancer.

Several reviews and meta-analyses have been published on PAH exposure and bladder cancer [6, 7, 72, 73]. In a meta-analysis of urinary bladder cancer [7], 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). In a more recent meta-analysis of cohort studies [6], 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. 28.3), 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). This meta-analysis was updated [73] and provided similar conclusions as Bossetti [6].

Diesel Engine Exhaust

The IARC classified diesel engine exhaust as a human carcinogen [43] 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), and polycyclic aromatic hydrocarbons (PAHs) including nitrated PAH derivatives. Diesel engine exhaust contains more particulate matter and lower levels of some gases compared to gasoline engines [43].

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 risk among transport workers exposed to engine exhausts including diesel [40, 74–77] even when adjusting for aromatic amine exposure [78, 79]. 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 [41] and four more studies in Canada, Belgium, and Sweden [77, 80–82]. 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. 28.4. Only the study in British Columbia [80] 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 [44]. A recent population-based case-control study from the Canadian National Enhanced Cancer Surveillance System evaluated diesel engine exhaust through a job-exposure matrix for engine emissions supplemented by expert review [45]. High concentrations of diesel emissions were associated with an increased risk for bladder cancer and this was highest in those with >10 years of exposure (OR = 1.64, 0.87–3.08).

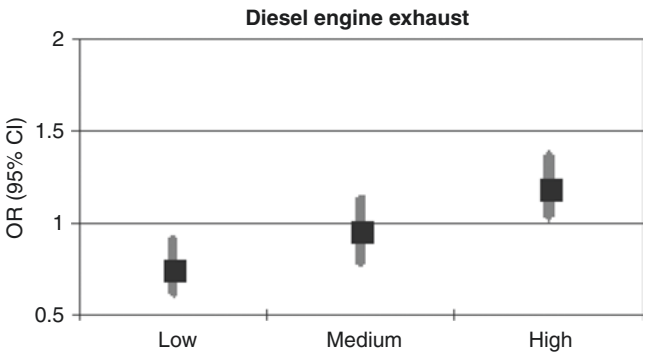

Fig. 28.4 Odds ratios for bladder cancer in European men by exposure to diesel engine exhaust, using a job-exposure matrix. Exposure was evaluated for different time periods as the product of the prevalence of exposure times the average exposure level in each occupation. Exposed subjects are classified 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. [124])

Painters

The IARC has evaluated that occupational exposure as a painter is *carcinogenic to humans* [18]. 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 [19] included around 2900 incident cases or deaths from bladder cancer among painters from 41 cohort studies (Fig. 28.5). 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). A recent update of the Nordic countries pooled analysis identified an increased bladder cancer risk among painters that was lower in recent years [46]. 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 [18].

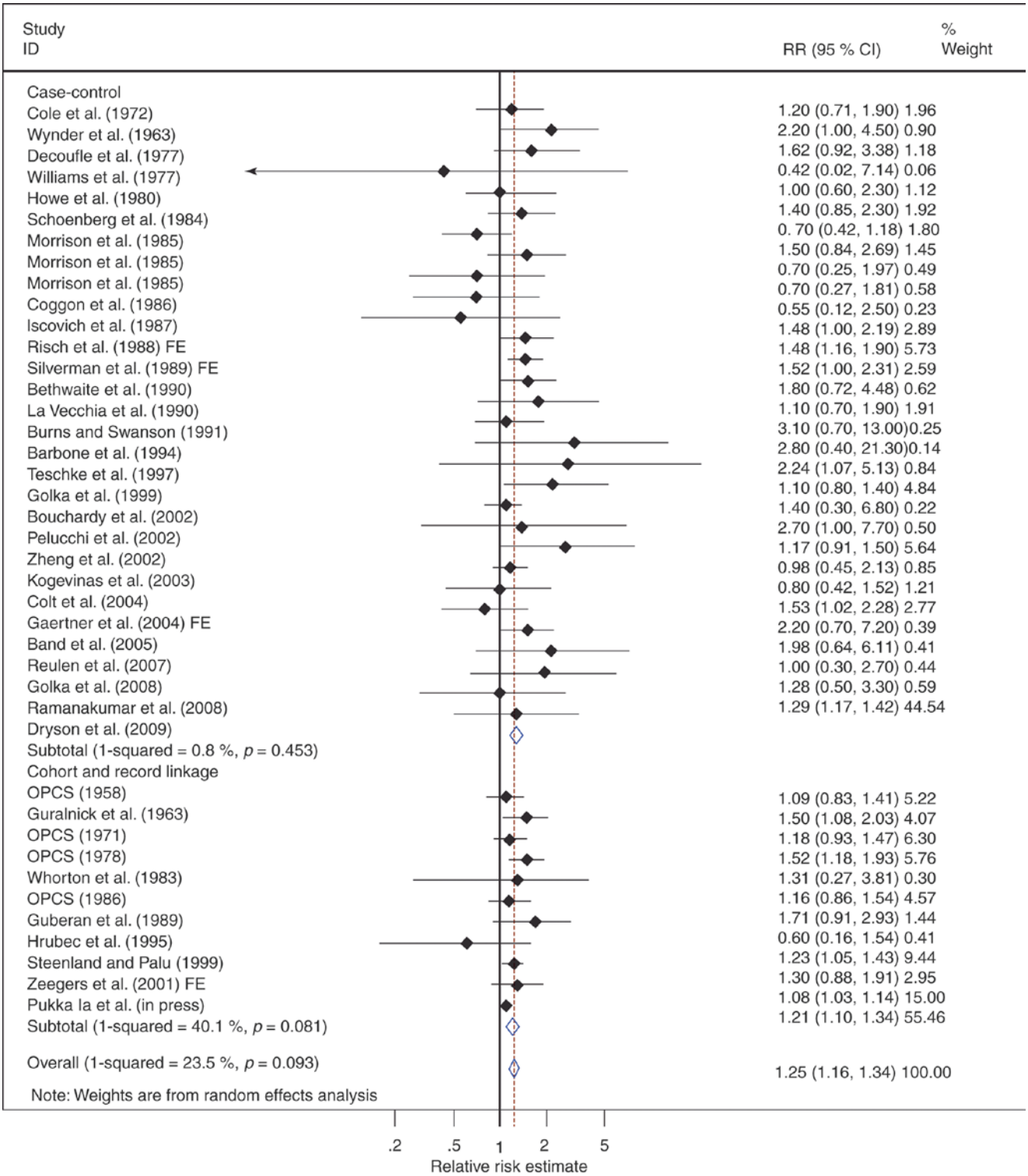

Fig. 28.5 Meta-analysis of all studies assessing bladder cancer among persons with occupation as a painter, stratified by study design. If only subgroup results (e.g., by gender, race, or duration of exposure) were reported, fixed effects (*FEs*) models were used to combine stratum-specific data into one summary estimate. (Reproduced from Guha et al. [19], with permission from BMJ Publishing Group Ltd.)

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 [9]. 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 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 [83], the relative risk estimate was 1.4 (183 observed vs. 129 expected). A 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 [39]. An update of the Nordic countries pooled analysis confirmed the earlier findings [46]. A recent analysis of the Canadian Census Health and Environment Cohort (CanCHEC) identified an increased risk among hairdressers (RR = 1.48 1.01–2.19) [84]. 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 [41, 47] did not find increases in risk among male (1.09) (95% CI 0.70–1.70) or female hairdressers (0.8) (95% CI, 0.4–1.7). 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 [36]. The epidemiological evidence on occupational exposures in dry cleaning has been evaluated by the IARC [36] 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, 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 [37, 38, 51]. 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 [51] 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 [38] 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). An update of the Nordic countries pooled analysis identified lower risks than previous analyses for launderers in both men (RR = 1.10, 0.95–1.28) and women (RR = 1.07, 0.95–1.22) [46]. 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 [40]. A European pooled analysis of 11 case-control studies [41] found an OR of 1.24 (95% CI 0.67–2.31) for launderers, dry cleaners, and pressers. A recent meta-analysis among tetrachloroethylene-exposed workers did not identify an increased risk (meta-relative risk (mRR) = 1.08, 95% CI: 0.82, 1.42; three studies; 463 exposed cases) [42]. The epidemiological evidence on tetrachloroethylene was [50] 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. 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 [48]. 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 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) [39]. A recent update of the Nordic countries study [46] identified printers as one of the occupations with highest bladder cancer risk (RR = 1.21; 95% CI 1.14–1.30). 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 and, of those, 20 found excess risks ranging from 1.1 to fivefold either in the whole study group or in subgroups. In the pooled analysis of European case-control studies [41], 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 [85] 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% CI 1.02–9.47). 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 textile industry was among the typical industries associated in the past with an increased bladder cancer risk. The epidemiological evidence on occupational exposures in the textile industry has been evaluated by the IARC [55] 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 from a few cohort studies but 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., [86–89]) tend to identify higher risks than those conducted in, for example, North America [90–92], although this pattern is not entirely consistent [69]. A study conducted in Spain including around 1200 cases and an equal number of controls is among the studies with more extensive exposure assessment [56]. 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 recent large study in New England [93] identified an increased risk for male textile, apparel and furnishings machine operators and tenders (OR = 2.0, 1.2–3.3) but not for female (OR = 1.0 0.6–1.9). ORs were higher for workers with more than 10 years employment in this industry. A large study in Shanghai, China, examined cancer incidence in a cohort of 267,400 women textile workers [57]. 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 large prospective record linkage study in the Nordic countries found a very low increased risk among textile workers (n = 2182 cases, RR = 1.06, 1.02–1.10) [46].

Machinists, Metal Workers, and Metal Working Fluids

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 [40, 41, 47, 69, 87, 90, 92, 94], and others. In many of these studies, higher than twofold risks were observed. No excess risks were found in some studies [75, 95]. 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 [41]. A review of all studies on bladder cancer [1] also identified the highest meta-risk for mortality among metal workers although the analysis for incidence indicated an increased but much lower risk (RR incidence = 1.14 (1.11–1.18)). A similar estimate was found for mechanics in the recent large pooled analysis of the Nordic countries population 1.10 (1.08–1.13) [46].

Several studies have evaluated metal working fluids as one of the exposures producing the increased risk among metal workers and mechanics. IARC [4]) evaluated mineral oils, untreated or mildly treated as Group 1 carcinogens

based on evidence on skin cancer (scrotum) noting that the evidence on bladder cancer was inconsistent. Two recent studies one in the USA [96] and one in France [97] identified increased risks for bladder cancer. In the larger US study, the OR for straight MWFs was 1.7 (95% CI = 1.1–2.8) and increased monotonically with increasing cumulative exposure; use of soluble MWFs was also associated with a 50% increased risk (95% CI = 0.96–2.5) while no increased risks were found for synthetic oils. A similar pattern was observed in the French study.

Evidence on Solvents

The exposures associated with a high risk of bladder cancer in many occupations are not well identified. Several occupations such as painters, printers, rubber workers, plastic product workers, chemical process workers, laundry workers, and metal plating and coating workers are all exposed to a variety of solvents. These include toluene, aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, perchloroethylene, trichloroethylene, and 1,1,1-trichloroethane. The evidence associating solvents exposure with bladder cancer is still not extensive. A powerful analysis was recently reported using the Nordic population record linkage study (NOKA) and evaluating exposure through the FINJEM [98]. Increased risks were observed for trichloroethylene (Hazard Ratio (HR) = 1.23, 95% CI 1.12–1.40), toluene (HR 1.20, 95% CI 1.00–1.38), benzene (HR 1.16, 95% CI 1.04–1.31), aromatic hydrocarbon solvents (HR 1.10, 95% CI 0.94–1.30), and aliphatic and alicyclic hydrocarbon solvents (HR 1.08, 95% CI 1.00–1.23) at high exposure level versus no exposure. Evidence from few other studies are based on relatively small numbers.

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. Among those the most consistent evidence is for plumbers, welders, and waiters [1, 46]. A negative association was found for bladder cancer in the largest study evaluating occupational exposure to perfluorooctanoic acid—PFOA [99]. The largest cohort on taconite miners did not find an association after adjusting for smoking [100]. The evidence on the association with lead exposure is not entirely consistent [101] although in the largest study an increased risk for bladder cancer was observed among workers with the highest blood level (BLs > 40 μg/dL) [102].

Most studies on agricultural workers have not found an association with bladder cancer and in the large Nordic record linkage study [46] gardeners and farmers had among the lowest SIRs (0.78, 0.75–0.80 and 0.70, 0.68–0.71 respectively). Earlier meta-analyses (for example, Reulen et al. [103]) did not identify an increased risk. An SIR of 0.59 (95% CI 0.51, 0.68) was observed for bladder cancer in the large Agricultural Health Study in the USA [104] while a similar estimate for decreased mortality was observed in an early follow-up of the French AGRICAN cohort study [105]. A recent analysis of the Canadian Census Health and Environment Cohort (CanCHEC) identified a slightly decreased incidence among agricultural workers [84]. Risk was elevated for use of specific pesticides in the US cohort and for specific subgroups and tasks in the French cohort, for example among field-grown vegetable workers and greenhouse farmers [106]. Increased risks have been found in several studies including studies of farmers in Egypt [107] and of their wives [108]. It has been postulated that part of the overall decreased risk for bladder cancer among agricultural populations may be due to lower prevalence of smoking [105].

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 [41, 69, 87, 109]. 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 [110]. 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. A recent Nordic countries record linkage study [46] identified increased risks among some white-collar occupations, for example sales agents (SIR 1.16, 1.13–1.20). Similarly, a recent analysis of the Canadian Census Health and Environment Cohort (CanCHEC) identified a slightly increased risk among administrative managers (RR = 1.11 1.04–1.19) [84].

Evidence from International Studies

Table 28.2 shows odds ratios for industries in Europe with increased risk for bladder cancer from a large international

Table 28.2 Industries showing a statistically significant excess bladder cancer risk among European men

Industry (ISIC code)	Odds ratio	95% confidence interval
Salt mining (2903)	4.41	(1.43–13.6)
Manufacture of carpets and rugs (3214)	4.07	(1.44–11.5)
Manufacture of paints, varnishes, and lacquers (3521)	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 [41]
[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 28.3 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 [41, 47]

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 28.3) were metal workers, textile workers, electrical workers and

Table 28.4 Occupations with the highest and lowest risk of bladder cancer (standardized incidence ratio (SIR) >1.20 or <0.80) in the Nordic countries 1961–2005, in men and women [46]

	SIR (95% confidence interval)
Highest	
Tobacco workers	1.57 (1.24–1.96)
Chimney sweeps	1.48 (1.21–1.80)
Waiters	1.43 (1.33–1.53)
Hairdressers	1.28 (1.18–1.40)
Seamen	1.22 (1.16–1.30)
Printers	1.21 (1.14–1.30)
Plumbers	1.20 (1.13–1.30)
Lowest	
Gardeners	0.78 (0.75–0.80)
Forestry workers	0.74 (0.70–0.78)
Farmers	0.70 (0.68–0.71)

painters, miners, transport operators, excavating-machine operators, and also nonindustrial workers such as concierges and janitors [41]. A series of analyses of census data from Denmark, Finland, Iceland, Norway, and Sweden evaluated up to 45 years of cancer incidence data (148,669 cases of bladder cancer; 111,458 men and 37,211 women from 1960 to 2005) by occupational category for these Nordic populations [39, 46]. Bladder cancer was considered as one of the cancer types most likely to be related to occupational carcinogens. Tobacco workers, chimney sweeps, waiters, and hairdressers had the highest risk of bladder cancer overall, while gardeners and farmers had the lowest (Table 28.4). This rank coincided with that for men. In women, the highest risks were observed for tobacco workers (with SIRs much higher than those of men), waiters, printers, and hairdressers. Correlation of occupational risks between lung and bladder cancer (indicative of potential confounding with smoking) was higher for men ($r = 0.66$) than women ($r = 0.2$).

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 [57]. 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 [46, 63, 87, 111–114]. 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 1266 controls from ten areas of the USA [92]. 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 2425 controls ([47], Table 28.3) 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 6792 female cases with bladder cancer [115], 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 (see section above), the highest risks among women were found for tobacco workers, printers, waiters, and hairdressers [39]. A large study in Shanghai, China (mentioned in the section on the textile industry) [57] 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 [116–119]. In the pooled analysis of European case-control studies which included recent studies on occupational bladder cancer [41], 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 [92], it was estimated that 11% of the bladder cancer cases could be attributed to occupational exposure. In the European study [47], 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 and rubber workers, no excess risk whatsoever was found among women. In a recent evaluation of occupational cancer in Britain [120], 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%). Similar proportions were used for an estimation in Canada [121]. There are no extensive and fairly representative data on exposure and time trends in most developing or newly developed countries [122], 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 [41] 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%). A similar pattern has been observed for bladder cancer risks in the rubber industry where studies conducted in late years mostly in Europe have either not identified an increased risk or identified risks clearly lower than in the past [68]. In the Nordic countries record linkage study [46], SIRs tended to decrease in time for most high-risk occupations (e.g., painters, printers, waiters, hairdressers) but not for others (tobacco workers, chimney sweeps) while some SIRs tended to increase in time (e.g., drivers, launderers). In the largest meta-analysis of occupational risks and bladder cancer [1], it was found that from the 1960s to the 1980s, there was a steady decline in standardized incidence ratio for both sexes while this trend reversed from the 1980s onwards. In the decade 2000–2010, the SIR for occupational bladder cancer increased to 1.13

(95% CI, 1.07–1.19) for men and 1.27 (95% CI, 1.12–1.43) for women. The authors report that this increase in incidence may be in part attributed to improved detection mechanisms and screening particularly in women.

Epidemiology of Bladder Cancer and Non-occupational Risk Factors

It has been estimated that there are approximately 550,000 new cases per year worldwide (http://gco.iarc.fr/today/home), most occurring among men and about two-thirds occurring in high income countries. Among the countries with the highest incidence are the USA, Spain, 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 [123, 124].

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 although recent evidence is inconsistent. Evidence from large cohort studies does not support an association with coffee consumption. Early studies mostly in animal experiments indicating that artificial sweeteners were associated with bladder cancer have not been confirmed in humans. There is consistent evidence from large cohort studies on a reduced bladder cancer risk associated with leisure-time physical activity. There is some evidence that voiding frequency and particularly increased nighttime voiding may be associated with decreased risk but this association is still poorly examined. 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 and recently pioglitazone an antidiabetic drug and aristolochic acid used in Chinese medicinal herbs). 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. Finally, that air-pollution may be associated with bladder cancer although evidence is not entirely consistent.

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 [125]. 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 [126] or lists of carcinogens by cancer site as identified by the IARC [2, 127] that are regularly updated.

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 [41] and other studies [60, 71, 128] have 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. The urinary bladder is one of the few organ sites for which the candidate gene approach to identify common susceptibility loci has proved to be successful due to the knowledge of bladder cancer carcinogenic pathways and polymorphisms in drug and carcinogen metabolism genes, including *NAT2* and *GSTM1*. Familial clustering of bladder cancer has been reported, and studies examining familial aggregation have found excess risks [129, 130], 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%. GWAS using an agnostic approach have identified SNPs in pathways known to be involved in bladder carcinogenesis, including carcinogen metabolism, urinary excretion, and oncogenes and tumor suppressors, specifically genetic variants at *UGT1A6* and *CYP1A2*.

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 [131–133]. A meta-analysis revealed a modest 30–50% increase in the risk of bladder cancer among slow compared to rapid acetylators [134]. 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 [135]. 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 [15]. 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 8500 cases and controls followed by a replication analysis in a much larger population [136]. 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. The largest evaluation of gene–environment interactions in bladder cancer focusing on occupation used information on high-risk occupations for 2258 case patients and 2410 control patients from two case-control studies in Spain and the USA [137], The authors reported that three of 16 known bladder cancer susceptibility variants [GSTM1 deletion polymorphism; rs11892031 (UGT1A); and rs798766 (TMEM129-TACC3-FGFR3)] showed statistically significant and consistent evidence of additive interactions with occupation. Among specific exposures, a statistically significant additive interaction was observed for rs798766 with straight metal working fluids.

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 have been unequivocally associated with bladder cancer. Exposure to polycyclic aromatic hydrocarbons (PAHs) in aluminum process workers and other industries has also been clearly associated with bladder cancer. Excess risks have been observed among painters, machinists and other metal workers, workers in the textile industry, printers, hairdressers, dry cleaners, and transport workers. Exposures associated with the increased risk in these occupations/industries include PAHs, industrial oils/cutting fluids, diesel engine exhaust, paints, dyes, chlorinated hydrocarbon solvents, and metals. A recent analysis of census data in the Nordic European countries identified tobacco workers, chimney sweeps, waiters, and hairdressers as the occupations with highest risks, a pattern that can, in part, be accounted for by smoking. Less consistent associations have been found for numerous other occupations, while 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%. 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. Recent evidence on gene–environment interaction identified statistically significant interactions with 3 out of 16 known GWAS bladder cancer genes with occupational exposures.

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Malignant Tumors of the Central Nervous System

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Classification

Brain cancer is an extremely heterogeneous group of tumor 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. 29.1), but also increasingly in genetic alterations of the tumor [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 and ependymoma. At present, all infiltrating gliomas—whether astrocytic or oligodendroglial—can be grouped as diffuse gliomas. As this publication focuses on occupational factors, childhood brain tumors are not covered here in any detail. Central nervous system (CNS) malignancies can also arise, e.g., from the lymphatic system (lymphoma, with a frequency 2–5% of the tumors) and connective tissue (sarcoma, rare) in the CNS.

Astrocytomas account for three quarters of all gliomas. They include diffuse astrocytoma (WHO grade II, approximately 5% of all astrocytic tumors), anaplastic astrocytoma (WHO grade III, 10% of all astrocytomas), and glioblastoma (WHO grade IV, also called glioblastoma multiforme, 60% of astrocytomas). Diffuse and anaplastic tumors have a tendency to progress toward a more malignant phenotype. The number of genetic aberrations (mutations and chromosomal changes) within a tumor increases with grade with a broad spectrum of changes in complex combinations. Diffusely infiltrating grade II-IV astrocytomas are subdivided into isocitrate dehydrogenase (IDH)-mutant and IDH-wild-type tumors [2]. Other common mutations include tumor suppressor TP53, alpha-thalassemia/mental retardation syndrome X-linked gene (ATRX), and telomerase reverse transcriptase (TERT) promoter region. Also, methylation of MGMT promoter region is frequently encountered.

The key features defining the grade are anaplasia (assessed as nuclear atypia), proliferative capacity (indicated by mitotic activity), as well as neovascularization and necrosis (the latter two features defining glioblastoma). Morphologically, grade II tumors show atypia, while grade III cancer exhibit also increased mitotic activity and the hallmark of grade IV is vascular proliferation and/or necrosis [3]. Perhaps the sharpest distinction is between grade I and grade II astrocytoma, which are regarded as distinct entities. The other neuroepithelial tumors, i.e., oligodendrogliomas and ependymomas are also divided into grades II and III (anaplastic tumors), with also some grade I tumor 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.

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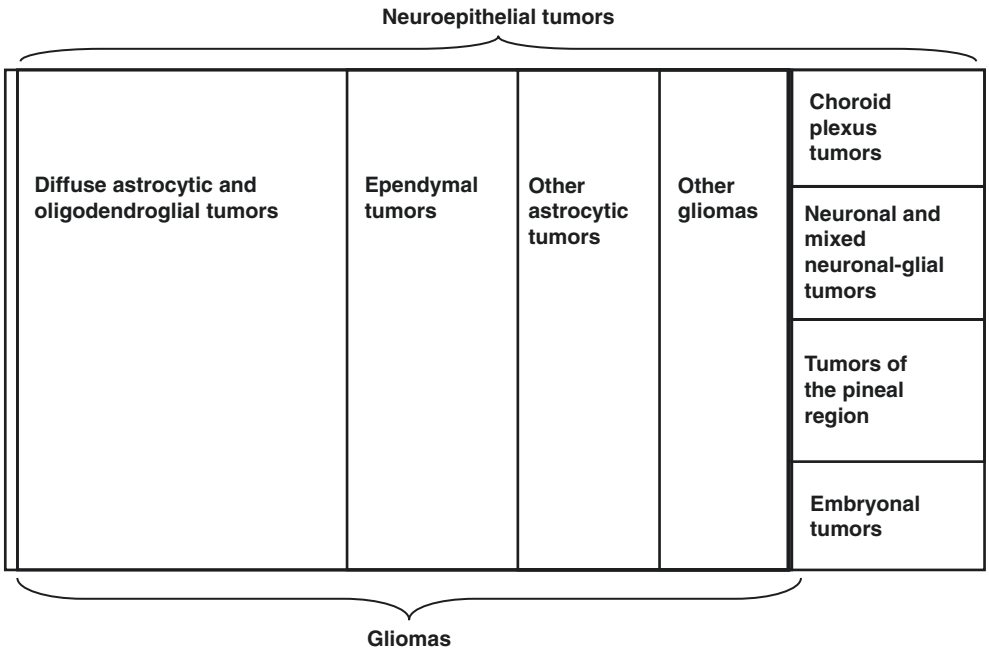

Fig. 29.1 A schematic representation of morphological classification of malignant brain tumors

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 [4]. 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 morphologic criteria. For astrocytoma, the diversity of genetic and molecular alterations increases with grade (Table 29.1).

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 [5, 6]. In addition to IDH mutation, chromosome 1p loss or 1p/19q co-deletion is typical for oligodendrogliomas [1]. IDH1 and IDH2 mutations in diffuse (grade II) and anaplastic (grade III) astrocytomas are 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].

Table 29.1 A summary of the most important genetic abnormalities in classification of the central nervous system tumors (WHO 2016)

Morphological tumor type	Defining genetic alterations
Astrocytoma incl. Glioblastoma	IDH1/2 mutant/wild-type
Oligodendroglioma	1p/19q co-deletion; IDH mutant
Ependymoma	C11orf95-RELA fusion positive/ negative
Medulloblastoma	WNT-activated; SHH-activated; TP53 mutant/wild-type

IDH isocitrate dehydrogenase, *WNT* wingless-related integration site, *SHH* sonic hedgehog

Multiple molecular and chromosomal abnormalities are typical for glioblastoma. Features that can distinguish glioblastoma from anaplastic astrocytoma, which mostly harbor IDH mutation, include p16 and PTEN deletions or mutations, as well as EGFR amplification [1, 3].

Primary glioblastoma arises de novo, while the less common secondary glioblastoma is preceded by a lower grade astrocytoma and evolves through gradual dedifferentiation [5]. These two tumor types are thought to involve partly different genetic mechanisms. Epidermal growth factor receptor (EGFR) mutation, overexpression, or amplification is common in primary glioblastoma, and also PDGFR amplification appears important for GBM [1, 4, 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 [4]. 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 glioblastomas [5]. PTEN mutations (or 10q loss) are found in a third of GBM cases, but rarely encountered in low-grade glioma [6]. Methyl-guanine 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 glioblastoma [3].

In oligodendroglioma, the IDH mutations and combined LOH of 1p and 19q are diagnostic [1]. The 1p/19q co-deletion is 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.

IDH mutations do not occur in ependymomas. These tumors display several cytogenetic aberrations, and genetic characteristics include NF2 mutation, YAP1 fusion gene and RELA fusion gene. The latter genetic change defines a new ependymoma subtype in the novel WHO classification, RELA-positive ependymoma [7].

More detailed and distinctive molecular characterization has also led to suggestions of abandoning the term oligoastrocytic tumors, as these appear to be mixed oligodendroglial and astrocytic components, and not a cell type of its own [1].

Occurrence

Brain and other CNS cancers make up 1.8% of all primary cancers (excluding skin cancer) and, with a global total of 256,000 cases in 2012, rank as the 17th most common type of cancer [8]. Age-standardized incidence among men was estimated as 3.9 per 100,000 and 3.0 per 100,000 among women. The age-standardized incidence rates for more developed countries were reported as 5.9 per 100,000 in men and 4.4 per 100,000 in women, while the corresponding rates in less developed populations were 3.3 and 2.7 [9]. In the global burden of cancer project, it was estimated that brain and CNS cancer cause 84 disability-adjusted life years (DALYs) per 100,000 in men and 69 in women [10].

Occurrence estimates from different source 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 the US 2000 standard population as reference is nearly a quarter higher than that shown using the world standard population.

The quality of the incidence estimates depends on completeness of coverage and ascertainment, availability of histological diagnosis, exclusion of metastases, and extent of double counting (failure to eliminate duplicate records). Classification of nervous system tumors is very heterogeneous in different registers, which makes compilation of information in a consistent fashion challenging. Revisions in diagnostic classification also make it demanding to provide incidence data with consistent definitions and comparable classifications over time.

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. 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. GloboCan [8] and Cancer Incidence in Five Continents [11] databases cover only malignant brain and nervous system tumors, while SEER and NordCan include both malignant and benign brain tumors. In the United States, the Central Brain Tumor Registry of the United States (CBTRUS) nowadays compiles detailed information on malignant and benign brain tumors from cancer registries within the SEER and NPCR programs covering all US states [12].

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 [13]. Similarly, more comprehensive reporting of tumor location can interfere with trends by specific site [14].

There is a slight male predominance in astrocytic tumors, with a male:female ratio of 1.2–1.5, with a slightly lower sex ratio for oligodendroglioma and little gender difference for ependymoma [12, 15, 16]. In the US SEER data, whites have higher incidence rates than other, with 30–50% lower rates for black and Asian people [17]. Hispanic whites also show lower rates than non-Hispanic.

Glioblastoma is by far the most common malignant brain tumor type in adults. The age-standardized incidence of glioblastoma has ranged from 3 to 5 per 100,000 among men and 2–3 per 100,000 in women [12, 13, 16, 18–20] (Fig. 29.2). Anaplastic astrocytomas constitute less than 10% of all gliomas and diffuse astrocytoma somewhat less. Incidence rates of around 0.3–0.4 per 100,000 have been reported for oligodendroglioma, while rates for ependymoma are slightly lower [12, 13, 16, 18, 19].

Gliomas in adults occur mainly in supratentorial parts of the brain, most commonly in anterior and cortical areas [12]. Frontal lobe is the most frequent location, also when adjusted for the difference in volume between the lobes [14, 21].

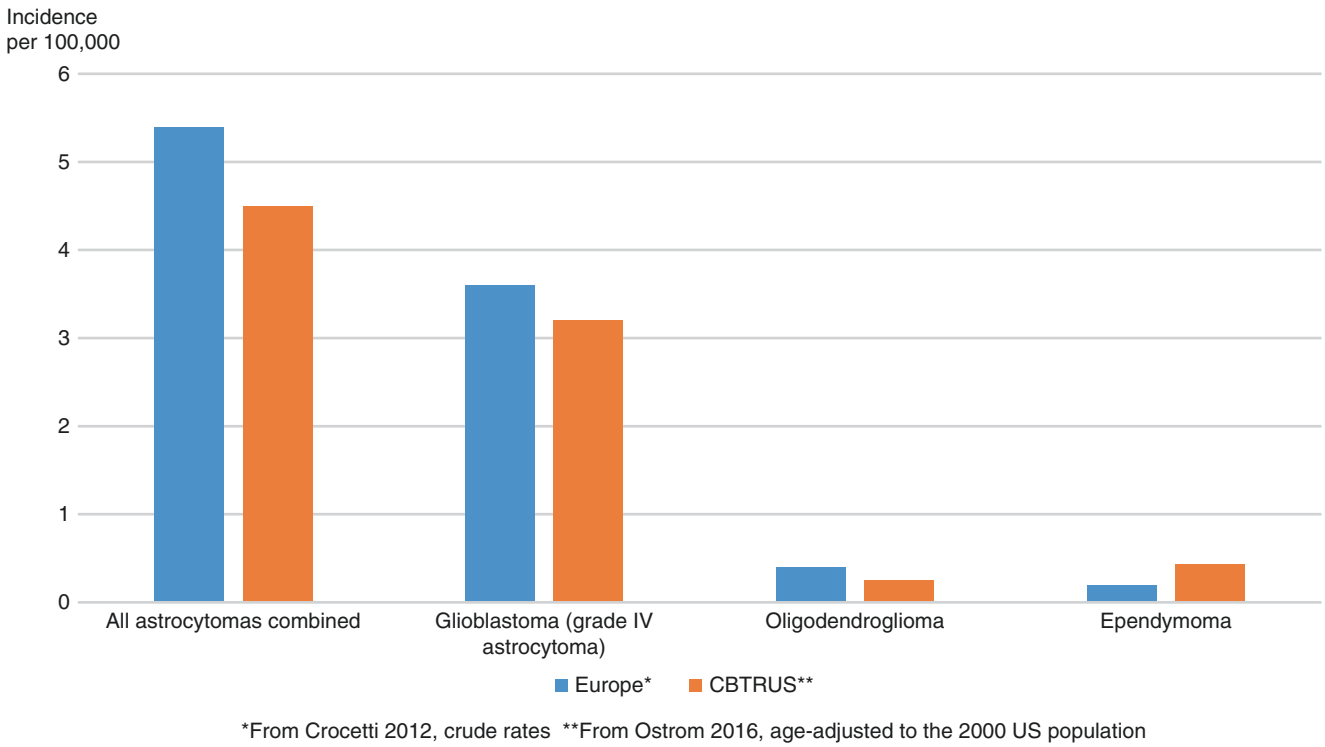

Fig. 29.2 Incidence rates of major brain tumor types in Europe and the United States

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 reduction in incidence [15]. The spectrum of astrocytic tumors changes with age, with the proportion of poorly differentiated tumors increasing [20]. For instance, diffuse astrocytomas tend to occur approximately 5 years earlier than anaplastic astrocytoma (median age at diagnosis 48 vs. 53 years), and age at diagnosis for glioblastoma is again 10 years older (median age 64) [12]. The age gradient for astrocytic tumors is steeper than for ependymoma and oligodendroglioma and, consequently, the proportion of astrocytic tumors increases with age.

An increase in brain cancer 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 [13, 15, 16, 18, 22–25]. It is unclear to what extent the earlier increase reflects improved coverage of registers and more accurate diagnostics, with developments in diagnostic technologies, primarily computer-assisted tomography (mainly in the late 1970s and early 1980s) and magnetic resonance imaging (in the 1980s and 1990s).

Differences 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. Age-specific incidence rates are largely comparable in Europe and the United States. The incidence rate of astrocytic tumors in the age group around 50 years for both sexes combined was roughly 6–7 per 100,000 and increase for ages 60 years and older though the morphological classification are not entirely consistent in various reports [12, 15, 16, 18]. In Asia, lower brain tumor rates are reported compared with the Caucasian populations, for instance, in India, Japan, and Korea often around 3 per 100,000 in men and 2 per 100,000 in women (though somewhat higher in China) [11]. Within the United States, incidence rates of malignant brain tumors vary between the states by a factor of 1.3 at most compared to the average national rate [12].

Globally, mortality from brain and nervous system cancer in 2012 has been estimated as 2.5 per 100,000 (3.0 for men and 2.1 for women), with 174,000 deaths occurring annually [8]. These figures place brain cancer as the 13th most common cause of cancer death. No substantial increase in brain cancer mortality is obvious from the international compilation of cancer statistics [11]. Mortality-incidence ratio of 0.7–0.8 indicates a high case-fatality.

Survival in adult brain tumors varies by histological type, molecular-genetic features 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 1 year or less, 2–3 years have been reported for anaplastic

(grade III) astrocytoma and 4–8 years for diffuse (grade II) astrocytoma [22, 26–29]. Five-year relative survival (survival among patients compared with population same age and sex) for glioblastoma is close to 5%, 30% for anaplastic astrocytoma, and 50% for diffuse astrocytoma [12, 30]. In low-grade glioma and anaplastic astrocytoma, cases with IDH mutation have twice as long median survival as wild-type tumors [31]. In oligodendroglioma, substantially lower 5-year relative survival has been reported from Europe compared with the United States (40% vs 50–80%) [12, 30]. The median survival has been 2–5 years for cases without 1p/19q co-deletion, and as high as 10+ years for those with this favorable prognostic indicator [32, 33]. Ependymoma has the most favorable prognosis of the main glioma types in adults, with median survival of approximately 10 years, and 5-year relative survival of 84% in the United States and 40–70% in Europe depending on age [12, 30, 34, 35]. The decrease in survival with age is more striking for astrocytic than oligodendroglial or ependymal tumors.

Non-occupational Risk Factors for Brain Cancer in Adults

Few etiologic factors have been firmly established for adult brain cancer. The known determinants are hereditary factors and high doses of ionizing radiation, but they account only for a minor fraction of all cases.

A two-fold risk of glioma has been found in first-degree relatives of glioma patients [36–40]. A number of rare hereditary syndromes including tuberous sclerosis, hereditary non-polyposis colorectal cancer syndrome (Lynch or Turcot syndrome involving mutations in DNA mismatch repair genes) and Li–Fraumeni syndromes (inherited mutation of the p53 gene), as well as neurofibromatosis 1/2, 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 1/3000). Genome-wide association studies have indicated more than 20 polymorphisms associated with an increased glioma risk though most showing only small to moderate effect sizes with odds ratios of 1.2–1.4 [41–43]. They involve genes such as EGFR, TERT, RTEL, and others. These explain only a minority of the estimated heritability of gliomas [44].

Several studies on the relation between allergic conditions and glioma have consistently shown a reduced risk associated with asthma and eczema by 20–50% [40, 45–53]. Meta-analyses have confirmed the protective effect for asthma, allergy, and eczema [54, 55]. Also, other markers of atopic constitution such as serum IgE levels and use of antihistamines have been associated with a reduced risk [46, 48, 56–62]. This has been postulated to result from immunological factors, possibly involving increased immunosurveillance with improved antitumor defense mechanisms. 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 [40].

History of chickenpox and antibodies against varicella zoster virus has also been associated with a reduced risk of malignant brain tumors in several studies [63–67].

N-nitroso compounds have been associated with brain tumors in animal models. For humans, the exposure patterns are complex, with intake from both diet and 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 [68]. Several studies have been conducted on smoking and alcohol use but with inconsistent results [69–71]. A meta-analysis of 17 studies showed a pooled RR of 1.1 for ever smokers [72]. 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 [73, 74], 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. Very crude classification such as “electric occupations” or farm-related occupations as proxies for pesticide exposure may lack both sensitivity and specificity. Even detailed classifications of occupational titles 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 for 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 data 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 [75].

The use of job-exposure matrices offers some refinement over occupational title though level of information attainable depends heavily on the input to the matrix, i.e., level of detail

in linking tasks, equipment, and facilities to categories used. A key characteristic is homogeneity of exposure within occupational groups, as a small but highly exposed sub-group is difficult to place meaningfully within a broader stratum. For instance, a job-exposure matrix may accurately reflect exposure within a manufacturing plant, but could add little to a job title if applied to a nationwide study. Direct measurement of exposure at the relevant time-period can be regarded as the gold standard for exposure classification, but is achievable only in prospective cohort studies.

Few studies have been able to address the etiology of 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 farming, physicians, 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 compared 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 [76]. 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 [77, 78]. Findings from the Agricultural Health Study do not show excess brain and nervous system cancer incidence or mortality [79–81].

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 and the results are not consistent [82–85]. Contacts with farm animals have not been associated with an increased risk [86–89].

Other studies addressing specific hypotheses have suggested increased risks in petroleum and pulp industries [90–92], but the results have not been consistent. Brain cancer risk among workers in the petrochemical industry was evaluated in more than 10 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) [93]. An international collaborative cohort study with 60,000 workers in pulp and paper industries did not indicate increased mortality from brain cancer [94].

Increased risks have also been reported for health care workers, mainly physicians, in several studies [90, 95–101]. 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 [95, 102–104]. In 1982, IARC concluded that the evidence for rubber industry was inadequate for brain tumors and in the latest evaluation brain cancer was not among the tumors linked to rubber industry [105]. A review covering a total of 90 studies also concluded that the results concerning brain tumors were inconsistent [106].

Some studies have reported elevated risks in the metal industry, but these have been obtained mainly in large exploratory studies [90, 98, 107, 108].

Specific Agents

Ionizing Radiation

Ionizing radiation refers to particles or waves with sufficient energy to remove electrons from atoms or molecules, consequently inducing a charge (examples include gamma rays and X-rays). 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. Exposure to ionizing radiation in humans occurs in variety of settings, including fractionated high-dose exposures (e.g., patients undergoing cancer radiotherapy), moderate to high dose exposures (e.g., Japanese atomic bomb survivors); chronic low-dose exposures (e.g., radiation workers), and fractionated low dose exposures (e.g., X-rays in diagnostic medical examinations). Currently, the primary sources of ionizing radiation to the population at large are through natural background radiation (e.g., residential radon) and from medical procedures and diagnostic tests (e.g., computed tomography (CT) scans). Occupations that involve exposure to higher than average levels of ionizing radiation include airline crew, physicians and medical technicians, uranium miners, nuclear workers, and laboratory researchers. Occupational exposure tends to be very low dose and highly fractionated. The magnitude of risk associated with these types of exposures, particularly for rare outcomes such as brain cancer, is difficult to estimate in epidemiological studies.

Biological damage by ionizing radiation occurs when energy absorbed by biological tissue interacts directly or indirectly with atoms of critical targets. As radiation moves through the tissue, energy is deposited along the track, causing ionization along the track as well as some clustering at the ends. Direct action occurs when the radiation itself causes ionization of the critical target(s). The majority of damage, however, is caused by indirect action that occurs when radiation interacts with other atoms or molecules in the cell, such as water, to produce reactive free radicals that can break chemical bonds and damage critical target(s). This initiates a series of biological events that eventually leads to cancer or other disease outcomes [109].

In 2000, the International Agency for Research on Cancer (IARC) classified ionizing radiation as a Class 1 Carcinogen [110]. It is noteworthy that this conclusion was based primarily on studies of medical and environmental exposures in childhood, rather than occupational or adult exposures.

At the time of publication of the 2000 IARC monograph, the authors reported an absence of convincing evidence of a significant excess of brain or CNS cancer associated with radiation in any occupational study [110–113]. Since then, several more occupational cohorts have been analyzed and published. Although there was some indication of increased brain cancer mortality in radiologic technologists that reported performing or conducting fluoroscopically guided interventional procedures [114], a cohort-wide analysis of occupational dose to the brain in the same cohort showed no association with malignant tumor mortality [115]. Other independent studies and reviews have also indicated null findings for the association between occupational radiation exposure and brain cancer risk across a wide range of professions including nuclear workers, airline crew, and physicians/medical technicians [116–120] (Table 29.2). These have also indicated null findings for the association between occupational radiation exposure and brain cancer risk.

Table 29.2 Cohort studies of occupational exposure to ionizing radiation and brain cancer

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Pukkala et al. [121]; 5 Nordic countries	10,032 male airline pilots	Occupation		Cases 18	SIR 0.84 (0.50–1.33)		
Cardis et al. (2007) [111]; 15 countries	407,391 nuclear industry workers	Dosimetric history based on personal dosimeters	Cumulative dose (mSv) <5 5 to <10 10 to <20 20 to <50 50 to <100 100 to <150 150 to <200 200–299	Deaths 153 19 25 25 5 5 3 0	O/E 1.01 0.83 1.09 1.17 0.51 1.52 2.00 0.00	Sex, age, calendar period, SES	O/E calculated from data in paper Expected numbers based on internal comparison population ERR/Sv <0
Muirhead et al. (2009) [112]; United Kingdom; 1965–2001	174,541 radiation workers with follow-up from 1965 through 2001	Radiation dose records	Lifetime dose (mSv) <10 10 to <20 20 to <50 50 to <100 100 to <200 200 to <400 400+	Cases 199 48 45 21 14 7 3	O/E 1.01 1.19 0.96 0.84 0.90 0.80 0.69	Age, gender, calendar period, industrial classification, first employer	O/E calculated from data in paper ERR/ Sv = 0.21, 95% CI:−1.49–0.69
Rahu et al. [122]; Estonia, Latvia and Lithuania; 1986–2007	17,040 Chernobyl cleanup workers	Recorded external radiation dose	Documented dose (cGY) <5.0 5.0–9.9 ≥10.0	Cases 6 6 10	Proportional Incidence Ratio 1.32 (0.48–2.86) 0.99 (0.36–2.16) 1.10 (0.53–2.03)	Age group, calendar period, country	

(continued)

Table 29.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Hammer et al. [116]; 10 countries; 1989–1999	93,771 commercial airline crew members	Occupation	Occupation/ sex Cockpit crew/male Cabin crew/ male Cabin crew/ female	Deaths 59 16 29	SMR 1.14 (0.83–1.54) 1.25 (0.64–2.18) 0.95 (0.59–1.46)	Sex, age, calendar period	
Sokolnikov et al. (2015) [117]; Russia; 1948–2008	25,757 nuclear workers	Estimated or recorded badge measurements		Cases 66		Sex, age, smoking	ERR/Gy <0
Berrington de Gonzalez et al. [118]; USA; 1979–2008	43,763 radiologists	Occupation		Deaths 52	0.76 (0.55–1.06)	Attained age, year of birth, year of medical school graduation	Compared to 64,990 psychiatrists
Kitahara et al. [115, 119]; USA; 1982–2012	110,297 radiologic technologists	Film badge measurements and work history		Deaths 193		Sex, attained age	ERR/Gy: 0.1, 95% CI: <−0.3–1.5
Linet et al. [120]; USA; 1979–2008	45,634 physicians likely to perform fluoroscopically guided interventions	Occupation		Deaths 54	0.74 (0.53–1.03)	Attained age, year of birth, year of medical school graduation	Analyses restricted to 41,486 male physicians
Richardson et al. (2018) [113]; France, UK, USA; 1944–2005	308,297 nuclear workers	Target organ dose based on individual annual estimates of whole body dose		Deaths 594	Excess relative risk/ Gray −0.92 (<−0.92, 8.76)	Attained age, country, sex, year of birth, socioeconomic status, duration of employment, exposure to neutrons	90% confidence interval provided

[a]Effect measure used in the study (rate ratio, hazard ratio, odds ratio, or standardised incidence ratio)

The concept of variability in individual sensitivity to radiation has long been supported by data from patients with some rare hereditary conditions such as ataxia-telangiectasia. Consequently, there has been increasing interest in extending the characterization of radiation risk beyond traditional assessment by epidemiologic methods to incorporate the biological evaluation of differences in susceptibility between individuals. Empirical studies of gene–radiation interactions, however, have yielded no convincing signals to date [123]. As tools for characterizing biological effects improve, it will be important to continue monitoring the possibility of increased risks in susceptible subgroups.

Non-ionizing Radiation

Non-ionizing radiation is lower energy than ionizing radiation and includes the radiofrequency fields produced by mobile phones and extremely low frequency range electromagnetic fields (EMF).

While not explicitly an occupational risk, the association between cellular phone use and brain cancer has been studied extensively. In 2011, based mainly on epidemiologic evidence of increased risk of gliomas and vestibular schwannomas in heavy cell phone users, the IARC monograph program deemed radiofrequency electromagnetic fields a Class 2B, i.e., "Possible" carcinogen largely based on studies of cellular phone use and brain tumors [124]. Studies published since the monograph have had mixed findings. Two case-control studies reported an association between self-reported cell phone use and risk of glioma [125, 126], but large cohort studies in Denmark and the UK did not replicate the findings [127, 128]. No association or dose–response association was reported between mobile phone use and malignant brain cancer risk in either cohort study. Possible risks associated with occupational exposures to RF-EMF have been evaluated in both cohort studies (Table 29.3) and case-control studies (Table 29.4). Results of cohort studies have been consistently negative and case-

Table 29.3 Cohort studies of occupational exposure to radiofrequency radiation and brain cancer

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Groves et al. [129]; US servicemen; follow-up 1955–1994	40,581 Navy veterans of Korean War with potential exposure to high-intensity radar; males only	Consensus decisions of Navy personnel	Radar potential exposure Low High	Deaths 51 37	1.01 (0.77–1.33) 0.71 (0.51–0.98)	Age at cohort entry, attained age, year of graduation, year of birth, duration of follow-up	Study provides information pertinent to long-term risks
Morgan et al. [130]; 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 9724 job titles into 1 of 4 RF exposure groups	Usual exposure High Moderate Low None Cumulative exposure ≥Median <Median none	Deaths 3 3 7 38 10 7 34	1.07 (0.32–2.66) 1.18 (0.36–2.92) 0.92 (0.50–1.80) 1.00 0.91 (0.41–1.86) 0.97 (0.37–2.16) 1.00	Age, gender, race, period of hire	44% women, who more often worked in jobs with low or no RF exposure Cohort relatively young (2/3 born 1905 or later)

[a]Effect measure used in the study (rate ratio, hazard ratio, odds ratio, or standardised incidence ratio)

Table 29.4 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)[a]	Adjustment for potential confounders	Comments
Berg et al. [131]; Germany, 2000–2003	366 glioma cases, aged 30–69 years drawn from four neurosurgical clinics	1494 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 No exposure Not probable Probable High Duration of high exposure Not highly exposed <10 years ≥10 years	1.00 0.86 (0.45–1.52) 0.75 (0.40–1.40) 1.17 (0.66–2.08) 1.00 1.07 (0.44–2.57) 1.31 (0.61–2.80)	Sex, age, center	
Grayson [132]; 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 Air Force personnel records; matched on year of birth and race	Job title-time exposure matrix	Cumulative exposure score None 2–48 49–127 128–235 236–610	1.00 1.26 (071–2.24) 1.50 (0.90–2.52) 1.26 (0.71–2.22) 1.51 (0.90–2.51)		Nested case-control study within approximately 880,000 members of US Air Force

(continued)

Table 29.4 (continued)

Reference, study location, and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Karipidis et al. [133]; 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 (W/m^2) Unexposed 1 2 3	1.00 0.57 (0.16–1.96) 1.80 (0.53–6.13) 0.89 (0.28–2.81)	Age, sex, education	
Baldi [134]; France; 1999–2001	221 brain cancer cases drawn from the population of Gironde, France	397 controls from local electoral rolls	Job title-time exposure matrix	Ever exposed (vs. never)	1.50 (0.48–4.70)	Matched on age, sex, and residential area. Controlled for education, treatment of houseplants, exposure to >1 occupational exposure	

[a]Effect measure used in the study (rate ratio, hazard ratio, odds ratio, or standardised incidence ratio)

control studies have shown some hints of increased brain tumor risks, but no consistent or convincing evidence overall.

Occupational groups believed to have the potential for high exposure to magnetic fields include electronics, electrical and electric utility workers. Early studies of electrical workers reported increased risk of brain cancer compared to the general population [135–138]. These studies were criticized for a lack of information about individual-level exposures to EMF and incomplete accounting for other possible risk factors such as soldering fumes and solvents. More recently conducted cohort studies that included transportation workers and welders and used job exposure matrices and cumulative exposure measures have not found a significant association [133, 139–142]. However, one Swedish cohort study reported a potential association between occupational EMF exposure among women, but not among men, and two case-control studies, one focusing on occupational exposure[143], reported increased risk of brain cancer within a specific exposure category (≥3.0 mG average dose and glioblastoma risk) [144] and latency (1–4 years prior to diagnosis) [145]. These specific findings amidst otherwise null results suggest potential Type I error as a result of multiple testing, but may nevertheless merit further exploration. It has been hypothesized that occupational EMF exposure may influence brain cancer risk as an effect modifier of chemical exposure risk (e.g., to inorganic lead), but this has not been heavily explored or conclusively established [146] (Tables 29.5 and 29.6).

Chemical Agents

Pesticides. Perhaps the most extensively studied class of occupational chemical exposures thus far is pesticides. 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 [151]. Also, some indirect exposure indicators (not washing or changing clothes after handling/spraying) have been associated with glioma risk, but this could be due to recall bias [89]. 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 29.7).

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), but overall the results do not indicate clearly increased risks [155–160].

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 [161, 162]. 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 [163].

Table 29.5 Cohort studies of occupational exposure to extremely low frequency radiation and brain cancer

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment for potential confounders	Comments
Savitz and Loomis [147]; 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 (micro-Tesla-years) 0 to <0.6 0.6 to <1.2 1.2 to <2.0 2.0 to <4.3 ≥4.3	Deaths 41 34 26 27 16	1.00 1.61 (0.99.2.63) 1.47 (0.84–2.56) 1.65 (0.92–2.95) 2.29 (1.15–4.56)	Age, calendar year, race, social class, work status (active/ inactive), PCB, and solvent exposure	
Theriault et al. [148]; 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 (≥median exposure) 0–5 0–20 ≥20	Cases 42 43 14 44	1.18 (0.63–2.21) 1.87 (0.93–3.75) 1.05 (0.20–5.38) 1.95 (0.98–3.86)	Year of birth, SES, ionizing radiation, potential chemical confounders (as identified by IARC)	Nested case-control design, with matching on year of birth
Håkansson et al. (2002) [143], Sweden; 1985–1994	537,692 men and 180,529 women employed in industries assumed to use resistance welding in production	Occupation on census linked to job exposure matrix	Mean workday exposure in micro-Tesla Men Low (<0.164) Medium (0.164–0.250) High (0.250–0.530) Very high (>0.530) Women Low (<0.164) Medium (0.164–0.250) High (0.250–0.530) Very high (>0.530)	Cases 105 256 90 47 51 76 40 9	1.00 (ref) 0.90 (0.7–1.1) 1.2 (0.9–1.6) 0.8 (0.5–1.1) 1.00 (Ref) 1.2 (0.8–1.7) 1.6 (1.0–2.4) 1.9 (0.9–3.9)	Age, socioeconomic status	Includes all CNS cancers. Paper also breaks down astrocytomas by grade
Röösli et al. [139]; Switzerland; 1972–2002	20,141 railway employees	Estimated cumulative exposure using years and type of employment	Cumulative exposure (micro-Tesla-years) Hazard ratio per 10-micro-Tesla-years increase	Deaths 38	0.94 (0.88–1.01)	Calendar period, age at cohort entry	
Koeman et al. [142]; Netherlands; 1986–2003	120,852 members of a population-based cohort study	Combining work histories with estimates of exposure for each job held	Level of exposure Men Background Low High Women Background Low High	Cases 74 69 17 40 40 0	1.00 1.01 (0.72–1.42) 1.45 (0.83–2.52) 1.00 0.92 (0.60–1.43) N/A	None	

[a]Effect measure used in the study (rate ratio, hazard ratio, odds ratio, or standardised incidence ratio)

Table 29.6 Case-control studies of occupational exposure to 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)[a]	Adjustment for potential confounders	Comments
Rodvall et al. [149]; Sweden; 1987–1990	84 newly diagnosed, histologically confirmed intra-cranial gliomas	155 population-based controls matched on year, month of birth, and parish	Electrical occupation types, expert opinion, job exposure matrix	Estimated daily dose (micro-Tesla) <0.2 0.2–0.4 >0.40 >0.40 (>5 years)	1.0 (Ref) 1.1 (0.4–2.7) 1.9 (0.8–5.0) 1.8 (0.7–5.11)	Age, population density, social class, self-reported occupational exposure to solvent and plastic materials	
Villeneuve et al. [150]; 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 (micro-Tesla) <0.3 0.3 to <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. (2009) [144]; United States; 1994–1998	489 histologically confirmed glioma cases enrolled through three hospitals; age 18–90 years	799 hospital-based controls 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 to <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. [140]; 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
Turner et al. [145]; 7 countries; 2000–2004	1939 glioma cases recruited from major treatment centers	5404 population controls frequency or individually matched by sex, age, and study center within country	Job history questionnaire combined with job exposure matrix	Cumulative exposure (micro-Tesla) <2.11 2.11 to <3.40 3.40 to <5.00 5.00 to <7.50 >7.50	1.00 1.00 (0.85–1.18) 0.93 (0.78–1.11) 1.07 (0.88–1.31) 0.80 (0.63–1.00)	Age, sex, country, region, educational attainment	Paper also included meningiomas (no association) Found a significant, positive association with exposure 1–4 years prior to diagnosis

[a]Effect measure used in the study (rate ratio, hazard ratio, odds ratio, or standardised incidence ratio)

Table 29.7 Summary of major studies on pesticides and brain cancer

Reference; setting	Study type and subjects	Exposure assessment	Main results	Adjustment
Kogevinas [151]; 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 [82], 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 [83]; 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 two-fold 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[152]; Iowa, Michigan, Minnesota, Wisconsin 1995–97	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 [153]; Iowa, Michigan, Minnesota, Wisconsin 1995–97	Case-control; 798 adult glioma cases, 1175 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 [84]; hospitals in Phoenix, Boston, and Pittsburgh 1994–98	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 life-time exposure to insecticides or herbicides, and no increased risk in the highest exposure categories	Age, hospital, and interview type
Ruder [154]; Iowa, Michigan, Minnesota, Wisconsin 1995–97	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
Yiin [85]; Iowa, Michigan, Minnesota, Wisconsin 1995–97	Case-control; 798 glioma cases and 1175 controls	Interview on farm exposure to pesticides; proxy for 45% of the cases	29% of the cases and 35% of the controls reported having applying pesticides on a farm. OR for insecticide use 0.97 (0.92–1.03), for herbicide use OR 0.78 (0.59–1.01), and fungicides OR 0.8 (0.2–3.2)	Age, sex, and education; results excluding cases with proxy respondents reported separately

The epidemiological evidence regarding occupational exposure to lead has failed to lend consistent material support for the hypothesis of increased risk of brain cancer [161, 164–171]. The potential excess risk was originally proposed in a study with measured blood lead concentrations but only 16 cases [168]. Possible gene–environment interaction has been proposed that might modify the susceptibility to glioblastoma in relation to lead exposure [172].

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 [169]. 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 later research also confirmed the lack of excess risk [170, 171].

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 [172]. 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 [173].

A large cohort study [92] suggested possible risks related to occupational exposure to mercury, but the result was confined to men, with no excess risk among women. Smaller earlier studies have not revealed an association with inorganic mercury.

Concluding Remarks

In summary, occupational etiology of adult 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.

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Occupational Exposures and Thyroid Cancer

30

Gianfranco Alicandro and Carlo La Vecchia

Epidemiology of Thyroid Cancer

Thyroid cancer accounts for the majority of all endocrine cancers, and it is one of the few non-sex-related cancers more common in women than in men. Papillary thyroid cancer is the most frequent histological type (70–80% of all cases) followed by follicular (about 10–15% of all cases) and medullary thyroid cancer (5–10% of all cases), while anaplastic cancers are rare (less than 2% of all cases). Incidence data relative to the first decade of the 2000s showed a high variability among countries and cancer registries [1]. Considering the registries that reported at least 100 cases, thyroid cancers account for 3.5% of total cancer incidence in women and 1% in men. However, some registries reported outlier figures, which in South Korea, reach 30% among women and 5% among men. In a registry from the USA (New York State: Asian and Pacific Islander), thyroid cancer accounts for 11.8% and 2.5% of total cancer incidence in US women and men, respectively. A registry from Italy (Latina) reports similar figures: 9.7% and 2.3% in Italian women and men, respectively.

The number of reported cases is increasing worldwide [2]. The estimated annual percent increase in incidence ranged from 1.27% in the UK men in the period 1960–2000 to 94.4% in South Korean men in the period 1996–2010, and from 1.07% in Switzerland women in the period 1974–1998 to 69.2% in South Korean women in the period 1999–2011. Remarkable increases were also found in Polish women between 1990 and 2001 (annual percentage increase: 67.9%), and in Belarusian women (annual percentage increase: 62.1%) between 1980 and 2001.

These trends are largely due to differences in diagnostic practices during the study periods and among countries, rather than a real increment of the disease [3, 4]. The widespread use of neck ultrasonography and fine-needle aspiration increased the detection of small subclinical cancers. In fact, including thyroid screening with ultrasonography to other cancer-screening tests grossly raised up thyroid cancer incidence in South Korea [4]. Similarly, the extent of thyroid surgery increased the rate of subclinical cancers detected incidentally. Moreover, mortality data support the hypothesis that increased incidence of thyroid cancer is mainly attributable to an increased risk of subclinical cancers with good prognosis. In fact, mortality from thyroid cancer data showed declining trends in the last three to four decades [5].

On the other hand, in the USA the increasing trend was not limited to small subclinical cancers but was found for all tumor sizes [6]. Increased exposure to medical radiations may have also contributed to the increased incidence of thyroid cancer worldwide [7].

Family history of thyroid malignancy and benign diseases are the main risk factors for thyroid cancer. Benign nodules/adenoma and goiter are well-established risk factors for thyroid cancer with relative risks around 5 [8]. In contrast, the role of obesity, dietary patterns, smoking, and alcohol drinking has not been clarified yet [8–12]. Genetic predisposition and environmental factors interact in the carcinogenic process leading to thyroid cancer [13], and single-nucleotide polymorphisms (SNPs) are associated with susceptibility to papillary thyroid cancer [14].

Thyroid tissue is very sensitive to the carcinogenic effect of ionizing radiation, and an acute exposure to high dose, especially during childhood and adolescence, increases the risk of benign as well as malignant thyroid tumors. Epidemiological studies showed a high risk of thyroid cancer in atomic bomb survivors [15], in subjects exposed to ionizing radiation after Chernobyl fallout [16, 17], as well as in children and adolescents who received radiation therapy for tumors [18–21], or fungal infections [22].

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Occupational Exposure to Ionizing Radiation

Exposure to ionizing radiation is the most widely studied occupational exposure related to thyroid malignancies. Table 30.1 gives a summary of the studies investigating the relationship between occupational exposure to ionizing radiation and thyroid cancer incidence or mortality.

Studies on workers employed in the cleanup after the accident at the Chernobyl nuclear power plant on April 26, 1986, showed a remarkable excess risk of thyroid cancer compared to the national populations [23–25]. More than 500,000 men from Belarus, Russian Federation, and Baltic countries were involved in the cleanup activities in the Chernobyl area. These workers had been exposed to external irradiation from γ-ray-emitting radionuclides and to internal irradiation due to inhalation of air and ingestion of foods contaminated by iodine-131 (^{131}I).

A study on a cohort of 150,813 Ukrainian cleanup workers included 196 thyroid cancer cases over the period 1986–2010 and reported a 3.5-fold increased risk of thyroid cancer [95% confidence interval (CI): 3.04, 4.03] compared to the male Ukrainian population [23]. The excess risk was higher at 10–20 years after the accident (age-standardized incidence rate, SIR: 4.62 for the period 1995–1999 and 4.80 for the period 2000–2004) and decreased thereafter (SIR: 2.79 for the period 2005–2010). Similar results were found in a cohort of 103,427 Russian cleanup workers, followed-up from 1986 to 2003 [25]. In that cohort, 87 cases were registered, with a 3.5-fold increased risk of thyroid cancer (95% CI: 2.80, 4.25) compared to the Russian male population. The highest risk was found among workers who arrived at the site between April and July 1986, when the radiation exposure in the contaminated zones was at the highest level (SIR: 6.62, 95% CI: 4.63, 9.09). The excess risk was similar at 4 and 10 years after the accident, ruling out any latent period effect. The analysis of personalized data on external radiation dose did not show a significant dose–response relationship.

A study of a Baltic cohort [24], including 17,040 cleanup workers from Latvia, Lithuania, and Estonia, with 18 thyroid cancer cases observed between 1986 and 2007, found a higher proportion of thyroid cancer among these workers (proportional incidence ratio, PIR: 2.76, 95% CI: 1.63, 4.36) compared to the male population of the three countries. The excess was remarkably higher among workers exposed during the first month after the accident (PIR: 6.38, 95% CI: 2.34, 13.89) and among workers who were exposed to more than 100 mGy (PIR: 4.12, 95%CI: 1.97, 7.57).

A case–control study nested in a cohort of cleanup workers from Belarus, Russia, and Baltic countries [26], including 107 thyroid cancer cases and 423 controls, reconstructed individual external and internal radiation exposure to analyze dose–response relationship. That study reported an excess relative risk (ERR) per 100 mGy of total radiation exposure of 0.38 (95% CI: 0.10, 1.09). The excess risk was particularly high for the two highest categories of exposure (300–399 mGy: OR 4.20, 95% CI 1.62, 10.9, and ≥ 400 mGy: OR 2.63, 95% CI 1.36, 5.09) and was similar between total and internal exposure.

Although all these studies reported a considerable excess risk of thyroid cancer among cleanup workers, this may be somewhat overestimated due to the closer medical surveillance and high ultrasonographic screening rate for thyroid cancer in these workers. The "screening effect" has been quantified in a 2.5-fold increase in thyroid cancer diagnoses [27]. Therefore, a residual excess risk still remains at least in workers exposed to high radiation dose, as confirmed by the dose–risk relationship.

A relevant "screening effect" was also confirmed by a study on workers in nuclear power facilities [28]. That study found an excess risk of thyroid cancer in a group of radiation-exposed workers (SIR: 5.93, 95% CI: 2.84, 10.9) and in a group of non-radiation-exposed workers from the same facilities, who had the same chance to be screened with ultrasonography (SIR: 5.20, 95% CI: 2.24, 10.2), when compared to the general population. However, the non-radiation-exposed workers shared the same risk of the radiation-exposed workers (RR: 1.06, 95% CI: 0.40, 2.87). The dose–response analysis did not show a linear relationship between the amount of radiation received and the risk of thyroid cancer. Only workers who received a cumulative dose over 100 mSv experienced an excess risk compared to non-exposed workers (RR: 18.5, 95% CI: 1.7, 204.3), although this estimate is based only on two cases, and thus imprecise.

Healthcare professionals using diagnostic or therapeutic tools that require radioactive isotopes might be exposed to low/medium doses of ionizing radiations, and thereby they may have some excess risk of thyroid cancer. In 2013, a prospective cohort study from the USA [29], carried out among 75,494 technologists, estimated the risk of thyroid cancer related to 11 selected type of X-ray procedures, including chest CT, cervical spine radiograph, skull radiograph, head CT, thoracic spine radiograph, dental radiographs, mammogram, upper gastrointestinal series, chest radiograph and lumbar spine radiograph. The study reported 251 cases of thyroid cancer and did not find any increased risk per unit of diagnostic procedures, with the only exception for dental radiograph that yielded a 13% increase in total thyroid cancer risk per 10-unit increase of dental radiographs (95% CI: 1.01, 1.26). The excess risk was similar for the papillary subtype (hazard ratio, HR for 10-unit increase in dental radiographs: 1.16, 95% CI: 1.02, 1.31).

A study from Canada [30] evaluated cancer incidence and mortality among a cohort of 191,042 medical workers registered in the National Dose Registry of Canada (NDR). The cohort included physicians, nurses, nuclear medicine technicians, radiation technologists, physicists, and other medical workers occupationally exposed to low levels of radiation (below 1 mSv yearly), with a maximum of 10.4 mSv yearly reported for nuclear medicine technicians at work between 1951 and 1970. After this period, the dose significantly decreased to 1.9 mSv. During the follow-up, 65 cases and only one death from thyroid cancer were reported, with an excess incidence rate compared to the general population

(SIR: 1.74, 95% CI: 1.40, 2.14). Similar results were found in a study on 90,305 radiologic technologists in the USA [31], who were followed during 1983–1998. On the basis of 124 observed cases, the study reported an increased risk of thyroid cancer among radiologic technologists compared to the general population (SIR: 1.61, 95% CI: 1.34, 1.88).

However, these results should be interpreted with caution, since an easier access to screening programs by medical workers may, at least in part, explain this association. This was supported by a study on 90,957 radiologic technologists, who responded to a 1994–1998 survey that collected information on whether they had ever worked with fluoroscopically guided interventional procedures, which exposes workers to low radiation dose (<100 mSv) [32]. In that study, the incidence of some cancer types, including thyroidal cancer, was collected in a subsequent survey during 2003–2005 and compared among radiologic technologists who ever worked with the procedure and those who did not. No excess risk was found among radiologic technologists who worked with the procedure.

In conclusion, although the causal relationship between acute or cumulative exposure to moderate/high radiation dose and thyroid cancer is well recognized, there is less clear evidence that chronic exposure to low dose increases the risk of thyroid cancer.

Occupational Exposure to Pesticides

Many molecules used in agriculture, including insecticides, herbicides and fungicides, may act as thyroid hormone disruptors by interfering with the hypothalamic–pituitary–thyroid axis [33]. The main reported consequence is the reduction in thyroid function, with increased level of thyroid-stimulating hormone (TSH) and decreased levels of free triiodothyronine (FT3) and free thyroxine (FT4) being the most common findings [34]. However, epidemiological studies on the association between exposure to these molecules and thyroid cancer are scarce. Table 30.2 gives a summary overview of those studies.

Findings from a prospective cohort study [35], including 57,310 licensed pesticide applicators in Iowa and North Carolina (the Agricultural Health Study, AHS), showed that intensity-weighted lifetime exposure to the herbicide atrazine is associated with increased incidence of thyroid cancer—the relative risk for the second and the fourth compared to the first quartile of exposure exceeds 4. In an international cohort study (the International Register of Workers Exposed to Phenoxy Herbicides and their Contaminants), workers employed in the production or spraying of chlorophenoxy herbicides or chlorinated phenols showed an increased mortality risk compared to non-exposed workers, although this estimate was based only on 4 deaths [36]. An excess risk was also found among female spouses of organophosphates applicators, with malathion, the most commonly used organophosphate, being associated with increased risk of thyroid cancer (RR: 2.04, 95% CI: 1.14, 3.63) [37]. However, these studies are based on a few cases and thus provide insufficient evidence of a causal link between exposure to pesticides and thyroid cancer risk.

Occupation-based studies of workers enumerated in the 1970 Swedish census did not find any excess risk in workers employed in agriculture [38], forestry, and fishing and in workers with possible exposure to pesticides and herbicides based on a job-exposure matrix [39]. A cohort study including 15 million people from Northern Europe did not find an increased risk of thyroid cancer among male farmers (SIR: 0.95, 95% CI: 0.88, 1.02), whereas it reported a slight excess risk among female farmers (SIR: 1.18, 95% CI: 1.07, 1.30) [40].

Other Occupational Exposures

Census- and industry-based studies suggested that some occupations are associated with an increased risk of thyroid cancer incidence or mortality. The main results of those studies are shown in Table 30.3.

Workers employed in semiconductor, wood, paper, and textile industries showed an excess risk as well as policemen, prison and reformatory officers, fishermen, and school employees. A cohort study of female textile workers in Shanghai who had been followed between 1989 and 1998 [41], using a job-exposure matrix to evaluate occupational exposure, found that possible exposure for at least 10 years to benzene (SIR: 6.43, 95% CI: 1.08, 38), organic or inorganic gases (SIR: 7.65, 95% CI: 1.14, 51), and formaldehyde (SIR: 8.33, 95% CI: 1.16, 60) increased the risk. The estimates were, however, largely imprecise, and no allowance was made for multiple tests. Women among military personnel showed an excess risk for both small (tumor size ≤2 cm, SIR: 1.48, 95% CI: 1.25, 1.74) and large tumors (tumor size >2 cm, SIR: 1.40, 95% CI: 1.08, 1.76) [42]. An increased risk was also documented among World Trade Center (WTC) rescue and recovery workers (SIR: 2.39, 95% CI: 1.70, 3.27) who were exposed to a mix of pollutants and carcinogens, including asbestos, silica, cement dust, glass fibers, heavy metals, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polychlorinated dibenzofurans, and dibenzodioxins [43].

However, differences in medical surveillance and the impossibility to accurately identify the source of exposure did not allow to infer on causality.

Conclusions

Workers exposed to high dose of ionizing radiation have an increased risk of thyroid cancer. However, the excess risk reported in the majority of studies is likely overestimated because of a higher surveillance among workers whose activity entails exposure to ionizing radiation.

It is not possible to draw firm conclusions on other exposure agents, including pesticides or other specific chemicals.

Summary of Evidence

Table 30.1 Studies on workers exposed to ionizing radiation

First author and calendar year of publication	Country	Study design/ number of workers	Job	Study period	Number of cases/ deaths among exposed	Exposure evaluation	Dose–response analysis	Comparison	HR/OR/RR/PIR/SIR/ SMR [95% CI]
Rajaraman et al. 2016 [32]	USA	Cohort study/90,957	Radiologic technologists who had ever worked with fluoroscopically guided interventional procedures	1994–2005	32 cases	Not evaluated	Not performed	Technologists who never worked with the procedures	SIR: 0.91 [0.61; 1.38]
Lee et al. 2015 [44]	South Korea	Cohort study/12,387	Radiologic technologists	1992–2010	42 cases (19 men, 23 women)	Individual dose Average annual effective dose range (0.77–2.75 mSv)	Retrospective cohort	National population	SIR men: 2.14 [1.29; 3.35] SIR women: 2.08 [1.32; 3.12]
Ostroumova et al. 2014 [23]	Ukraine	Cohort study/150,813 men	Chernobyl cleanup workers	1986–2010	196 cases	Not evaluated	Not performed	National population	SIR: 3.50 [3.04; 4.03]
Neta et al. 2013 [29]	USA	Cohort study/75,494	Radiologic technologists	1983–2005	251 cases	For a series of radiological procedures, participants were asked whether they had ever had the procedure, the number of times, and the year they had the procedure for the first time	SIR per 10 dental radiographs (all thyroid cancer type): 1.13 [1.01; 1.26] No significant relationship with unit increase of cervical spine radiograph, skull radiograph, other head and neck radiograph, angiogram, mammogram, chest radiograph, upper gastrointestinal series, barium swallow, lumbar/ thoracic spine radiograph	–	–
Rahu et al. 2013 [24]	Estonia, Latvia, and Lithuania	Cohort study/17,040 men	Chernobyl cleanup workers	1986–2008	18 cases	External radiation dose obtained from military passports. Average dose of 109 mGy (interquartile range: 52–163 mGy)	PIR < 50 mGy: 2.44 [0.50; 7.13] PIR 50–99 mGy: 1.82 [0.37; 5.31] PIR ≥ 100 mGy: 4.12 [1.97; 7.57]	National populations	PIR: 2.76 [1.63; 4.36]

Choi et al. 2013 [45]	Korea	Cohort study/36,394	Diagnostic radiation workers	1996–2002	16 cases (7 men and 9 women)	Individual radiation exposure 5% of male workers and 1% of female workers experienced more than 5 mSv/year of radiation exposure	In females, the risk of thyroid cancers in the highest quartile dose group was significantly higher than that in the lower three quartiles dose groups	National population Q4 vs. Q1–Q3	SIR men: 1.45 [0.38; 2.53] SIR women: 0.97 [0.34; 1.61] HR men: 3.55 [0.85–14.81] HR women: 3.88 [1.09–13.75]
Kesminiene et al. 2012 [26]	Belarusian, Russian, and Baltic liquidators	Case–control study/107 cases and 423 controls	Chernobyl cleanup workers	1993–2000	107 cases	Individual doses to the thyroid from external radiation and from iodine-131 (^{131}I) were estimated for each subject The median radiation dose from all radiation types was estimated to be 70.4 mGy in Belarus, 63.0 mGy in Russia, and 55.5 mGy in Baltic countries	The excess relative risk per 100 mGy was 0.38 [95% CI: 0.10, 1.09]	Controls randomly selected from the roster of the study population in each country	–
Jeong et al. 2010 [28]	Korea	Cohort study/8429 men	Radiation workers (nuclear power facility)	1992–2005	18 cases	Individual doses	Excess relative risk per Sievert not significantly different from 0 RR for 1–50 mSv: 1.57 [0.16; 13.9] RR for 50–100 mSv: 5.62 [0.22; 74.4] RR for >100 mSv: 18.5 [1.7; 204]	National population Non-radiation workers	SIR: 5.93 [2.84; 10.9] RR: 1.06 [0.40; 2.87]
Zielinski et al. 2009 [30]	Canada	Cohort study/67,562	Medical workers occupationally exposed to ionizing radiation	1951–1987	65 cases (14 men and 51 women)	Dosimetry information was obtained from the National Dosimetry Services. For all job categories, the mean yearly dose was below 3 mSv/year in the period 1951–1970 and below 1 mSv/year in the period 1971–1987 with the exception of 12 workers who received a dose over than 10 mSv/year	Not evaluated	National population	SIR men and women: 1.74 [90% CI: 1.40–2.10] SIR men: 2.10 [1.27; 3.29] SIR women: 1.66 [1.30; 2.10]

(continued)

Table 30.1 (continued)

First author and calendar year of publication	Country	Study design/ number of workers	Job	Study period	Number of cases/ deaths among exposed	Exposure evaluation	Dose–response analysis	Comparison	HR/OR/RR/PIR/SIR/ SMR [95% CI]
Ahn et al. 2008 [46]	Korea	Cohort study/79,679	Workers under medical surveillance because of ionizing radiation exposure	1984–2004	72 cases (13 among workers in medical institute, 24 among workers in power plants, 10 among workers in education and research and 14 among industry workers)	Individual radiation exposure	Excess relative risk per Sievert not significantly different from 0	Automobile workers	SIR for workers in medical institutes: 2.05 [0.95; 4.27] SIR for workers in power plants: 2.59 [1.33; 5.13] SIR for workers in education and research: 1.51 [0.65; 3.30] SIR for industry workers: 1.35 [0.64; 2.82]
Ivanov et al. 2008 [25]	Russia	Cohort study/103,427 men	Chernobyl emergency workers	1986–2003	87 cases	Individual external radiation dose was available for 72.8% of the cohort. Mean dose was 168 mGy in 1986 and decreased to 33 mGy in the period 1988–1990	No significant dose–response	National population	SIR: 3.47 [2.80; 4.25]
Lie et al. 2008 [47]	Norway	Cohort study	Nurses potentially exposed to ionizing radiation as indicated by their work history	1953–2002	18 cases	Not evaluated	Not performed	Non-exposed workers	RR for workers exposed 1–19 years: 0.64 [0.23; 1.75] RR for workers exposed 20–39 years: 0.92 [0.45; 1.88] RR for workers exposed 40+ years: 0.96 [0.36; 2.61]

Zabel et al. 2006 [48]	USA	Cohort study/73,080	Radiologic technologists	1982–1998	121 cases	Not evaluated	Not performed	X-ray technologists who held patients less than 50 times X-ray technologists who worked less than 5 years X-ray technologists who worked after 1970 X-ray technologists who worked after 1950	HR for X-ray technologists who held patients 50 or more times: 1.46 [0.86; 2.46] HR for X-ray technologists who worked more than 25 years: 2.29 [0.99; 5.32] HR for X-ray technologists who worked before 1950: 2.44 [0.74; 8.06] HR for X-ray technologists who worked more than 5 years before 1950: 3.04 [1.01; 10.78]
Lope et al. 2006 [49]	Sweden	Cohort study/NA	Workers potentially exposed to ionizing radiation based on job-exposure matrices	1971–1989	51 (23 men and 28 women)	Job-exposure matrices	No significant dose–response	Unexposed	RR men: 0.79 [0.52–1.20] RR women: 1.13 [0.78–1.65]
Sigurdson et al. 2003 [31]	USA	Cohort study/90,305	Radiologic technologists	1983–1998	124 cases (17 men and 107 women)	Not evaluated	Not performed	National population	SIR men: 1.54 [1.24; 1.83] SIR women: 2.23 [1.29; 3.59]
Fincham et al. 2000 [50]	Canada	Case–control study/100 cases and 192 controls	Workers potentially exposed to ionizing radiation as inferred by job titles	1986–1988	65 cases	Not evaluated	Not performed	Population control subjects	OR: 1.03 [0.60; 1.77]
Haselkorn et al. 2000 [51]	Los Angeles County, USA	Cohort study	Radiologic technicians	1972–1995	9 cases (5 men and 4 women)	Not evaluated	Not performed	Other occupations	PIR men: 4.26 [1.37; 9.94] PIR women: 1.14 [0.31; 2.91]
Muirhead et al. 1999 [52]	UK	Cohort study/124,743	Workers exposed to ionizing radiation	1955–1992	12 cases	Individual radiation exposure	No significant trend in thyroid cancer risk with dose (ERR: 4.24 Sv^{-1}, 90% CI: –0.79, 77.9)	National population	SMR: 1.52 [90% CI: 0.79; 2.66]

(continued)

Table 30.1 (continued)

First author and calendar year of publication	Country	Study design/ number of workers	Job	Study period	Number of cases/ deaths among exposed	Exposure evaluation	Dose–response analysis	Comparison	HR/OR/RR/PIR/SIR/ SMR [95% CI]
Omar et al. 1999 [53]	England	Cohort study/14,319	Workers at nuclear fuel plants	1947–1992	6 deaths	Individual dose	Not performed	Population of England and Wales	SMR plutonium worker: 1.50 ($P > 0.05$) SMR other radiation exposure: 4.29 ($P < 0.05$) SMR non-radiation workers: 2.53 ($P > 0.0\%$)
Wingren et al. 1995 [54]	Sweden	Case–control study/185 cases, 426 controls	Dentist/dental assistants	1977–1989	7 cases	Not evaluated	Not performed	Population of the same areas	OR: 13.1 [2.1; 289]
Hallquist et al. 1993 [55]	Sweden	Case–control study/9 cases and 10 controls	X-ray workers	1980–1989	9 cases	Not evaluated	Not performed	National population	OR for all thyroid cancer: 1.7 [0.7; 5.1] OR for papillary thyroid cancer: 2.9 [1.1; 8.3]
Kendall et al. 1992 [56]	United Kingdom	Cohort study/95,217	Workers in nuclear industries	1976–1988	9 deaths	Individual dose	Excess relative risk per Sievert not significantly different from 0	National population	SMR unlagged analysis: 2.14 ($P < 0.05$) SMR lagged (first 10 years excluded) analysis: 3.03 ($P < 0.01$)
Wang et al. 1990 [57]	China	Cohort study/27,011	Radiologists and technicians	1950–1985	8 cases	Not evaluated	Not performed	Physicians who worked at the same hospitals during the same period	RR: 1.7 [0.6; 4.7]

CI confidence intervals, *HR* hazard ratio, *OR* odds ratio, *PIR* proportional incidence ratio, *RR* relative risk, *SIR,* age-standardized incidence ratio, *SMR* age-standardized mortality ratio

Table 30.2 Studies on workers exposed to pesticides

First author and calendar year of publication	Country	Study design/ number of workers	Job	Follow-up	Number of cases/ deaths among exposed	Exposure evaluation	Dose–response analysis	Comparison	OR/RR/PMR/RR/ SIR/SMR [95% CI]
Lerro et al. 2015 [37]	Iowa and North Carolina, USA	Cohort study/30,003 women	Spouses of organophosphates (OP) applicators	1993–2011	24 cases	Referred exposure	Not evaluated	No OP users	RR for any OP: 1.27 [0.70, 2.30] RR for Malathion: 2.04 [1.14, 3.63]
Beane Freeman et al. 2011 [35]	Iowa and North Carolina, USA	Cohort study/57,310 (36,357 atrazine users)	Atrazine applicators	1993–2007	29 cases	Lifetime days of use Intensity-weighted lifetime days of use: a measure of exposure obtained by multiplying the lifetime days by a measure of exposure intensity based on handling practices	RR Q4 vs. Q1 of lifetime days: 2.32 [0.66–8.22] RR Q4 vs. Q1 of intensity-weighted Lifetime days: 4.84 [1.31; 17.93]	–	–
Lope et al. 2009 [39]	Sweden	Cohort study/2,992,166	Swedish workers who were gainfully employed at the time of the 1970 census	1971–1989	96 cases among workers with possible exposure to pesticides/ herbicides (84 men and 12 women)	Swedish job-exposure matrix	Not performed	No exposure	SIR for men probable exposed to pesticides/ herbicides 0.97 [0.77; 1.23] SIR for women probable exposed to pesticides/ herbicides 0.84 [0.35; 2.03]
Pukkala et al. 2009 [40]	Denmark, Finland, Iceland, Norway, Sweden	Cohort study/15,000,000	Farmers	1961–2005	639 men 420 women	Not evaluated	Not performed	National populations	SIR men: 0.95 [0.88; 1.02] SIR women: 1.18 [1.07; 1.30]
Lope et al. 2005 [38]	Sweden	Cohort study/not reported	Swedish workers in agriculture, forestry, and fishing who were gainfully employed at the time of the 1970 census	1971–1989	214 cases (132 men and 82 women)	Not evaluated	Not performed	The whole cohort of workers	RR men: 1.01 [0.84; 1.21] RR women: 1.06 [0.85; 1.33]

(continued)

Table 30.2 (continued)

First author and calendar year of publication	Country	Study design/ number of workers	Job	Follow-up	Number of cases/ deaths among exposed	Exposure evaluation	Dose–response analysis	Comparison	OR/RR/PMR/RR/ SIR/SMR [95% CI]
Lee et al. 2004 [58]	Iowa and North Carolina, USA	Cohort study/26,510	Alachlor applicators	1993–2000	10 cases	Referred exposure	RR Q4 vs. Q1 intensity weighted exposure: 2.89 [0.22; 38.7]	Non-exposed workers	RR: 1.63 [0.42; 6.37]
Fincham et al. 2000 [50]	Canada	Case–control study/45 cases and 97 controls	Farmers	1986–1988	45 cases	Not evaluated	Not performed	Population control subjects	OR: 0.92 [0.64; 1.32]
Franceschi et al. 1993 [59]	North-east Italy	Case–control/20 cases and 2476 controls	Farmers	1985–1991	20 cases (1 men, 19 women)	Not evaluated	Not performed	Patients admitted in hospital for acute conditions	OR for women born before 1930: 0.8 [0.3; 1.9] OR for women born after 1930: 1.4 [0.7; 1.3]
Blair et al. 1993 [60]	USA	Study based on death certificates	Farmers	1984–1988	39 deaths among white men, 1 death among white women, 1 death among non-white men and 1 death among non-white women	Not evaluated	Not performed	Non farmer workers	PMR among white men: 1.34 [0.95; 1.83]
Hallquist et al. 1993 [55]	Sweden	Case–control study/24 cases and 53 controls	Farmers	1980–1989	24 cases	Not evaluated	Not performed	National population	OR: 0.8 [0.4; 1.5]
Saracci et al. 1991 [36]	Australia, Austria, Canada, Denmark, Finland, Italy, Netherlands, New Zealand, Sweden, UK	Cohort study, 18,910	Workers exposed to chlorophenoxy herbicides or chlorinated phenols	1955–1987	4 deaths	Exposure reconstructed through questionnaires, factory records, and job history	Not performed	WHO population	SMR: 3.67 [1.00; 9.40]
Carstensen et al. 1990 [61]	Sweden	Cohort study/2,920,000 workers	Farmers, fishermen, hunters	1961–1979	5 (2 men and 3 women)	Not evaluated	Not performed	Whole population	SIR men: 0.28 (NS) SIR women: 0.54 (NS)

CI confidence intervals, *OR* odds ratio, *PMR* proportional mortality ratio, *RR* relative risk, *SIR* age-standardized incidence ratio, *SMR* age-standardized mortality ratio

Table 30.3 Studies on other occupational exposures

First author and calendar year of publication	Country	Study design/ number of workers	Job	Follow-up	Number of cases/deaths	Exposure evaluation	Dose–response analysis	Comparison	OR/SIR/SMR [95% CI]
Ruder et al. 2004 [62]	Indiana, Massachusetts, and New York	Cohort study/25,062	Workers exposed to polychlorinated biphenyls (PCBs)	1940–2008	3 deaths	Plant-specific job-exposure matrices	Not performed	National population	SMR: 0.52 [0.11; 1.53]
Solan et al. 2013 [43]	New York, New Jersey, Connecticut, and Pennsylvania, USA	Cohort study/20,984	World Trade Center (WTC) rescue and recovery workers	2001–2008	39 cases	Exposure variable using a 4-point scale (very high, high, intermediate, and low) was created based on total time spent working at Ground Zero, exposure to the dust cloud, and work on the debris pile	Not performed	National population	SIR: 2.39 [1.70; 3.27]
Enewold et al. 2011 [42]	USA	Cohort study/not reported	Military personnel	1990–2004	743 cases (410 men and 333 women)	Not evaluated	Not performed	National population	SIR men: tumor size ≤2 cm: 1.03 [0.86, 1.22] tumor size >2 cm: 1.18 [0.97, 1.42] SIR women: tumor size ≤2 cm: 1.48 (1.25, 1.74) tumor size >2 cm: 1.40 [1.08, 1.76]
Lee et al. 2011 [63]	Korea	Cohort study/108,443 for incidence and 113,443 for mortality	Semiconductor workers	1998–2007 (incidence)/2008 (mortality)	100 cases (38 men and 62 women) 0 deaths	Not evaluated	Not performed	National population	SIR men: 2.11 [1.49; 2.89] SIR women: 0.99 [0.76; 1.27] SMR men: 0 [0.00; 14.21] SMR women 0 [0.00; 64.24]
Johnson et al. 2011 [65]	USA	Cohort study/4116	Seafood workers	1966–2003	3 deaths	Not evaluated	Not performed	National population	SMR: 6.1 [1.3; 18.0]

(continued)

Table 30.3 (continued)

First author and calendar year of publication	Country	Study design/ number of workers	Job	Follow-up	Number of cases/deaths	Exposure evaluation	Dose–response analysis	Comparison	OR/SIR/SMR [95% CI]
Kuzmickiene et al. 2010 [66]	Lithuania	Cohort study/3447 women	Workers in a flax textile factory	1978–2002	2 cases among workers in spinning-weaving unit 3 cases among workers in dyeing-finishing unit	Not evaluated	Not performed	National population	SIR spinning-weaving unit: 0.48 [0.06; 1.73] SIR dyeing-finishing unit: 5.00 [1.03; 14.6]
Lope et al. 2009 [39]	Sweden	Cohort study/2,992,166	Swedish workers who were gainfully employed at the time of the 1970 census	1971–1989	2599 cases (89 men and 11 women among workers with possible exposure to solvents)	Swedish job-exposure matrix The chemicals included in the matrix were arsenic, asbestos, chromium/nickel, lead, mercury, metal compounds, oil mist, polycyclic aromatic hydrocarbons, pesticides or herbicides, pesticides or herbicides at peak exposure (mainly sprayers), petroleum products, quartz, solvents, and textile dust	Not performed	No exposure	SIR women probable exposed to solvents: 1.91 [1.05; 3.45] No significant excess risk were found in men and/or other chemicals in women
Bates et al. 2007 [67]	USA	Case–control/3659	Firefighters	Study period: 1988–2003	32 cases	Not evaluated	Not performed	All other cancers	OR: 1.06 [0.75; 1.51]
Wong et al. 2006 [41]	Shanghai, China	Case–cohort study nested in a cohort/67,400 women	Textile workers	1989–1998	130 incident thyroid cases	Historical monitoring information from government and factory inspection reports	Dose–response was evaluated only for cotton dust and endotoxin. No dose–response association was found	Never vs. 10 years exposure	SIR workers exposed to benzene: 6.43 [1.08; 38] SIR workers exposed to organic or inorganic gases: 7.65 [1.14; 51] SIR workers exposed to formaldehyde: 8.33 [1.16; 60] No significantly differences for exposure to pesticides, electromagnetic field/ nonionizing radiation, endotoxin, and solvents

Lope et al. 2005 [38]	Sweden	Cohort study/2,845,992	Swedish workers who were gainfully employed at the time of the 1970 census	1971–1989	2599 cases	Not evaluated	Not performed	The whole cohort of workers	SIR men: Construction carpenters and joiners: 1.41 [1.06–1.80] Paper pulp workers: 2.11 [1.00; 4.45] Policemen: 2.12 [1.23; 3.60] Prison and reformatory officers: 3.56 [1.48; 8.57] Manufacturer of agricultural machinery: 2.23 [1.06; 4.69] Manufacture of office, computing, and accessories: 2.16 [1.12; 4.16] Public administration: 1.90 [1.41; 2.54] SIR women: Medical technician: 3.30 [1.06; 10.2] Shop managers: 1.80 [1.10; 2.94] Tailors and dressmakers: 1.81 [1.00; 3.28] Shoe cutters, lasters, and sewers: 2.46 [1.10; 5.48] Manufacture of prefabricated wooden building: 2.56 [1.22; 5.38] Electric installation work: 2.53 [1.14; 5.64] Wholesale of live animals, fertilizers, oilseed, and grain: 2.83 [1.27; 6.31]
McLean et al. 2004 [64]	New Zealand	Cohort study/6647	Workers in meat processing plants	1988–2000	3 cases 2 deaths	Not evaluated	Not performed	National population	SIR: 1.84 [0.38; 5.38] SMR: 15.55 [1.88; 56.15]

(continued)

Table 30.3 (continued)

First author and calendar year of publication	Country	Study design/ number of workers	Job	Follow-up	Number of cases/deaths	Exposure evaluation	Dose–response analysis	Comparison	OR/SIR/SMR [95% CI]
Veys et al. 2004 [68]	West Midlands	Cohort study/6454 men	Rubber workers	1965–1985	4 deaths	Not evaluated	Not performed	National population	SMR: 3.49 [0.95; 8.94]
Mallin et al. 2004 [69]	USA	Cohort study/2885	Electrical capacitor manufacturing workers	1944–2000	3 deaths	Not evaluated	Not performed	National population	SMR: 15.2 [3.1; 44.5]
Shaham et al. 2003 [70]	Israel	Cohort study/4300	Laboratory workers	1960–1997	11 cases among women No cases among men	Not evaluated	Not performed	National population	SIR women: 1.61 [0.80; 2.87]
Sathiakumar et al. 2001 [71]	Illinois, USA	Cohort study/5641	Workers at a petrochemical research facility	1986–1997	7 cases	Not evaluated	Not performed	Illinois general population	SIR: 2.65 [1.06; 5.46]
Fincham et al. 2000 [50]	Canada	Case–control study/14 cases and 10 controls	Wood processing, pulp, paper making	1986–1988	14 cases	Not evaluated	Not performed	Population control subjects	OR: 2.83 [1.27; 6.29]
Fillmore et al. 1999 [72]	USA	Study based on death certificates	Workers exposed to silica	1984–1993	149 deaths among men 17 deaths among women	Not evaluated	Not performed	National population	PMR men: 0.89 [0.75; 1.04] PMR women: 1.29 [0.75; 2.07]
Reynolds et al. 1999 [73]	USA	Cohort study/271,490	School employees	1987–1992	133 cases	Not evaluated	Not performed	National population	SIR men: 1.87 [1.26; 2.67] SIR Women: 1.28 [1.04; 1.55]
Frich et al. 1997 [74]	Norway	Cohort study/1,200,000 of whom 40,839 had a spouse employed in fishing, whaling and sealing work	Women registered in the 1960,1970, and 1980 census having a spouse with an occupation	1960–1992	174 cases	Not evaluated	Not performed	National population	SIR: 1.91 [1.65; 2.21]
Blair et al. 1990 [75]	USA	Cohort study/5365	Dry cleaners	1945–1979	3 cases	Based on job history and duration	Not performed	National population	SMR: 3.3 [0.7; 9.8]

Carstensen et al. 1990 [61]	Sweden	Cohort study/2,920,000 workers	Classified as full employed in the 1960 census	1961–1979	4167 cases	Not evaluated	Not performed	Whole population	Occupation or industries which showed a significant excess risk: SIR men (N): Stenographers and typists: 3.47 (5) Drivers: 1.39 (63) Textile workers: 2.01 (12) Petroleum refineries: 3.85 (5) Road passenger transport: 2.14 (14) Medical and other health service: 1.82 (22) SIR women (N): X-ray operators: 2.24 (9) Buyers, dealers: 2.61 (8) Canning and preserving industry workers: 2.28 (9) Canning and preserving fish and other seafood: 2.99 (7) Restaurant: 1.49 (38)
Delzell et al. 1983 [76]	North Carolina, USA	Study based on death certificates	Textile industry female employees	1976–1978	8 deaths	Not evaluated	Not performed	Non-textile workers	PMR: 2.2 [1.0; 5.0]

CI confidence intervals, *OR* odds ratio, *PMR* proportional mortality ratio, *RR* relative risk, *SIR* age-standardized incidence ratio, *SMR* age-standardized mortality ratio

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Lymphohematopoietic Malignancies

31

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Introduction

Lymphohematopoietic malignancies are common cancers in both males and females [1]: estimated number of cases for 2018 in the USA are 41,730 for non-Hodgkin lymphoma and 35,030 for leukemia, for males; the corresponding figures for females are 32,950 and 25,270, respectively [1]. Taken together, these lymphohematopoietic malignancies rank third among cancers both in males (approximately 9%, after prostate and lung and bronchus) and females (approximately 8%, after breast and lung and bronchus).

According to the data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute of the USA [2], the incidence of non-Hodgkin lymphoma almost doubled for both sexes since the mid-1970s to the late-1990s (the rates in men being 50% greater than in women), whereas most of the other lymphohematopoietic malignancies did not increase. Globally, age-standardized death rate for non-Hodgkin lymphoma seems to be stable in the last decade, whereas it seems to be declining (more or less) for all other lymphohematopoietic malignancies [3].

Hematopoietic stem cells are the ancestor of the common myeloid and common lymphoid progenitors [4]. As such, it would be possible that a multipotent, occupational carcinogen (e.g., ionizing radiations or tobacco smoke) could give rise to cancer either of the myeloid or lymphoid lineage, or both: however, in this chapter we will consider separately the evidence linking occupational carcinogens to myeloid and lymphoid malignancies.

A major drawback of the research about occupational lymphohematopoietic malignancies, already underlined in the previous edition of this book, is that they are a highly heterogeneous set of possibly very different diseases and this may explain the relative inconsistency of the different studies on this topic, apart some stable results regarding, for example, ionizing radiation or benzene.

For this purpose, before analyzing the evidence linking some occupational exposures to hematopoietic and lymphatic malignancies, we recall the actual international classification of these cancers.

Principles of Classification of Lymphohematopoietic Malignancies

The tumors of the hematopoietic system are highly heterogeneous, in terms of both biology and clinical presentation, as they derive from many types of cells at different stages of their differentiation and maturation. The purpose of a classification rests on the fact that it should provide a common "language" (i.e., disease definitions and disease nomenclature) among experts in the field, along with the information that allows a correct individuation of the diagnosis and the application of the most suitable treatment. The guiding principle of the World Health Organization (WHO) classification, both of its initial editions and of the present revision, is therefore the existence of a consensus among hematopathologists and clinicians, which accounts for its reproducibility in real life and in clinical trials.

According to the Editors of the 2017 revised WHO classification, "*a classification should contain diseases that are clearly defined, clinically distinctive, and non-overlapping (i.e. mutually exclusive), and that together constitute all known entities (i.e. are collectively exhaustive). A classification should provide a basis for future investigation and should be able to incorporate new information as it becomes available*" [5].

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Morphology is the first aspect in defining a disease, as many entities can be recognized according to peculiar features or may display typical morphologic hallmarks. Immunophenotyping corroborates the morphological evaluation and immunohistochemistry is regarded as a tool applied routinely to distinguish between neoplastic and nonmalignant processes, to establish the lineage of clonal diseases, to identify certain entities within a broader subgroup of diseases. Genetic abnormalities and molecular markers may also be useful in defining a disease, in evaluating its prognosis, in monitoring the outcomes of its treatment or in finding out potential targets for therapy. Several recent findings in basic investigation, along with the continuous refinement of laboratory techniques, have led to the discovery of genetic and molecular abnormalities that are characteristic of a specific disease (such as the *BCR-ABL1* gene fusion in chronic myeloid leukemia) or a disease subgroup (like *JAK2* mutations within Philadelphia-negative chronic myeloproliferative neoplasms). Given that our understanding of the processes underlying blood diseases is continuously evolving and that a huge bulk of new data is constantly produced, it is implied that the classification is dynamic and warrants periodical updates: consequently, new disease entities are progressively added, and previous provisional categories are often accepted as definite entities.

The combination of morphology, immunophenotype, genetic aberrations and molecular features is functional to provide objective and widely acknowledged diagnostic criteria.

Clinical information is also important to establish the correct diagnosis: patient's age, disease presentation (nodal versus extranodal, localized versus disseminated), performance status, history of cytotoxic treatments, involvement of a specific (or even more than one) anatomical site, peripheral blood counts, all contextualize, and corroborate laboratory data. Therefore, a continuous dialogue between clinicians, pathologists, and molecular biologists should always be encouraged.

Classification of Myeloid Malignancies

Myeloid leukemias or myeloproliferative syndromes are neoplastic diseases of the hematopoietic system characterized by an abnormal production of mature or immature cells of the myeloid lineage, including granulocytes, monocytes, erythrocytes, and platelets. The cell of origin is postulated to be the pluripotent hematopoietic stem cell, and the elements that originate from its neoplastic transformation all display a myeloid phenotype, hence the definition of myeloproliferative diseases. Myeloid malignancies may be clinically characterized as acute and chronic: this distinction depends mainly on the course and duration of any single disease, but it also reflects the grade of differentiation and maturation of the neoplastic elements, in comparison to their normal cell counterparts. In other words, acute myeloproliferative syndromes (acute myeloid leukemias) display an abortive differentiation of the hematopoietic stem cell, although it can be commissioned at least in part to the myeloid lineage and consist of the accumulation of immature blasts within the bone marrow and the peripheral blood, without signs of maturation of all of the three myeloid lineages. Contrarily, chronic myeloproliferative syndromes are characterized by both a defect in cell maturation and a hyperproliferative potential of leukemic cells, which results in an excessive production of granulocytes (as in chronic myeloid leukemia), erythrocytes (polycythemia vera), or platelets (essential thrombocythemia), with the presence of an increased amount of immature granulated precursors both in the peripheral blood and in the bone marrow, along with a variable degree of marrow fibrosis. Myelodysplastic syndromes (previously defined *subacute* myeloid leukemias) are instead characterized by ineffective hemopoiesis, which leads to one or more peripheral blood cytopenias, which constitute the hallmark of the disease, without any marked excess of myeloid blasts. Chronic myeloproliferative syndromes and myelodysplastic syndromes may evolve to an acute leukemia over time as the terminal event of their natural history.

This clinical distinction, however, is not always easy, as patients may contemporarily show signs of myeloid proliferation (which may induce clinicians to consider them as having a chronic myeloproliferative neoplasm) and of ineffective hemopoiesis: patients with these features cannot fit into any of the previous disease categories, thus the most recent WHO classification acknowledges an intermediate category, which groups together myelodysplastic/myeloproliferative syndromes showing the clinical aspects of both entities.

The current classification of myeloid neoplasms is therefore rather complex, as it considers biologically and clinically heterogeneous diseases, sometimes with areas of overlap, as discussed. Myeloid tumors are classified as follows [6, 7].

- Myeloproliferative neoplasms
- Mastocytosis
- Myeloid/lymphoid neoplasms associated with eosinophilia and rearrangements of *PDGFRA*, *PDGFRB*, or *FGFR1* or with *PCM1-JAK2*
- Myelodysplastic/myeloproliferative neoplasms
- Myelodysplastic syndromes
- Myeloid neoplasms with germ line predisposition
- Acute myeloid leukemia and related precursor neoplasms (including blastic plasmacytoid dendritic cell neoplasm)
- Acute leukemias of ambiguous lineage

We will briefly discuss in this paragraph the current classification criteria for the most relevant disease categories.

Myeloproliferative Neoplasms

The myeloproliferative neoplasms are clonal disorders of the hematopoietic stem cell which present with the proliferation of cells of one or more myeloid lineages. The maturation of myeloid elements is not ineffective and leads to an increased number of granulocytes (and their precursors), erythrocytes, and platelets in peripheral blood; this is associated with an age-matched bone marrow hypercellularity, with some distinctive morphologic changes regarding erythropoiesis and megakaryocytopoiesis (panmyelosis, erythroid and granulocytic prominence, megakaryocyte nuclear alterations and cluster formation, increased reticulin or collagen marrow fibrosis, osteosclerosis).

Splenomegaly and hepatomegaly are frequently encountered, because of sequestration of excess blood cells or proliferation of abnormal hematopoietic progenitors (myeloid metaplasia). Each myeloproliferative neoplasm has the potential to evolve in marrow failure (with myelofibrosis and ineffective hematopoiesis), as well as into an acute blast phase.

Clonal abnormalities involving genes encoding protein kinases or occurring in genes regulating these pathways, which lead to the constitutive activation of proliferative signaling, may be used as a tool to define the diagnosis or can provide proof that the myeloid proliferation is neoplastic (or clonal) than reactive. The *BCR-ABL1* gene fusion in chronic myeloid leukemia is the hallmark of the disease. It is the consequence of the t(9;22) translocation that creates a small 22q$^-$ derivative chromosome (Philadelphia chromosome) and acts as the major determinant of leukemogenesis. The fusion protein codified by the fusion gene is the specific target of treatment, which is based on older and newer tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib), and the determination of RNA transcripts is necessary to establish the depth of response to inhibitors. Acquired somatic mutations in *JAK2*, at chromosome band 9p24, have a pivotal role in the pathogenesis of many cases of *BRC-ABL1*-negative myeloproliferative neoplasms. The *JAK2* V617F mutation is the most common genetic alteration, with a pathogenetic role as it promotes transformation and proliferation of hematopoietic progenitors. This mutation is almost invariably found in patients with polycythemia vera, and in about half of the patients with essential thrombocythemia and primary myelofibrosis. Activating mutations of *JAK2* at exon 12 are characteristically found in patients with polycythemia vera lacking V617F. Mutations of the *MPL* gene may also be documented in patients with essential thrombocythemia and primary myelofibrosis, as well as mutations of the calreticulin gene (*CALR*) in patients wild-type for both *JAK2* and *MPL*.

Myelodysplastic/Myeloproliferative Neoplasms

This group includes diseases that at the time of diagnosis are associated with some findings that support a diagnosis of a myelodysplastic syndrome and other more consistent with a myeloproliferative neoplasm. A hypercellular bone marrow is an index of hyperproliferation in one or more myeloid lineages; dysplastic changes may be encountered, with signs of ineffective hematopoiesis consisting of one or more peripheral cytopenias. Splenomegaly may be frequently encountered. Bone marrow blasts are by definition lower than 20%. Chronic myelomonocytic leukemia is the paradigm of myelo dysplastic/myeloproliferative neoplasms and requires the presence of peripheral blood monocytosis (monocytes ≥1000/mmc) and a percentage of at least 10% monocytes on differential counts. This is true regardless white blood cell counts.

Myelodysplastic Syndromes

They are a heterogeneous group of clonal diseases characterized by ineffective hematopoiesis, which causes one or more peripheral blood cytopenias (mainly anemia, which can be isolated, but also bilinear cytopenia or pancytopenia). The diagnostic hallmark is the presence of dysplastic changes in at least 10% of the cells in any hematopoietic lineage within the bone marrow (with a myelogram needed to be performed on at least 200 nucleated cells), which may be accompanied by the presence of bone marrow blasts, always less than 20% of all nucleated marrow elements (otherwise a diagnosis of acute leukemia should be established). Importantly, the lineage (or the lineages) that shows significant morphologic dysplasia does not necessarily correlate with the specific cytopenia(s) observed in peripheral blood in individual cases. This is why the most recent WHO classification identifies all diagnostic entities with the term *myelodysplastic syndrome* (Table 31.1), with further qualifications regarding the number of lineages involved, the amount of blasts observed ,and the presence of specific cytogenetic abnormalities, and leaves away the previous terminology of *refractory anemia* or *refractory cytopenia*, which may appear misleading.

Table 31.1 Myelodysplastic syndromes (MDS)

MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q) (5q$^-$ syndrome)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of the childhood

Myelodysplastic syndrome-defining cytogenetic abnormalities found in bone marrow blood in cytopenic patients and demonstrated by conventional karyotyping may confirm a diagnosis even in the absence of diagnostic morphologic dysplasia. Specific cytogenetic alterations, such as the del(5q), define clinically, therapeutically, and prognostically unique diseases. Some cytogenetic features (deletion of 7q, gain of chromosome 8, loss of chromosome 7, complex karyotype) are associated with higher risk disease. Recurrent mutations found in patients with myelodysplastic syndromes (*SF3B1*, *TET2*, *ASXL1*, *SRSF2*, *DNMT3A*, *RUNX1*) are informative in terms of prognosis and integrate the currently adopted risk stratification systems [8].

Acute myeloid leukemia

New diagnoses of acute myeloid leukemias involve 2.5–3 patients per 100,000 population each year, with higher incidence in the Western countries and in Australia. The pathogenesis is complex, and mostly related to the transformation of a proto-oncogene into an oncogene, as a result of a mutation or a chromosomal translocation, as well as a consequence of the inactivation of oncosuppressor genes. This is why agents capable of damaging the DNA, like ionizing radiations, benzene, and anticancer drugs (particularly alkylators and epipodophyllotoxins), have been associated with the pathogenesis of leukemia.

The current classification focuses on significant cytogenetic and molecular characteristics as the main classification criterion of acute myeloid leukemias. This is because of the prognostic relevance of some peculiar abnormalities, such as the presence of t(8;21)(q22;q22.1) or t(16;16)(p13.1;q22) translocations, as well as the inv. (16)(p13.1q22) or the *PML-RARA* fusion, all indicating a disease with a favorable course. Some mutations involve transcript factors (like mutations of the nucleofosmin gene, *NPM*); some other affect signal transduction, as they hit *FLT3*, *NRAS* and *KRAS*, or alter epigenetic regulators like *TET2*, *IDH1*, *IDH2*, and *DNMT3A* [9]. Mutations in these biological pathways generally coexist in many cases and cooperate in inducing the progression from normal hematopoietic stem cells to a preleukemic phase and finally to an overt leukemic transformation.

These peculiar cytogenetic and molecular aberrancies may guide treating physicians in applying specific treatment approaches, for example, the use of *all-trans* retinoic acid and arsenic trioxide in acute promyelocytic leukemia with *PML-RARA* fusion; the use of targeted agents during induction or consolidation; the need of an allogeneic transplantation after consolidation treatment. The same peculiar alterations may also work as a tool to monitor the disease status while patients are on treatment or during their follow-up.

When specific cytogenetic or molecular changes are lacking, acute myeloid leukemias are classified according exquisitely to the morphological appearance of leukemic blasts—as it was in the French-American-British Classification developed in 1976 which considers their grade of differentiation and the extent of their maturation, along with the presence of signs of monocytoid, erythroid, or megakaryocytic maturation of immature elements [10]. These cases are diagnosed as acute myeloid leukemia, not otherwise specified (Table 31.2).

Table 31.2 Acute myeloid leukemia (AML), not otherwise specified

AML with minimal differentiation (FAB cytotype M0)
AML without maturation (FAB cytotype M1)
AML with maturation (FAB cytotype M2)
Acute myelomonocytic leukemia (FAB cytotype M4)
Acute monoblastic/monocytic leukemia (FAB cytotype M5a and M5b)
Pure erythroid leukemia (FAB cytotype M6)
Acute megakaryoblastic leukemia (FAB cytotype M7)
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis

FAB French-American-British classification

Table 31.3 Acute myeloid leukemia with recurrent genetic abnormalities

AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
AML with inv. (16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
Acute promyelocytic leukemia with *PML-RARA*
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1); *DEK-NUP214*
AML with inv. (3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*
Provisional entity: AML with *BCR-ABL1*

Fusion genes and involved genes are reported in italics

The requisite blast percentage for a diagnosis of acute leukemia is at least 20% either in peripheral blood or in the bone marrow. Monoblasts, promonocytes, and megakaryoblasts are all considered blast equivalents. The diagnosis can also be made when the blast percentage is lower than 20% provided a diagnostic cytogenetic lesion is reported (Table 31.3).

The WHO classification also underscores the importance of a previous diagnosis of myelodysplastic syndrome or a history of cytotoxic therapy for any neoplastic condition: acute myeloid leukemias with myelodysplastic-related changes (both morphologically and cytogenetically) and therapy-related myeloid neoplasms (collectively termed *secondary* acute myeloid leukemias) constitute, in fact, separate disease entities, mainly because of their refractoriness to standard approaches and an adverse prognosis.

Classification of Lymphoid Malignancies

Lymphoid neoplasms are clonal diseases arising from B, T, and natural killer lymphocytes, either from immature (or precursor) lymphoid cells or mature (or peripheral) lymphocytes. The neoplastic elements tend to reproduce the

morphologic, phenotypic, and genetic features of the normal counterpart they derive from, and sometimes they may also maintain their functional characteristics.

The first attempts of classification of lymphoid neoplasms were mainly based on cell phenotype (either B- or T-cell origin of the neoplastic elements) and on the clinical aggressiveness of the disease, thus distinguishing between high-grade (or aggressive) lymphomas and low-grade (or indolent) ones. The Kiel's classification, proposed in Europe by Karl Lennert, mainly considered the clinical behavior of lymphoid malignancies, whereas clinicians from the National Cancer Institute, who developed the Working Formulation, mainly classified lymphoid diseases from a morphological point of view, although integrating with the distinction between high-, intermediate-, and low-grade malignancies. Given that the underlying classifying principles were different, these two classification systems were profoundly incomparable, thus giving rise to several controversies between European and North American centers.

The Revised European American Lymphoma (REAL) classification [11], published in 1994, changed the original classification criteria based on phenotype and biological aggressiveness into an ordinate list of disease categories, each of them defined according to a set of objective (or, in other terms, worldwide reproducible) scientific criteria. The REAL classification put the basis for the development of the WHO classification of tumors of the hematopoietic and lymphoid tissue, which has now reached its fourth edition, with a revision published in 2017 [2, 7]. Any lymphoid entity currently acknowledged in the latest WHO classification is defined by epidemiological data, anatomical site of involvement, morphologic features, phenotype of the neoplastic cells, clinical features, specific genetic abnormalities, postulated normal cell counterpart (when known), and prognosis. Some categories are provisional, as their definition is based on data not fully validated in large studies: provisional entities may become definitive as soon as additional biologic, molecular, and genetic elements become available and confirm their uniqueness as peculiar anatomo-clinical subtypes.

Lymphoid tumors are schematically subdivided into the following areas:

- Precursor lymphoid neoplasms (B, T, and NK lymphoblastic leukemias and lymphomas)
- Mature B- and T/NK-cell neoplasms
- Hodgkin lymphomas
- Immunodeficiency-associated lymphoproliferative disorders
- Histiocytic and dendritic cell neoplasms

Precursor Lymphoid Neoplasms

Acute lymphoblastic leukemia is the most frequent tumor in the pediatric population, and although being rarer in adults, it represents nearly 15% of all leukemias. Approximately 10,000 cases are diagnosed in Europe each year, with an incidence of 1.3 cases out of 100,000 individuals for men and 0.9 for women. It is a disease of the pluripotent hematopoietic stem cell, committed to either a B- or T-lineage, whose neoplastic transformations lead to the proliferation and accumulation of leukemic blasts in the bone marrow, peripheral blood, secondary lymphoid organs, and sometimes extranodal tissues, with a propensity to invade the central nervous system (including cerebrospinal fluid), testes, and breasts.

An increased risk of incidence of B-acute lymphoblastic leukemia is widely acknowledged in patients with Down syndrome, neurofibromatosis, Schwachman syndrome, ataxia telangiectasia, and Langerhans cell histiocytosis. The exposure to ionizing radiations and to chemicals has also a recognized role in leukemogenesis, which is driven by both a dysregulation of structurally intact genes and by the formation of fusion genes that encode for chimeric proteins. The current WHO classification recognizes several B-lymphoblastic leukemia types with recurrent genetic abnormalities (Table 31.4).

T-lymphoblastic leukemia is much rarer and roughly represents a quarter of cases of all acute lymphoblastic leukemias in adults.

When lymphoblastic neoplasms mainly present with nodal masses with no or minimal involvement of peripheral blood and bone marrow, these processes are more correctly defined as lymphoblastic lymphomas. Differently from acute myeloid leukemias, there is not an agreed-upon threshold of bone marrow blasts percentage required to confirm the diagnosis.

Mature B- and T/NK-Cell Neoplasms

This is the highly heterogeneous group of non-Hodgkin lymphomas and monoclonal gammopathies, a series of lymphoid

Table 31.4 B-lymphoblastic leukemia/lymphoma (B-ALL) with recurrent genetic abnormalities

B-ALL with t(9;22)(q34.1;q11.2); *BCR-ABL1*
B-ALL with t(v;11q23.3); *KMT2A*-rearranged
B-ALL with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-ALL with hyperdiploidy[a]
B-ALL with hypodiploidy[b]
B-ALL with t(5;14)(q31.1;q32.1); *IGH/IL3*
B-ALL with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-ALL, BCR-ABL1-like
B-ALL with iAMP21

Fusion genes and involved genes are reported in italics

[a]More than 55 chromosomes (usually <66) without translocations or other structural alterations

[b]Less than 46 chromosomes (near-haploid: 23–29 chromosomes; low-hypodiploid: 33–39 chromosomes; high-hypodiploid: 40–43 chromosomes; near-diploid: 44–45 chromosomes)

diseases arising from B-lymphocytes at different stages of maturation within peripheral lymphoid organs (Table 31.5) and from post-thymic T-lymphocytes (Table 31.6).

B-cell lymphomas are far more common than T-cell counterparts, accounting for more than 90% of all lymphomas. This group also includes plasma cell neoplasms, among which multiple myeloma is the clinically more complex and more frequent disease.

The WHO classification defines each entity as indolent or aggressive, as a consequence of disease clinical behavior over time: aggressive lymphomas tend to be symptomatic at diagnosis and may display a rapid progression if left untreated; on the contrary, indolent diseases are rarely symptomatic at onset, and their survival is predictable in years, even without treatment (which may be deferred until clinical symptoms or high disease burden become evident). More than 50 disease entities are acknowledged in this broad category. Clinical and biological features may be different within the same disease category in terms of presentation (nodal, extranodal, leukemic), proliferation rate or apoptosis, expression of markers with prognostic implications, genetic alterations, and intrinsic or acquired resistance to certain drugs. Among the main disease categories, diffuse large B-cell lymphoma and follicular lymphoma are the two most widely represented diseases, being the paradigm of aggressive and indolent non-Hodgkin lymphoma, respectively. Chronic lymphocytic leukemia, prolymphocytic leukemia, and hairy cell leukemia mainly display a leukemic presentation during any phase of the disease. Some marginal zone lymphomas have a clear tendency to invade extranodal organs, such as gastrointestinal tract, some exocrine or endocrine glands, lungs, and skin. Mantle cell lymphoma is a disease that invariably involves both lymph nodes and the gastrointestinal tract. Mycosis fungoides is an exquisitely cutaneous form of T-cell lymphoma. Multiple myeloma is a disease that comes from the expansion of a plasma cell clone within the bone marrow, which is able to

Table 31.5 The classification of mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Lymphoplasmocytic lymphoma/Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance, IgM
Monoclonal gammopathy of undetermined significance, IgG/A
μ-, γ-, α-Heavy-chain disease
Plasma cell myeloma
Solitary plasmacytoma of the bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases
Extranodal marginal zone of the MALT[a] type
Nodal marginal zone lymphoma
Follicular lymphoma
Pediatric-type follicular lymphoma
Large B-cell lymphoma with IRF4 rearrangement
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma, not otherwise specified
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL[b] of the central nervous system
Primary cutaneous DLBCL[b], leg-type
EBV$^+$ DLBCL[b], not otherwise specified
EBV$^+$ mucocutaneous ulcer
DLBCL[b] associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8$^+$ DLBCL[b] not otherwise specified
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration
HGBCL[c], with *MYC* and *BCL2* and/or *BCL6* rearrangements
HGBCL[c], not otherwise specified
B-cell lymphoma, unclassifiable[d]

Provisional entities are listed in italics
[a]*MALT* mucosa-associated lymphoid tissue
[b]*DLBCL* diffuse large B-cell lymphoma
[c]*HGBCL* high-grade B-cell lymphoma
[d]With features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Table 31.6 The classification of mature T- and NK-cell neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood
Hydroa vacciniforme-like lymphoproliferative disorder
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders[a]
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8$^+$ T-cell lymphoma
Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder
Peripheral T-cell lymphoma, not otherwise classified
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma
Nodal peripheral T-cell lymphoma with TFH[b] phenotype
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$
Breast implant-associated anaplastic large-cell lymphoma

Provisional entities are listed in italics
[a]Category includes lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma
[b]*TFH* T follicular helper

secrete (and sometimes also to excrete) a monoclonal immunoglobulin (M protein) and which determines progressive organ damage in the form of hypercalcemia and bone lesions (due to plasma cell-induced bone lysis and reabsorption), renal insufficiency (due to tubular damage resulting from monoclonal light chain proteinuria) and anemia (as a consequence of bone marrow substitution).

The incidence of non-Hodgkin lymphomas has increased in the last two decades, and the trend is likely to increase further in the next future. They tend to occur more frequently in developed areas, and their incidence increases with age, with aggressive entities being more frequent in young adults in their third to fourth decade and indolent forms and multiple myeloma being mostly represented in elder adults. Geographic variations are seen among disease entities: follicular lymphoma and chronic lymphocytic leukemia are mostly observed in Western countries, being almost unknown in Asia; on the contrary, Burkitt lymphoma is endemic in Equatorial Africa, whereas T/NK-cell lymphomas are frequent in Asia, although being rarer in Europe and the United States.

The huge variety of these diseases in terms of clinical presentation and biologic features accounts for the great variability of therapeutic approaches, which are mainly based on chemotherapy. Targeted agents, like monoclonal antibodies, and new compounds aimed at blocking the biologic mechanisms that specifically sustain these neoplasms are now routinely applied as first-line approaches or as salvage treatments for patients who relapse or who show refractoriness to induction therapy.

Some lymphoproliferative disorders may arise as a consequence of prolonged immunosuppression, either primary (common variable immunodeficiency syndrome, severe-combined immunodeficiency, X-linked immunodeficiency, ataxia-telangiectasia, Wiskott–Aldrich syndrome, autoimmune lymphoproliferative syndrome) or secondary to an underlying medical condition (immunosuppressive drugs, as it happens in solid organ transplant recipients) or infection (human immunodeficiency syndrome).

Hodgkin lymphomas

Hodgkin lymphoma (historically referred to as Hodgkin's disease) is not a single disease, but differences are recognized in terms of morphology, immunophenotype, and cellular background, as well as prognosis and treatment approaches (Table 31.7).

This is why the current WHO classification clearly distinguishes between a classical Hodgkin lymphoma and a nodular lymphocyte predominant Hodgkin lymphoma (formerly called paragranuloma). Classical Hodgkin lymphoma accounts for the vast majority of the cases (at least 90%), with a higher incidence in individuals in their second to fourth decade. The Reed–Sternberg cells are the hallmark of the disease, being characteristically a peculiar form of post-germinal center B-lymphocytes, although lacking specific B-cell markers (like CD20 and PAX5) and strongly expressing the CD30 antigen. These cells are rather scarce within the tumor mass, which is mainly composed by a heterogeneous *pabulum* of normal blood elements (granulocytes, eosinophils, macrophages), in close relationship with Reed–Sternberg elements. Poly-chemotherapy has permitted a high rate of cure when applied first-line, with a chance of long-lasting complete remissions in nearly 75–80% of cases. Autologous stem cell transplantation is able to save roughly half of those who relapse after first-line treatment or who do not show a satisfactory response to conventional chemotherapy. New agents targeting the CD30 antigen or enhancing the immune response to the neoplastic Reed–Sternberg cell are now widely used worldwide.

Table 31.7 Classification of Hodgkin lymphomas

Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma, on the contrary, is a clearly B-cell preserved malignancy, although sometimes partly losing its B-cell phenotype. This variety of the disease displays a rather indolent course, with possible relapses, and responds effectively to CD20-directed agents like rituximab.

Occupational Causes of Lymphohematopoietic Malignancies

The International Agency for Research on Cancer (IARC) [12] maintains an updated list of putative carcinogens by cancer site; the current version, updated on November 2018, summarizes findings up to volume 123. Table 31.8 lists the putative carcinogens for lymphoid, hematopoietic, and related tissue, as classified by IARC.

Many listed carcinogens are drugs, mostly anti-cancer (azathioprine, busulfan, chlorambucil, cyclophosphamide, cyclosporine, etoposide with cisplatin and bleomycin, melphalan, MOPP or vincristine-prednisone-nitrogen mustard-procarbazine mixture, semustine, thiotepa, treosulfan), some are microorganisms (Epstein–Barr virus, *Helicobacter pylori*, hepatitis C virus, human immunodeficiency virus type 1, human T-cell lymphotropic virus type 1, Kaposi sarcoma herpes virus), and some are personal habits (tobacco smoking).

Table 31.8 List of classifications by cancer sites with sufficient or limited evidence in humans, volumes 1 to 123

Carcinogenic agents with sufficient evidence in humans	Agents with limited evidence in humans
Azathioprine	Benzene[a]
Benzene[a]	Bischloroethyl nitrosourea (BCNU)
Busulfan	Chloramphenicol
1,3-Butadiene	DDT
Chlorambucil	Diazinon
Cyclophosphamide	Dichloromethane (methylene chloride)
Cyclosporine	Ethylene oxide
Epstein–Barr virus	Etoposide
Etoposide with cisplatin and bleomycin	Glyphosate
Fission products, including strontium-90	Hepatitis B virus
Formaldehyde	Magnetic fields, extremely low frequency (childhood leukemia)
Helicobacter pylori	Malathion mitoxantrone nitrogen mustard painting (childhood leukemia from maternal exposure)
Hepatitis C virus	Petroleum refining, occupational exposures
Human immunodeficiency virus type 1	Polychlorinated biphenyls
Human T-cell lymphotropic virus type 1	Polychlorophenols or their sodium salts (combined exposures)
Kaposi sarcoma herpes virus	Radioiodines, including Iodine131
Lindane	Radon-222 and its decay products
Melphalan	Styrene
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)	Teniposide
Pentachlorophenol	Trichloroethylene
Phosphorus-32	2,3,7,8-Tetrachlorodibenzopara-dioxin
Rubber production industry	Tobacco smoking (childhood leukemia in smokers' children)
Semustine (methyl-CCNU)	Malaria (caused by infection with Plasmodium falciparum in holoendemic areas)
Thiotepa	
Thorium-232 and its decay products	
Tobacco smoking	
Treosulfan	
X-radiation, gamma-radiation	

Lymphoid, hematopoietic, and related tissue

[a]A double classification is presented for benzene. On the one hand, IARC considers evidence in humans sufficient only for acute non-lymphocytic leukemia (including acute myeloid leukemia). On the other hand, the agency classifies as limited the evidence in humans for non-Hodgkin lymphoma, chronic lymphoid leukemia, multiple myeloma, chronic myeloid leukemia, and acute myeloid leukemia in children

The other carcinogenic agents listed (which are encountered also in workplaces) are ionizing radiations (including fission products, phosphorus-32, strontium-90, thorium-232 and its decay products), benzene, 1,3-butadiene, formaldehyde, two pesticides (lindane and pentachlorophenol), and a generically identified industrial process (rubber production industry). We will now review the current information about these agents, which are of occupational interest. It will be assumed that the reader is already familiar with the nature of the agents discussed or has reviewed the basic information about an agent on one of the several freely available, good quality, scientific information sources.

In this chapter we will not review the issue of hematopoietic malignancies in connection with occupational exposure to antineoplastic agents (production, use) as the epidemiological studies available do not yet provide enough reliable data.

Classification of Malignancies in Occupational Studies

As we described in the first part of this chapter, several major changes occurred over the time for the state-of-the-art classification of tumors of hematopoietic and lymphoid tissues. Hematologic cancers encompass a heterogeneous group of diseases arising from different mature or immature cells. Also, there are well-known differences in the natural history, clinical characteristics, and responsiveness to therapies within hematologic cancers possibly arising from the same cell. For these reasons, the fourth version of the 2017 revised WHO classification is extremely articulated. In principle, clinicians are expected to apply such a classification with the highest available detail.

On the contrary, most etiological studies on hematologic malignancies have applied a very broad case definition. For instance, a well-conducted cohort study published in 2019, analyzing cancer mortality among workers of the rubber industry, reported about "leukemia mortality" without any further subclassification [12]. The use of "simplified" or "limited" classifications is common among epidemiologists when studying hematologic neoplasms. As a better example, we can cite the pooled analyses of occupational risk factors from the InterLymph Consortium [13]. In this large collaborative effort, the authors tried to investigate separately the different non-Hodgkin lymphoma subtypes. Nevertheless, the report included information only on the following four subtypes: diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and peripheral T-cell lymphoma.

As expected, the limited information available from epidemiological studies, with a scarce detail on diagnostic classification, influenced the subsequent evaluation process performed by IARC. Indeed, IARC experts classified carcinogens for hematologic neoplasms often adopting very broad case definition. For instance, the current statement for the classification of 1,3-butadiene [14] as a carcinogen with "sufficient evidence in humans" is: "*There is sufficient evidence in humans for the carcinogenicity of 1,3-butadiene. 1,3-Butadiene causes cancer of the haematolymphatic organs*."

The use of simplified case definition in occupational studies is somehow expected, and it is the consequence of the

limited available data. Some lymphohematopoietic malignancies are difficult to be investigated in epidemiological studies because of the very small number of observed cases. In other cases, epidemiologists performed register-based studies without access to detailed diagnostic definitions (e.g., mortality studies are based on the limited coding available in the International Statistical Classification of Diseases and Related Health Problems). In epidemiology, the use of broad and nonspecific case definitions is a known case of outcome misclassification. As a result, risk estimates might be asymptotically biased toward the null hypothesis. In other words, it is likely the magnitude of the association between some occupational risk factors and risk of specific hematologic neoplasms is underestimated.

Nevertheless, the general claim that the misclassification of the outcome necessarily causes an underestimation of the association is not correct. First, in the presence of continuous exposure metrics (e.g., cumulative exposure to benzene measured in ppm/year), the bias in each single study can be in both directions (under/overestimation) [15]. Second, an overestimation observed in repeated studies is possible when the causal pathway is complex and involves effect modifiers as well as unmeasured/misclassified confounders. Third, an outcome misclassification can be differential with respect to personal characteristics (e.g., different access to healthcare due to socioeconomic factors): again, in such a scenario the bias might be in both directions.

We believe that broad case definitions of hematologic neoplasms might be applied for hypothesis generating studies: on the contrary, modern hypothesis testing studies must be conducted adopting state-of-the-art classification of diseases.

Myeloid Malignancies

Herein we discuss the issue of occupational myeloid malignancies.

Ionizing Radiations

Ionizing radiations (X-rays, gamma-rays, ionizing radiations emitting materials) are probably the confirmed human carcinogenic agent most widely (deliberately) employed: their use in the medical and other field will not find suitable substitute for the foreseeable future. Because of this, relatively large number of workers are (and will be) exposed to ionizing radiations because of their occupation. In addition, it should be considered that exposure to ionizing radiation (trough natural sources) is an unavoidable consequence of living on our planet and most of the current doses of ionizing radiations currently received by workers in the medical field (and others) are comparable (or below) to the doses received by natural sources).

Atomic bomb survivor studies, as well as others, have definitely associated exposure to ionizing radiations to an increased (4–5 times) risk of death for leukemias, other than chronic lymphatic leukemia [16]: the risk increases sharply and reaches its peak within 10 years from the irradiation.

However, this body of scientific evidence has been acquired studying exposure up to several Sievert (Sv) of cumulative dose, whereas with the current permissible level of exposure in the USA and in Europe (100 mSv over a period of 5 years), a worker is expected to reach a maximum cumulative dose of 0.8 Sv over a 40 years working life (not considering that the actual doses effectively absorbed in occupational settings are, generally, well below this limit). So, the crucial issue to be considered is, nowadays, whether the current limit of exposure is protective enough for the workers, that is, in other words, whether the actual exposure of the workers is associated to an increased leukemia risk.

The issue has been discussed by the BEIR Committee in the BEIR VII report [17]. They concluded that, to provide direct estimates of the effects of long-term, low-dose, low-LET radiation, the most comprehensive and precise estimates to date were those derived from the UK National Registry of Radiation Workers and the three-country study (Canada-United Kingdom-United States), which had provided estimates of leukemia and all cancer risks.

The comparison of estimates of excess relative risk per unit of absorbed dose of radiation (Gray) showed a reduction of the risk of all cancers (but leukemia) in nuclear workers [Three-country study: −0.07 (−0.39, 0.30); National Registry of Radiation Workers study: 0.09 (−0.28, 0.52)] when compared to atomic bomb survivors [0.24 (0.12, 0.4)]. The comparison of estimates of excess relative risk of leukemia (excluding chronic lymphocytic leukemia) per unit of absorbed dose of radiation, on the contrary, showed that those estimates were comparable in the three groups [Three-country study: 2.2 (0.1, 5.7); National Registry of Radiation Workers study: 2.6 (−0.03, 7.2); Atomic Bomb Survivors: 2.2 (0.4, 4.7)]. The authors of the report [16] concluded that "*Although the estimates are lower than the linear estimates obtained from studies of atomic bomb survivors, they are compatible with a range of possibilities, from a reduction of risk at low doses to risks twice those upon which current radiation protection recommendations are based. Overall, there is no suggestion that the current radiation risk estimates for cancer at low levels of exposure are appreciably in error. Uncertainty regarding the size of this risk remains as indicated by the width of the confidence intervals.*"

The issue of extrapolation of the results obtained in atomic bomb survivors' studies to occupational setting is not simple. In atomic bomb survivors:

- The cumulative dose of ionizing radiation was estimated, not measured
- The dose was absorbed almost all instantly (fall-out contribution being generally much lower than direct irradiation)

In occupational settings, on the contrary:

- The cumulative dose is generally measured (with a reasonable degree of accuracy)
- The dose is absorbed at a low level over many years

The way in which the cumulative dose is delivered to the body may well affect the biological response. An additional issue to consider is a relevant difference between the two populations: the atomic bomb survivors are a population in which females and older men (young men were deployed in the combat areas) are overrepresented in comparison to workers occupationally exposed to ionizing radiation. And, in addition, that population, before being struck by the atomic bombs, had to endure the deprivation imposed by years of war.

Recently, other studies have been published reporting mortality experience of occupational cohorts exposed to ionizing radiation, both externally and internally [18–25].

Taken together, the new evidence does not modify significantly the conclusions of the BEIR VII report, that is, at the current levels of cumulative occupational exposure to ionizing radiation (that is, below 100 mSv in the working life), the estimate of the risk of leukemia (other than chronic lymphocytic leukemia) is compatible with both an increase and a reduction, in comparison with occupationally unexposed people. The average exposure to ionizing radiations from natural sources for American citizens has been estimated in 3 mSv per year [26], so 100 mSv is the dose absorbed by natural sources by an American citizen in first 33 years of life.

Benzene

Although widely used in the past as a solvent, benzene is now produced to be used in the synthesis of numerous chemicals: it has been estimated that the world production of benzene in 2017 exceeded 50 million of metric tons and will continue to grow in the next future [27]. It has been estimated that 50% of benzene produced is used in the synthesis of ethylbenzene and cumene, while another 20% is used for the synthesis of cyclohexane and nitrobenzene.

Therefore, benzene continues to be a compound to which numerous workers are exposed; while, in the general population, the main sources of benzene exposure are vehicular traffic and tobacco smoke.

The hematotoxicity of benzene, in both animals and humans, had already been recognized at the end of the 1800s: at the time, probably due to the massive exposure in the workplace, the most prevalent cases of chronic benzene intoxication were those of bone marrow aplasia, which prompted to propose the use of benzene as a treatment for leukemia [28].

Throughout the first half of the twentieth century, cases of both bone marrow aplasia and leukemia were repeatedly observed in workers exposed to benzene: in the 1960s and 1970s, thanks to the studies of Vigliani, Aksoy and others, the scientific community accepted the relationship between occupational exposure to benzene and risk of leukemia. Those studies were followed by epidemiological investigations of groups of exposed workers, among which those on workers involved in the production of pliofilm, a rubber-based plastic material, already widely used in the 1930s [29–33].

Based on the available studies, there is sufficient evidence in humans for the carcinogenicity of benzene, for acute myeloid leukemia/acute non-lymphocytic leukemia [34]. The same evidence is available for experimental animals.

Before taking into consideration the levels of exposure to benzene that constitute an appreciable carcinogenic risk to humans, it is worthwhile to mention the most recent information on the link between exposure to benzene and myelodysplastic syndromes. As previously stated, myelodysplastic syndromes are a heterogeneous group of clonal diseases characterized by ineffective hematopoiesis, which causes one or more peripheral blood cytopenias (mainly anemia, which can be isolated, but also bilinear cytopenia or pancytopenia). The diagnostic hallmark is the presence of dysplastic changes in at least 10% of the cells in any hematopoietic lineage within the bone marrow (with a myelogram needed to be performed on at least 200 nucleated cells), which may be accompanied by the presence of bone marrow blasts, always less than 20% of all nucleated marrow elements (otherwise a diagnosis of acute leukemia should be established).

The diagnostic criteria of myelodysplastic syndromes were only recently codified and the term "Myelodysplastic syndrome" was not used until the 1980s [35]: it is easy to understand why this condition could be underdiagnosed in the studies on groups of workers exposed to benzene, being it often confused with either leukemia or other hematological diseases.

During the last 20 years several studies on myelodysplastic syndromes in workers exposed to benzene have been published [36]: globally considered, the aggregate of available data supports the notion that occupational exposure to benzene may be a cause of myelodysplastic syndromes, an effect numerically in the ratio 1:5 with the excess mortality attributable to leukemia. Based on the data currently available, the increase of the risk per unit of exposure results of the same entity as that of leukemia.

The occupational exposure limits to benzene for an 8-hour working day range from 0.5 ppm (1.6 mg per cubic meter of air), recommended by ACGIH, to 1 ppm (3.25 mg per cubic meter of air), binding maximum limit of exposure for EU countries after the EU Directive 2017/2398.

In Europe, however, the Committee for Risk Assessment of the European Chemicals Agency has recommended in March 2018 the adoption of an Occupational Exposure Limit of 0.05 ppm (0.16 mg/cubic meter) for benzene [37], stating that "*The limit so derived, will avoid exposures that induce chromosomal damage in workers, is considered to have no significant residual cancer risk and will also avoid other adverse effects*" adding that "*Since the proposed limit value relies on a mode of action-based threshold for the leading genotoxic effects, which are the likely critical trigger events in benzene leukemia, some uncertainties may remain as to a residual cancer risk. ... Considering, however, that multiple thresholded MoAs* [modes of action] *likely contribute to benzene leukaemia development and in view of the overall experimental and epidemiological evidence available supporting a genotoxic-threshold for benzene, the remaining uncertainties are considered to be very low. Given this evidence, estimated excess cancer risks as derived by linear extrapolation can be seen as overly conservative.*"

The limit proposed by the Committee for Risk Assessment of the European Chemicals Agency is 10 times lower than the current ACGIH recommendation and 20 times lower than the maximum limit of occupational exposure still present in the European legislation.

1,3-Butadiene

1,3-Butadiene is used in the synthesis of different chemical products, mainly elastomers: it is estimated that world's production of 1,3-butadiene in 2017 exceeded 15 million tons and will continue to grow in the near future [38]. It is estimated that 70% of the 1,3-butadiene produced is used in the synthesis of styrene-butadiene rubber, polybutadiene rubber, and acrylonitrile-butadiene-styrene resin elastomers.

Therefore, 1,3-butadiene keeps being a compound to which numerous workers are exposed; however, currently the general population has no significant sources of exposure to 1,3-butadiene, with concentrations that, in the late 1990s, were well below 1 μg/m^3 of outdoor air [39].

The carcinogenicity of 1,3-butadiene has been studied with reference to both hematological and lymphatic malignancies. Several cohort studies have been conducted in 1,3-butadiene-exposed workers (predominantly males) in 1,3-butadiene production and styrene-butadiene rubber production: regarding leukemia (not otherwise specified) some studies did not find a statistically significant excess mortality, while others did [40]. Based on this evidence, IARC listed 1,3-butadiene as a confirmed human carcinogen as it "*causes cancer of the haematolymphatic organs*" [14, 40].

As 1,3-butadiene production is increasing and several tens of thousands of workers are potentially exposed to 1,3-butadiene worldwide, it is worthwhile to review some of the most widely used occupational exposure limits.

In the USA, the currently adopted ACGIH TLV-TWA for 1,3-butadiene is 2 ppm (4.4 mg per cubic meter of air). Based on much of the evidence reviewed by IARC, however, ACGIH has classified 1,3-butadiene in category A2, that is, suspected human carcinogen [41].

In the European Union, the EU Directive 2017/2398 [42] has set up for 1,3-butadiene a binding maximum limit of exposure for EU countries of 1 ppm (2.2 mg/cubic meter), based on a recommendation from the Scientific Committee on Occupational Exposure Limits which has provided different estimates of excess leukemia risk in males workers for levels of exposure from 0.1 to 10 ppm. The SCOEL document reports [43] that the estimates may be illustrated as follows: "*In a population of 1.000 adult males experiencing a mortality rate similar to that of the male population of England and Wales, occupational exposure to 1 ppm of 1,3-butadiene for a working life (40 years between the ages of 25 and 65), will cause from 0.0 to 10.78 extra leukaemia deaths between the ages 25-85 years, in addition to the 5 leukaemia deaths expected to occur in the absence of exposure to 1,3-butadiene*". No STEL or "skin" notation was considered necessary.

As stated in the IARC monograph [40], current occupational exposure levels to 1,3-butadiene is generally below 1 ppm (whereas periods of short-duration, higher-level exposure may occur): at this level of exposure for the whole working life, the SCOEL estimate reported above associates a number of excess cases of leukemia ranging from −0.09 to 10.78 per 1000 workers [43]. The lower part of the estimate range is compatible with one provided by a recent analysis of the dataset developed by the University of Alabama at Birmingham study of North-American workers in the styrene butadiene rubber industry, on 0.025 excess leukemia cases per 1000 workers [44].

Formaldehyde

Formaldehyde is a compound widely used in various industrial sectors: it is used to produce melamine formaldehyde resins, phenol formaldehyde resins, urea formaldehyde resins, and several other compounds. It is well used "as is" in the healthcare sector, in embalming and in consumer goods. Other main sectors in which formaldehyde is used are production of plywood and construction. It is estimated that world's production of formaldehyde in 2017 exceeded 50 million tons and will continue to grow in the near future [45].

Therefore, formaldehyde keeps being a compound to which hundreds of thousands of workers are exposed worldwide, whereas the general population is exposed to endogenous metabolic production of formaldehyde and other sources such as indoor air contamination (mostly due to release from furniture and other products), outdoor air contamination by industrial emissions, combustion, and secondary formation of formaldehyde through the oxidation of volatile organic compounds and reactions between ozone and alkenes.

Levels of formaldehyde in outdoor air range from less than 10 μm/m^3 to more than 100: in several studies indoor levels exceeded the outdoor ones [46].

Formaldehyde has been evaluated for carcinogenicity to humans since the early 1980s: in 1981 IARC classified formaldehyde in Group 2B (possibly carcinogenic to humans) [47]. Later on, in 1987 [48], IARC classified formaldehyde in Group 2A and kept this classification in the subsequent 1994 revision [49]. In all those cases, the end-point taken into consideration by IARC was that of nasal tumors. For leukemia, the evidence but considered inadequate. In 2004, IARC [50] classified formaldehyde in Group 1 (compounds carcinogenic to humans) finding sufficient the epidemiological eventuality for nasopharyngeal cancers, thus ruling on leukemia (that was already mentioned in the 1987 report: "*There is strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde. Increased risk for leukemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers*".

In 2009 IARC [51] confirmed the classification of formaldehyde in Group 1, affirming, with regard to leukemia, the existence of sufficient evidence in humans, even though with an unusual formulation, more appropriate for a political body than for a scientific agency: "*The Working Group was not in full agreement on the evaluation of formaldehyde causing leukemia in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited.*"

Therefore, it is between the 2004 and 2009 evaluations that IARC finds that the evidence on the carcinogenicity of formaldehyde to humans in relation to leukemia has increased from insufficient to sufficient: the findings were based on an update of the cohort of the National Cancer Institute [52], of a nested case–control study among funeral industry workers [53], and of three meta-analyses [54–56].

Since the last update of formaldehyde carcinogenicity by IARC, two other large industrywide cohort mortality studies have been updated: the NIOSH garment workers [57] and the UK industry-wide formaldehyde producers and users [58]. In addition, new data have been published: a large population registry-based case–control study of incident cases of acute myeloid leukemia in the Nordic countries [59] two small occupational studies in Italy [60, 61] and a large multicenter European study of occupational exposures in a cohort established to study nutritional and metabolic risk factors in cancer risks have been published [62].

The whole history of formaldehyde evaluation from 1981 onwards was recently reviewed [63], evaluating the epidemiological evidence about the relation between formaldehyde exposure and leukemia, experimental evidence in animals, evidence related to action modality, the dose–response relation and the ways to integrate all the available lines of evidence into an overall assessment.

As far as epidemiological evidence goes, the studies published after the 2009 IARC evaluation [51], globally considered, do not support the hypothesis that formaldehyde is a cause of leukemia and specifically of acute myeloid leukemia.

With regard to studies in animals, there is no convincing evidence that formaldehyde can cause leukemia or lymphohematopoietic malignancies. Recent studies confirm the absence of association between formaldehyde and lymphohematopoietic malignancies [63]. As far as the modalities of action are concerned, since formaldehyde penetrates into the organism through the respiratory system (and therefore its association with nasal cancers is plausible), its causal role in the genesis of leukemia postulates that it arrives unaltered to the bone marrow or that it acts on circulating stem cells of the bone marrow, which, once mutated, return to the level of the bone marrow and determine the disease. There is no evidence that this is plausible nor is it happening. The available data, therefore, do not support the thesis that formaldehyde can cause remote effects from the sites of entrance in the body [64].

With regard to the dose–response relation between inhalation of formaldehyde and leukemia, the large discrepancy between results obtained using approaches that relies on molecular dosimetry data versus those that relies upon uncertain retrospective occupational exposure reconstructions call into question the credibility of attributing increases in human mortality from leukemias to occupational exposure to formaldehyde.

In summary, the available evidence between formaldehyde inhalation exposure and the potential for leukemia risk shows that there is at most only limited, suggestive positive evidence, in contrast with the bulk of evidence suggesting no such association, and thus no causal relationship.

Rubber Manufacturing Industry

In 1981 IARC [65] stated that the rubber manufacturing industry had to be considered an occupational activity causally associated with the development of leukemia in workers. In 2009 IARC [66] re-evaluated this aspect by concluding that "*there was an increased risk for leukaemia among workers in the rubber-manufacturing industry. The excess risks may be associated with exposure to solvents, in particular benzene.*"

With reference to this last point, it should be noted that the statement of "*the excess risks may be associated with exposure to solvents*" is not consistent with what IARC reports about all causal agents for leukemia [67], among which it includes only benzene and no other solvents. Furthermore, the studies on the rubber manufacturing industry and leukemia have been conducted in years during which exposure to benzene in that industry was likely to be high. Therefore, at present, if benzene exposure in the rubber manufacturing industry is not relevant (see the section of this chapter on benzene), the risk of leukemia can be considered absent.

Lymphoid Malignancies

Herein, we discuss occupational risk factors of lymphoid malignancies.

Ionizing Radiations

As stated in BEIR V [16], an increase in the frequency of some forms of lymphoid malignancies has been associated with irradiation in humans and/or laboratory animals. In humans, these malignancies are multiple myeloma, in which the tumor cells proliferate primarily in the bone marrow, and non-Hodgkin's lymphoma, in which the tumor cells proliferate primarily in the lymph nodes. Multiple myeloma and non-Hodgkin's lymphoma, like chronic lymphocytic leukemia, are malignancies of B lymphocytes.

Of the three diseases, however, only multiple myeloma and non-Hodgkin's lymphoma have been observed to increase in frequency after irradiation in humans.

In A-bomb survivors, mortality from multiple myeloma has been observed at doses below 1 Gy; in these populations the relative risk increased with dose in males and females aged 20–59 years at the time of bombing but did not become evident until 20 years after exposure. Taken together, the data from A-bomb survivors imply that for multiple myeloma the minimal latent period is appreciably longer, the relative risk smaller, and the age distribution later than for leukemia [16].

The issue of lymphoid malignancies in occupationally exposed workers has been discussed by the BEIR Committee in the BEIR VII report [17]. They noted that statistically significant (p-value <0.05, one-sided) positive associations between cumulative external radiation dose and mortality from multiple myeloma were found in the Hanford and Sellafield studies [68, 69]. A similar association was also found in the National Registry for Radiation Workers [70] and three-country analyses [71], largely reflecting the previously reported associations in individual cohorts. The association in the Hanford study was not significant (p-value 0.1) when follow-up was extended to 1986 [72]: association became significant only after additional (likely post-hoc) analyses.

As noted previously (discussing the myeloid malignancies), recently other studies have been published reporting mortality experience of occupational cohorts exposed to ionizing radiation, both externally and internally (see the references reported in the above section): taken together, the new evidence does not modify significantly what was already known: that is, at the current levels of cumulative occupational exposure to ionizing radiation (below 100 mSv in the working life), the estimate of the risk of multiple myeloma and non-Hodgkin's lymphoma is compatible with both an increase and a reduction, in comparison with occupationally unexposed people.

Benzene

IARC reviewed benzene in 2018 [34] considering studies published until 2015. The conclusion was that "*There is sufficient evidence in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia in adults. Positive associations have been observed for non-Hodgkin lymphoma, chronic lymphoid leukaemia, multiple myeloma, chronic myeloid leukaemia, acute myeloid leukaemia in children, and cancer of the lung.*"

After 2015 a few studies have been published on lymphoid malignancies and benzene exposure on both adult (occupational, residential) and pediatric subjects. One of the studies on adult subjects [73] is a reanalysis of the Shanghai Women's Health Study, already taken into consideration by the IARC Monograph, with the same results, i.e., a positive association between estimated benzene exposure and non-Hodgkin lymphoma.

Two other studies have taken into consideration residential exposure to benzene, estimated through the residential address. The study by Teras et al. [74] found a significant association between estimated benzene exposure and incidence of any hematologic malignancy, myelodysplastic syndromes, T-cell lymphoma, and follicular lymphoma; however, no significant associations were observed for

women only. The study by Switchenko et al. [75] found a significant association between estimated benzene exposure and incidence of non-Hodgkin lymphoma.

In summary, the available evidence between benzene exposure and the potential for lymphoid malignancies shows that there is at most only limited, suggestive positive evidence, which is not enough to consider benzene exposure, for the time being, as a cause of these malignancies in humans.

1,3-Butadiene

As reported previously, according to IARC [14]: "*There is sufficient evidence in humans for the carcinogenicity of 1,3-butadiene. 1,3-Butadiene causes cancer of the haematolymphatic organs.*". According to IARC, "*Overall, the epidemiological evidence from the styrene-butadiene and the butadienemonomer industries clearly indicates an increased risk for haematolymphatic malignancies. Studies from the styrene-butadiene industry show an excess of leukaemia, and a dose-response relationship with cumulative exposure to butadiene, while studies from the monomer industry show an excess of haematolymphatic malignancies in general, attributable both to leukaemia and malignant lymphoma. The evidence for an association between exposure to butadiene and cancer of the haematolymphatic organs has gained some support by findings of an association between environmental levels of butadiene and risk for leukaemia in children. The epidemiological evidence for an association with specific subtypes of haematolymphatic malignancies is weaker, mainly since numbers are lower, giving imprecise risk estimates. However, when malignant lymphomas and leukaemias are distinguished, the evidence is strongest for leukaemia.*"

Although apparently comprehensive, the IARC evaluation is mainly based on studies focusing on leukemia. Regarding non-Hodgkin lymphoma, it is noted that: "*The strongest evidence of an association between exposure to butadiene and non-Hodgkin lymphoma comes from studies in the butadiene-monomer industry (Ward* et al.*, 1995, 1996; Divine & Hartman, 2001). Although this association did not become stronger with duration of exposure, it was more pronounced among workers who had been exposed during the Second World War, when exposures had presumably been higher.*"

In a study of North American synthetic rubber industry workers, published in 2015, cumulative exposure to 1,3-butadiene was not associated with non-Hodgkin lymphoma risk [76]. On the balance, the evidence supporting an association between 1,3-butadiene and non-Hodgkin lymphoma is limited. At the time of the IARC evaluation, it was not possible for the Working Group to assess the dose–response relationship: after that, the most relevant occupational cohort study did not identify an increased risk of non-Hodgkin lymphoma associated with 1,3-butadiene.

Formaldehyde

The investigation of the National Cancer Institute's formaldehyde cohort [52] suggested "*a possible link between formaldehyde exposure and lymphohematopoietic malignancies, particularly myeloid leukemia but also perhaps Hodgkin lymphoma and multiple myeloma.*"

Other studies, however, including the most recent [60, 77], did find an increase of neither leukemia risk in workers exposed to formaldehyde nor lymphoid malignancies.

Lindane

Lindane (any material containing >99% γ-hexachlorocyclohexane) has been used worldwide for its insecticidal properties. However, its use has largely decreased over the past decades; production in countries that are members of the United Nations Economic Commission for Europe took mainly place from 1950 or earlier until 1970 and stopped from 1970 onward. The world production of lindane is estimated to have decreased from 38,000 tons per year in 1985 to 3222 per year in 1990–1995.

According to IARC [78], "*There is sufficient evidence in humans for the carcinogenicity of lindane. Lindane causes non-Hodgkin lymphoma.*"

An important source of knowledge on the possible effects of lindane is the Agricultural Health Study, a large cohort study of American farmers: an analysis of 533 cases of non-Hodgkin lymphoma suggested a possible causal relation of exposure to lindane with this group of diseases [79]. However, the association was observed only in the highest category of exposure and based on solely 14 observed cases on non-Hodgkin lymphoma. Due to the limited number of events, an analysis for non-Hodgkin lymphoma subtypes was only performed for a binary exposure (never/ever exposed to lindane); the strongest association was observed for follicular B-cell lymphoma (16 cases classified as ever exposes).

Pentachlorophenol

Pentachlorophenol is an organochlorine compound used as a pesticide and a disinfectant. As pentachlorophenol is produced through a multistage chlorination process, it might contain, as impurities, dioxins, furans, and other chlorophenols. It is reasonable to assume that the products commer-

cialized in Western countries were composed of approximately 90% pentachlorophenol and 10% impurities. The manufacture of pentachlorophenol has ceased in most countries, and there is no known current European production. According to IARC [80], "*there is sufficient evidence in humans for the carcinogenicity of pentachlorophenol. Pentachlorophenol causes non-Hodgkin lymphoma.*" The statement is based on the four cohort studies available to the IARC working group: all of the studies reported an increased risk of non-Hodgkin lymphoma. According to IARC experts, the Canadian study of sawmill workers [81] was pivotal to the evaluation. This study also reported an increased risk of myeloma.

At present, there is no solid epidemiological evidence on the association between pentachlorophenol and specific non-Hodgkin lymphoma subtypes.

Rubber Manufacturing Industry

According to IARC evaluation [66], "*there is sufficient evidence in humans for the carcinogenicity of occupational exposures in the rubber-manufacturing industry. Occupational exposures in the rubber-manufacturing industry cause leukaemia, lymphoma, and cancers of the urinary bladder, lung, and stomach.*" The same Agency noted that "*No data in experimental animals with relevance to the rubber-manufacturing industry were available to the Working Group.*" Therefore, it must be assumed that the IARC statement was entirely based on epidemiological evidence available before 2009 (date of most recent evaluation). After that, several reports from well conducted-occupational cohort studies have been published.

In particular, a large analysis of 16,026 Swedish and UK rubber workers (397,975 person-years) published in 2017 did not show any significant increased risk of cancer risk among subjects firstly employed after 1975. Also, the incidence of non-Hodgkin lymphoma (standardized incidence ratio = 0.67) and myeloma (standardized incidence ratio = 0.93) were below the expected [82]. Similar conclusions were drawn by a parallel analysis of mortality in rubber workers from these and three additional European countries [83].

After that, two reports from the same large cohort study of UK workers employed in the rubber and cable manufacturing industry did not support the IARC evaluation [84, 85]. Indeed, deaths due to leukemia, non-Hodgkin lymphoma, and multiple myeloma were in line with the expected counts. However, a more detailed analysis of cumulative exposure levels to specific chemical compounds (N-nitrosamines, N-nitrosodimethylamine, and N-nitrosomorpholine) confirmed a possible increase in the risk of leukemia, multiple myeloma, and non-Hodgkin's lymphoma.

Considering the current IARC position, in light of new epidemiological evidence, we can conclude that large and well-conducted cohort studies analyzing recent periods (after 1975) dismissed the putative association between working in the rubber production industry and the risk of lymphohematopoietic malignancies. Rather than the production sector per se, some residual risk of cancer might stem from specific compounds (including nitrosamines): recent advances in industrial hygiene may have probably contributed to eliminate any appreciable increase in the incidence of lymphohematopoietic malignancies among workers employed in modern industries.

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Occupational Cancer Burden

32

Lesley Rushton, Sally J. Hutchings, and Kurt Straif

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 the 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. Before 2001 there were a number of studies estimating the burden of cancer attributable to a limited number of occupational exposures for specific countries and using a variety of methods. These have burden estimates ranging 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 a structured approach to estimating attributable burden carried out in the UK and presents key results from this study. More recent studies in several countries and globally are then described. Interpretation of results from cancer burden studies is discussed together with examples of the impact they are making on the effort to reduce occupationally related cancer.

Overview of Burden Estimation Methods

There are a number of approaches useful for calculating the occupational 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 (1) a risk estimate of the cancer type of interest associated with exposure to the carcinogen of concern with (2) an estimate of the proportion of the population exposed to

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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 when the occupational exposure 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. 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].
4. The use of newly occurring incident cases over a period of time to estimate the percentage caused by occupational exposures, for example, the study by Deschamps et al. [17].
5. The use of linkage analysis of national databases such as census, cancer registry, and death certificate data [18, 19].

The Approach of the British Study

Estimation of the Current Burden

The British occupational burden of cancer study, funded by the UK Health and Safety Executive (HSE), developed a structured approach to evaluating the burden of occupationally related cancer in Britain by estimating the attributable fraction (full details of methods and results are published in a series of papers [20] and technical reports which are available at http://www.hse.gov.uk/cancer/). The study considered all carcinogenic agents and occupations classified by IARC until the end of 2008 (the time of the study) as Group 1 (definite) or 2A (probable) carcinogens (over 40 carcinogens and 20 cancer sites were included). The most recent IARC evaluations are available at http://monographs.iarc.fr/ENG/Classification/index.php.

The study consisted of two related parts: estimation of (1) the current burden due to occupational exposures in the past and (2) the future burden of occupational cancer and forecast of the impact of alternative policy decisions affecting future workplace exposure levels.

There are several statistical methods for the estimation of the population attributable fraction (PAF). Levin's method is appropriate if risk estimates come from an industry-based study or a review or meta-analysis together with the estimates of the proportion of the population exposed from independent national sources of data [21]:

$$\mathrm{PAF} = \mathrm{pE} * \left(\mathrm{RR} - 1\right) / \left\{1 + \mathrm{pE} * \left(\mathrm{RR} - 1\right)\right\}$$

where pE 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 come from a population-based study [22]:

$$\mathrm{PAF} = \mathrm{pE}|D * \left(\mathrm{RR} - 1\right) / \mathrm{RR}$$

where pE|D is the proportion of cases exposed.

In practice, in the British study Levin's equation was used for all estimation [23].

Risk estimates were obtained from published literature. Meta-analyses or pooled studies were generally used where available. Alternatively key individual studies that were either British or from populations similar to Britain were used; expert judgment was used to assess whether the patterns of exposure and potential confounders such as smoking paralleled those of Britain. Where possible, risk estimates adjusted for important confounders or nonoccupational risk factors were selected, 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, a combined estimate of the relative risks was calculated using appropriate statistical methods. Formal systematic reviews and meta-analyses were carried out to determine 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. Where no suitable risk estimate could be identified from the literature for a low level of exposure, an estimate was derived by combining the ratios of the risk estimates for high against low exposure from all the other carcinogens where data were available [23].

Cancer latency, that is, the window of time relevant to the development of cancer many years later, was taken into account by defining a Risk Exposure Period (REP) as the exposure period relevant to a cancer appearing in the year of burden estimation; 10–50 years was used for solid tumors and 0–20 years for hematopoietic cancers.

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. Earlier studies used estimates of staff turnover to estimate proportions exposed [6–9]. The British study extended this to also account for life expectancy and adjust for changes in employment patterns over the REP [23].

For the British study, AFs were estimated across all ages. However, it is also possible to estimate age-group-specific PAFs to account for variation in cancer rates by age, an approach taken in subsequent studies based on the methods developed for the British study [24–26]. The age-group-specific numbers ever exposed are divided by the equivalent age estimates of the population ever of working age in the REP and alive in the target year. Occupational attributable age-group-specific numbers are then obtained by applying the age-group-specific PAFs to total disease incidence by age. Attributable numbers can then be summed across ages and divided by total incidence of this cancer for an estimate of overall (all age) PAF (note: the attributable fractions cannot be summed across the age groups).

National data sources such as the CARcinogen EXposure database (CAREX) [27], the UK Labour Force Survey (LFS) [28], and Census of Employment [29] were used for the British study 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 1990–1993. 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. 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. For each attributable fraction, a random error confidence interval was calculated using Monte Carlo simulations [30]. The PAFs 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, PAFs derived from these were used for the estimation of attributable registrations and vice versa. Similarly if separate PAFs 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 (1) mesothelioma due to asbestos exposure which was derived directly from several UK mesothelioma studies; (2) lung cancer due to asbestos exposure, which was estimated using a ratio of 1:1, mesothelioma to lung cancer deaths; and (3) 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 [23].

PAFs for all the relevant carcinogenic agents and occupational circumstances were combined into a single estimate of PAF for each separate cancer. To take account of potential multiple exposures, strategies including partitioning exposed numbers between overlapping exposures and 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 PAFs were then combined to give an overall PAF for that cancer using a product sum [31]:

$$\mathrm{PAF}_{\mathrm{overall}} = 1 - \Pi_k \left(1 - \mathrm{AF}_k\right) \quad \text{for} \quad k \,\text{exposures}$$

This can be shown to minimize bias that is introduced if the exposures are disjoint (not occurring concurrently) or are not independent [23]. An overall PAF for all cancers was estimated by summing the attributable numbers for each and dividing by the total number of cancers in Britain.

At a later date the British study extended the methods to estimate the PAF by age group as described above and applied this to estimation of cutaneous malignant melanoma (CMM) associated with occupational exposure to solar radiation [32]. CMM was not estimated in the earlier project because of uncertainty in the relative contributions of leisure and occupational sun exposure to melanoma risk. The recent literature is still somewhat equivocal. However, it seems plausible that work exposure should contribute to the overall risk. The method takes account of variation in cancer rates by

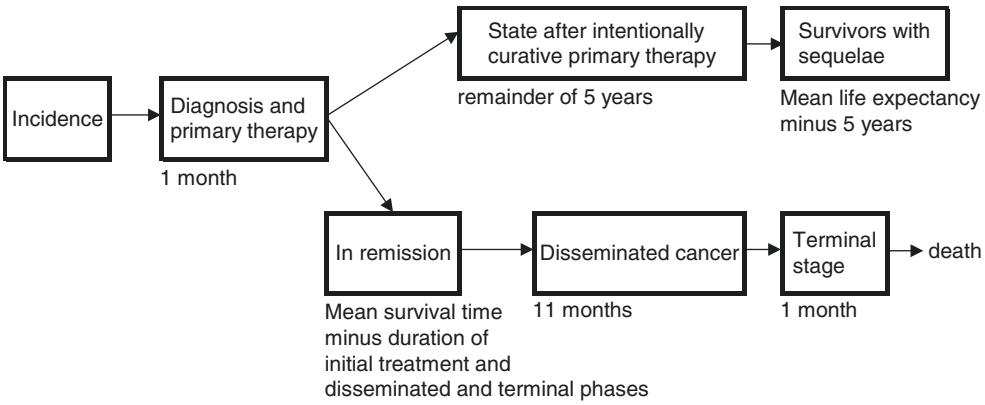

Fig. 32.1 General disease stage model for estimating cancer YLDs

age; the exposed population and national working population were assumed to have the same age structure and workers were assumed to enter the workforce between ages 15–45 years and retire at 65 years.

Extension to Measures of Lost Quality of Life

In addition to the attributable factions and numbers, quality of life measures can be estimated. 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 (1) a measure of lost years of life through premature mortality (YLL) and (2) a measure of lost quality of life to the individual, the years of future life time lived with a disability (YLD). Together these give disability-adjusted life years (DALY). DALYs are disease specific and use disability weights which are based on expert judgment. 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. DALYs 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.

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. The disease-specific disability weights for DALYs are based on secondary data and expert opinion, placing different conditions along a continuum of disability. 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 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 different cancers (Fig. 32.1).

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.

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 (up to 50 years), 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 [33]. Expanding from the high/low levels used for the current burden estimation, for the future predictions, risk estimates and proportions exposed were obtained wherever possible for "high," "medium," and "low" exposure levels with a "background" level, where appropriate, assumed to have zero excess risk.

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 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.

Alternative scenarios of change can be based on (1) historic and forecast employment and exposure level trends, (2) introduction of a range of possible exposure standards or reduction of a current exposure limit if exposure level estimates are available, (3) improved compliance to an existing exposure standard, or (4) 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 (1) above.

Extension to Estimation of Economic Impact: UK and EU Studies

In addition to PAFs and attributable numbers, estimation of the economic impacts of work-related cancer gives an additional dimension for risk management and regulatory decision-making. Approaches include using estimated burden in terms of cancer registrations and associated YLLs and YLDs (DALYs) to evaluate the economic impact regarding direct costs (such as inpatient, outpatient home care), indirect (such as loss of income) and intangible costs (disfigurement, functional limitations).

The HSE in their estimate of the costs of mortality due to work-related cancer used a constant "value of preventing a fatality" (VPF). This does not take account of age at death, i.e., assumes that the value society places on a life should not be sensitive to age or other personal characteristics [34]. An alternative approach estimates values of "life years" lost or saved using a constant monetary value of a life year (VOLY), which thus adjusts for the age of the affected population, as older people on average have fewer years of life remaining. As the number of life years lost is lower for conditions that occur at older ages, like many work-related cancers, adjusting for age leads to a much lower valuation for work-related cancer.

The estimation of the impact of morbidity of a work-related cancer utilizes the total years lived with a disability (YLDs) for both fatal and non-fatal cases. YLDs are multiplied by an estimate of the monetary value of a life year to derive the total human costs of cancer, again for both fatal and non-fatal cases. There can be considerable variation in the value given to a statistical life year depending on factors such as the cancer type, the period of progressive illness and associated pain, anxiety, distress, and medical intervention. Some form of discounting impacts that occur in the future is often applied to reflect evidence that people generally place a lower weight on future costs and benefits compared with those occurring in the present. The HSE study refers to the cost component that represents the willingness to pay to avoid cancer over and above the (theoretical) loss of the consumption of goods and services that would no longer be enjoyed as "human costs."

EU Carcinogen Study

A project that adapted the British cancer burden methodology was funded by the European Commission DG Employment to carry out a socioeconomic, health, and environmental impact assessment of possible changes to the EU Carcinogens Directive [25]. It included 25 carcinogens which were a mixture of IARC Class 1, 2A, 2B and modeled the effect of introduction and/or reduction of different workplace exposure limits. OEL values for five substances were suggested by the European Commission: hard wood dust, vinyl chloride monomer, hexavalent chromium, respirable crystalline silica, and 1,3-butadiene. All others were selected as "typical" of existing OEL values among EU member states. Costs of predicted future cancers from these changes were compared with costs to industry of implementation. Constant figures for the value of life years lost for cancer and also for the cost of illness (morbidity) were used. Future health costs were discounted at an annual rate of 4% as compliance cost estimates.

To assess compliance costs of meeting the introduction/reduction of a limit value, the main uses within industry sectors leading to exposures in excess of the proposed OEL were considered, together with possible risk management measures that might be applied. Background information on all agents in the project were obtained from published literature and stakeholder contacts to identify:

- The uses and activities that lead to workplace exposure
- The structure of the sectors in which exposure occurs (e.g., numbers employed, demographics of employees, and geographical distribution of firms in the EU)
- Exposure control measures currently in place, available and required to meet the proposed OEL
- The possible costs of exposure control measures.

Information was obtained on the number of enterprises operating in different sectors, the number of workers employed in those enterprises, the distribution of enterprises in the EU and financial measures such as turnover, personnel costs, and research and development expenditure. Estimates were made of (1) the number of firms needing to apply risk management measures; (2) the costs of implementation over the same time period as future predicted health benefits (2010–2069); (3) the administrative burden of implementing the OEL (e.g., the cost of monitoring and audit); (4) the potential effect on the market for the substance by the imposition of the OEL. The costs and benefits of the "do nothing" or "business as usual" situation were compared with scenarios of introducing/reducing OELs.

The Australian Approach

An alternative to the PAF approach, which estimates the burden now from exposure in the past, is the lifetime risk approach which addresses burden from a different perspective by predicting how many workers exposed now would develop a cancer in the future. The lifetime risk approach is useful if information on past exposure is scarce; however, it requires prediction of future general population disease risk which is a potential source of inaccuracy.

The method has been extended in an Australian study [35] to estimate the prevalence of exposure for Australians exposed to workplace carcinogens using the Australian Work Exposures Study (AWES), which surveyed a random sample of just over 5000 currently employed men and women and interviewed them by telephone about their current job [36]. A web-based application (OccIDEAS) [37] was utilized in which participants were asked about their job tasks and predefined algorithms were then used to automatically assign exposures. About 37.6% were assessed as being exposed to at least one occupational carcinogen in their current job, suggesting that 3.6 million (40.3%) current Australian workers could be exposed to carcinogens in their workplace. Exposure prevalence was highest among farmers, drivers, miners, and transport workers.

The "future excess fraction" model developed by Fritschi et al. (2016) [35] estimates the lifetime excess fraction due to a workplace carcinogen exposure and is based on the person-years of the disease-free population rather than the total population. It takes account of age-specific survival and uses a risk estimate obtained from the literature for each carcinogen and its associated cancer site. It should be noted that the future excess fraction is not directly comparable with the PAF. For the cohort of Australian working population (aged 18–65 years) in 2012, the future person-years at risk was estimated using life tables and adjusting for competing causes of death. Relative risk estimates for high and low exposures for each of the 53 cancer-carcinogen combinations in the study were obtained from the literature with, in the majority of cases, the relative risks selected being the same as those used in the British study. Where these were unsuitable for Australian circumstances (e.g., melanoma and solar radiation exposure), a literature review was conducted. Projected cancers were predicted based on past cancer registrations.

Selected Results from the British, EU, and Australian Studies

Selected results from the above studies 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 32.1 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 (see [38] for the 95% confidence intervals). The PAFs 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 cutaneous malignant melanoma [32] and soft tissue sarcoma (STS), with in addition for men melanoma of the eye (due to welding) and non-Hodgkin's lymphoma (NHL).

Figure 32.2 shows for each carcinogen with >20 total registrations the total number of cancer registrations by cancer 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%, 3909, 4216; laryngeal cancer 0.37%, 3, 8; lung cancer 5.91%, 1937, 2223; mesothelioma 95.09%, 1937, 1937; stomach cancer 0.58%, 32, 47), silica (0.53%, 789, 907), diesel engine exhaust (DEE) (0.43%, 652, 801), mineral oils (0.38%, 563, 1722), shift work (0.37%, 552, 1957), 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). Figure 32.2 demonstrates that many carcinogenic exposures in the workplace affect multiple cancer sites.

Table 32.1 Estimated attributable fractions, deaths (in 2005), registrations, DALYs by cancer site (in 2005) for the British study for cancer sites with a total of >20 cancer registrations

Cancer site[a]		Attributable fraction (%)			Attributable numbers						Disability-adjusted life-years (DALY) (years)			
					Deaths (2005)			Registrations (2004)			Year life lost (YLL)	Years lived with disability	DALYs	Mean YLL
	ICD-10 code	Male	Female	Total (based on deaths)	Male	Female	Total	Male	Female	Total	Total (male + female)			
Bladder	C67	7.1	1.9	5.3	215	30	245	496	54	550	2543	567	3110	10.7
Breast	C50		4.6	4.6		555	555		1969	1969	9600	4196	13,797	17.3
Larynx	C32	2.9	1.6	2.6	17	3	20	50	6	56	290	123	414	14.6
Leukemia[b]	C91–C95	0.9	0.5	0.7	18	5	23	30	9	38	390	33	423	17.6
Lung	C33–C34	21.1	5.3	14.5	4020	725	4745	4627	815	5442	62,848	3164	66,012	13.7
Melanoma[c]	C43	3.2	0.9	2.0	39	8	48	154	57	241	820	218	1038	16.5
Mesothelioma[d]	C45	97.0	82.5	94.9	1699	238	1937	1699[e]	238[e]	1937[e]	26,942	796	27,738	14.0
NHL	C82–C85	2.1	1.1	1.7	43	14	57	102	39	140	964	65	1,029	17.4
NMSC[f]	C44	6.9	1.1	4.5	20	2	23	2513	349	2862	203	67	270	8.7
Esophagus	C15	3.3	1.1	2.5	156	28	184	159	29	188	2528	163	2691	13.5
Ovary	C56		0.5	0.5		23	23		33	33	383	35	418	16.8
Sinonasal	C30–C31	43.3	19.8	32.7	27	10	38	95	31	126	622	181	802	16.8
STS	C49	3.4	1.1	2.4	11	3	13	22	4	27	286	38	324	22.5
Stomach	C16	3.0	0.3	1.9	101	6	108	149	9	157	1324	129	1453	12.4
Total	C00–C97													
Based on deaths		**8.2**	**2.3**	**5.3**	**6355**	**1655**	**8010**				109,672			15.1
Based on registrations		**5.7**	**2.1**	**4.0**				**9988**	**3611**	**13,598**		9662	119,334	
Total GB 15+ cancers					**77,912**	**72,212**	**150,124**	**175,399**	**168,184**	**343,583**				

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]PAF applicable to all leukemias

[c]Cutaneous malignant melanoma (CMM), cancer registrations for 2011, deaths 2012, excluded from the totals which for the other cancer sites were for 2004/2005

[d]Includes cases described as due to para-occupational or environmental exposure to asbestos

[e]Taken as equal to attributable deaths for this short survival cancer

[f]Based on registrations

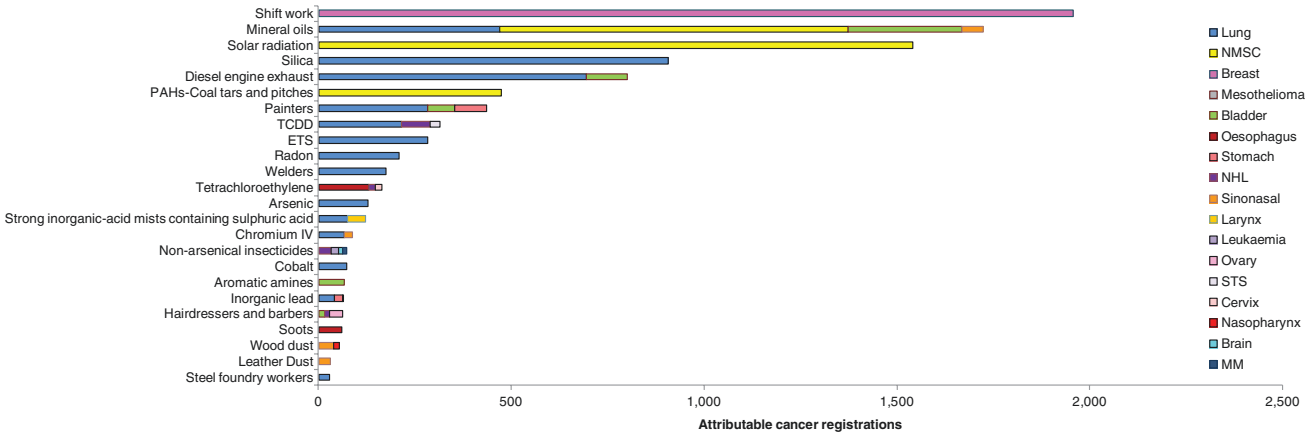

Fig. 32.2 Total numbers of cancer registrations (2004) by carcinogen and cancer site

Table 32.1 also shows 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.

The analyses for CMM gave an overall AF for CMM of 2.0% (3.2% for men, 0.9% for women), giving 48 (39 men, 8 women) deaths (in 2012) and 241 (184 men, 57 women) registrations (in 2011) attributable to occupational exposure to solar radiation [32]. Higher results for men reflect both higher exposure and larger numbers exposed to solar radiation. The average YLL through early death was approximately 17 years, with a total of 1038 DALYs. Over 50% (128) of the CMMs occurred after retirement (65+ years), highlighting the issue of many similar long latency occupational cancers occurring many years after leaving work.

The Health and Safety Executive estimates of the economic cost of exposures to workplace carcinogens in Britain gave total economic costs to the society of new cases of work-related cancer in Britain in 2010, arising from past working conditions, to be about £12.3 billion particularly from lung cancer (£6.8 billion), mesothelioma (£3.0 billion), and breast cancer (£1.1 billion). The vast majority (98%) of the costs of work-related cancer (£12.0 billion) were shown to be borne by individuals due largely to "human" costs—a monetary value on the effects of cancer on quality of life or loss of life for fatal cancers (£11.4 billion) [34]. By comparison, only £461 million was borne by employers. The authors highlight the fact that due to the often very long latency between occupational exposure to carcinogens and development of cancer, the cancer occurs after workers have retired so that employers do not incur costs such as disruption from sickness absence and paying sick pay.

The British study, unlike many other previous studies, estimated the 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 32.2). 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 (1) asbestos, DEE, silica, and solar radiation in the construction industry; (2) asbestos, DEE, ETS (nonsmokers), soots, and tetrachloro-

Table 32.2 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 and 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										1252
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**	**1722**
Construction	2773		15	0	4	290	36		31	
Painters and decorators (construction)										
Roofers, road surfacers, roadmen, paviors (construction)										
Total construction	**2773**		**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]	**4216**	**66**	**129**	**89**	**73**	**801**	**284**	**63**	**65**	**1722**

Table 32.2 (continued)

Industry sector/carcinogenic agent	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]
Total agricultural, hunting, fishing, and forestry	**72**			**1**			**135**			**55**			**1**	**263**
Iron and steel basic industries		4		1			0		3	75	1		0	135
Manufacture of industrial chemicals	1			2		1			16	11			0	116
Manufacture of instruments and photographic and optical goods				1									0	206
Manufacture of machinery except electrical				9		28			13		18		0	111
Manufacture of other chemical products				2		10			20				0	119
Manufacture of transport equipment				5		11	5		12		6		0	182
Metal workers														1252
Mining				0		29	31							296
Nonferrous metal basic industries				1		4	9		14	50	1		0	156
Painters (not construction)			102											102
Printing, publishing, and allied industries				4			3				2		0	282
Welders												175		181
Total manufacturing industry, mining, quarrying, electricity, gas, water	**2**	**4**	**102**	**62**		**200**	**163**		**122**	**254**	**60**	**175**	**23**	**3909**
Construction				9		707	841				11		29	4668
Painters and decorators (construction)			334											334
Roofers, road surfacers, roadmen, paviors (construction)		471												471
Total construction		**471**	**334**	**9**		**707**	**841**				**11**		**29**	**5439**
Land transport				4			6				3		0	498
Personal and household services				6			14	60			89			670
Public administration and defense				12			240							273
Shift work					1957									1957
Wholesale and retail trade and restaurants and hotels				42			6			7				246
Total service industries				**137**	**1957**		**402**	**60**	**0**	**7**	**94**		**1**	**4007**
Total[a,b]	**73**	**475**	**437**	**209**	**1957**	**907**	**1541**	**60**	**122**	**316**	**164**	**175**	**54**	**13,598**

[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

ethylene in personal and household services; (3) asbestos and DEE in land transport (railway, road, pipeline); (4) asbestos, DEE, silica, and solar radiation in mining; (5) ETS (nonsmokers) and solar radiation in public administration and defense; (6) asbestos, ETS (nonsmokers), and radon in the wholesale and retail trade, restaurants, and hotels; and (7) dioxins, nonarsenical 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, and soft tissue sarcoma), nine for construction (bladder, brain, larynx, lung, mesothelioma, NMSC, esophagus, sinonasal, and stomach), and 12 for personal and household services (bladder, breast, cervix, kidney, leukemia, lung, mesothelioma, non-Hodgkin's lymphoma, esophagus, ovary, sinonasal, stomach).

The main industries of concern for CMM were construction (21 deaths, 101 registrations), agriculture (11 deaths, 55 registrations), public administration and defence (5 deaths, 26 registrations), and land transport (4 deaths, 21 registrations).

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 [33]. 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 (1) different reductions of the WEL in 2010, (2) delaying reduction of the WEL to 2020 or 2030, (3) improving compliance to the current WEL, (4) simultaneously improving compliance and reducing the WEL, and (5) improving compliance in different sizes of workplace. The intervention scenarios tested are described in Table 32.3 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 nonoccupational 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

Table 32.3 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

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. 32.3. 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 (0.1 mg/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

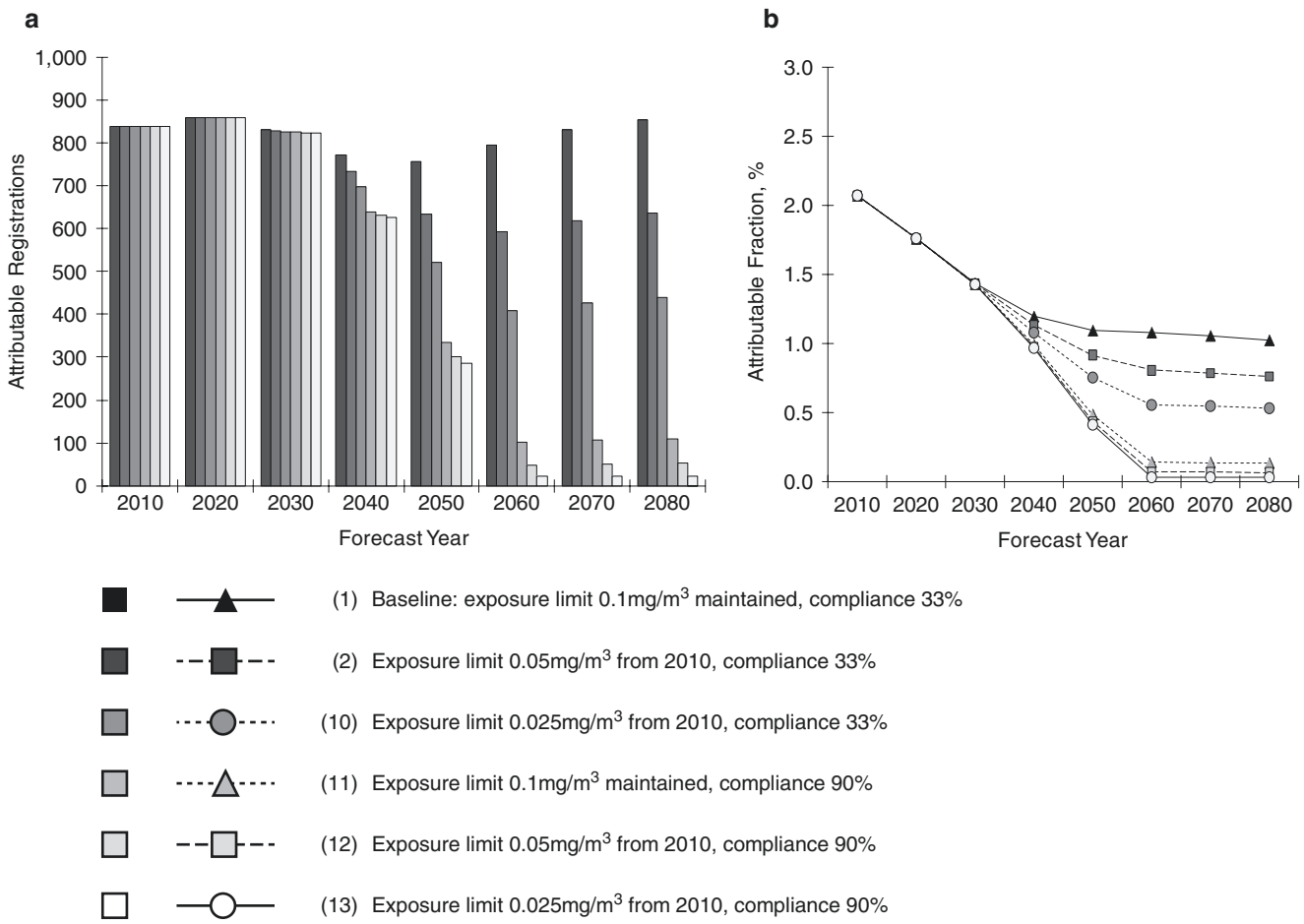

Fig. 32.3 Effect of reducing workplace exposure limits and improving compliance for respirable crystalline silica associated with lung cancer. (**a**) attributable registrations, (**b**) attributable fractions

British study showed that, without intervention, occupational attributable cancers were forecast to remain at over 10,000 annually by 2060. With modest intervention nearly 2500 or with stricter interventions over 8100, cancers could be avoided by 2060 although due to long latency no impact would be seen until at least 10 years after intervention. Effective interventions 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 [39].

Results from the EU Study

The estimated number of workers in the EU currently exposed to the 25 carcinogens ranged from under 1000 for bromoethylene to over seven million for benzo[a]pyrene [25]. Figure 32.4 shows the numbers of deaths predicted in 2010–2069, assuming no changes were made to occupational limits (baseline), and compares this to the numbers if the most stringent of the suggested OELs was introduced. It was estimated there would be more than 1000 cancer deaths occurring in the EU over the next 60 years for nine substances if no action was taken (>700,000 cancer deaths for these substances). The greatest numbers of excess incident cancers were predicted for respirable crystalline silica, diesel engine exhaust, and mineral oils as used engine oils. Table 32.4 shows the impact of introducing different OELs for the seven substances where the ratio of health benefit costs to compliance cost was greater than 0.

The largest benefits arise from the introduction of OELs for respirable crystalline silica, hardwood dust, hexavalent chromium, and rubber fume. The monetized health benefits from introducing an OEL were greatest for respirable crystalline silica (between €21,000 and €74,000 million, depending on the OEL and the uncertainties involved in the estimation). Health benefits were also large for the introduction of OELs for hexavalent chromium (around €500–€1300 million for a limit of 0.025 mg/m^3) and rubber process fume (€580– €1200 million). Other substances where the weight of evidence (e.g., high risk estimates, high health burden with no action, or many workers currently exposed) supports the introduction of a limit include diesel engine exhaust emissions, rubber fume/dust, benzo[a]pyrene, trichloroethylene, hydrazine, epichlorohydrin, *o*-toluidine, mineral oils, and used engine oil and MDA.

Results from the Australian Study

For the cohort of workers estimated to be exposed to a workplace carcinogen in 2012, the Australian study predicted the number of cancers that might be expected in this cohort up to

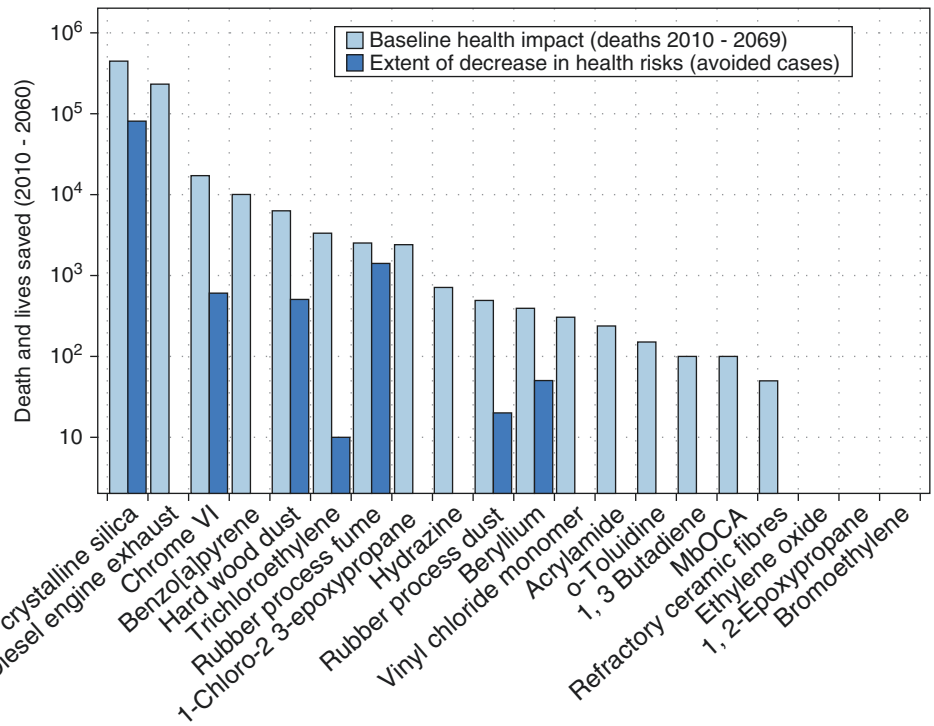

Fig. 32.4 Baseline health and impact and avoided cases 2010–2069 for 25 carcinogens

Table 32.4 OEL values tested, predicted cancers prevented by introducing an OEL, and health and compliance costs 2010–2069

Substance or mixture	OEL value tested (mg/m^3)	Decrease in health risks (avoided cases 2010–2069)	Total compliance costs (€m)	Total health benefits (€m)	Benefit to cost ratio[§]
Respirable crystalline silica	0.2 0.1 0.05	80,000 99,000 110,000	€10,000 €19,000 €34,000	€21,000–€56,000 €26,000–€68,000 €28,000–€74,000	2.3–5.4 1.5–3.5 0.9–2.1
Hard wood dust	3 1	500 3900	€0 €3800–€8600	€11–€51 €61–€297	– 0.01–0.05
Chrome VI	0.1 0.05 0.025	600 1400 1800	€9000–€37,000 €18,000–€67,000 €30,000–€115,000	€159–€456 €340–€991 €461–€1327	0.006–0.03 0.007–0.03 0.006–0.03
Rubber process fume	0.6	1400	€470–€3200	€580–€1200	0.25–1.5
Trichloroethylene	273	10	€61	€0	0
	50	580	€428	€120–€430	0.3–1.0
Beryllium/beryllium compounds	0.002	50	€18,000–€34,000	€11–€30	0.0004–0.001
Rubber process dust	6	20	€55–€280	€24–€46	0.1–0.5

[§]The 5th and 95th percentile points of a Monte Carlo simulation of the ratio of values drawn from the underlying cost ranges

Table 32.5 Estimated occupational future excess fractions (%) and future excess numbers (*n*) arising among the cohort of working age Australians in 2012, by selected cancer site

Cancer site	Future excess fraction (%)			Future excess number (*n*)[a]		
	Male	Female	Total	Male	Female	Total
Bladder	2.0	0.3	1.6	2000	<500	2500
Breast	1.1	0.7	0.8	<500	6000	6000
Colorectal	0.1	0.0	0.1	1000	0	1000
Larynx	10.9	1.2	9.7	3000	<100	3000
Leukemia	5.9	4.6	5.6	6500	1500	8000
Lip	10.5	1.9	7.3	3000	500	3500
Lung	6.1	0.3	3.6	25,000	1000	26,000
Melanoma of the skin	1.4	0.2	0.9	5000	500	5500
Mesothelioma	31.7	0.2	21.9	7500	<100	7500
Nasal	23.9	1.0	15.9	1500	<100	1500
Occular melanoma	8.2	1.4	5.4	1000	<500	1000
Stomach	2.1	0.1	1.3	2000	<100	2000
Overall	**2.5**	**0.4**	**1.4**	**58,500**	**10,000**	**68,500**

[a]All numbers rounded to the nearest 500 to avoid a false sense of precision

2094 for 19 cancer sites [40]. Table 32.5 shows the future excess fractions (FEF) and numbers (FEN) for those cancer sites with more than 1000 future excess numbers of cancers. The cohort of the Australian working age population in 2012 was estimated to be 14,594,000 in total, and an estimated 4,831,500 cancers were predicted to occur over their lifetime (2,345,000 cases in males and 2,486,500 in females). For the 2012 working age population, it was estimated that 1.4% (n = 68,500) of future cancer registrations would occur in those who were exposed to occupational carcinogens in that year, as a result of their exposure (2.5%, n = 58,500 males; 0.4%, n = 10,000 females). The highest FEFs for males were for mesothelioma (32%), nasal cancer (24%), and laryngeal cancer (11%) (Table 32.1). For females, the highest FEFs were for leukemia (5%), lip cancer (2%), and ocular melanoma (1%). Overall, asbestos exposure contributed the largest number of cancer registrations, followed by solar ultraviolet radiation and benzene. Lung cancer was the largest contributor to the overall FEN of occupational cancers. Thirteen occupational exposures were considered as causing lung cancer, with silica being the largest contributor for males, followed by diesel engine exhaust and asbestos and polycyclic aromatic hydrocarbons other than vehicle exhausts, followed by environmental tobacco smoke and silica for females. Leukemia had the next highest number of registrations due to occupational exposure, primarily due to benzene exposure.

Discussion

The results from occupational burden studies 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.

Differences between the cancer burden estimates from different studies 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 in the UK since 1981 has made a major contribution to the increase [41, 42]. More recent estimates of occupational cancer have been made for Australia [43] (5000 invasive cancers and 34,000 NMSCs) and France [44] (4335 (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 (7832 for men, 3662 for women) [45]; NMSC was excluded 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. [46] acknowledge this point. Their estimate could be considered as a "lower bound" 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 [47, 48].

There are a number of important issues which may affect the results, the impact of which is not fully captured in the random confidence intervals. These include assumptions about cancer latency and thus the length of the relevant exposure window before cancer development; lack of data on the proportions exposed at different exposure levels within industry sectors or jobs; choice of the risk estimates and whether the studies from which these are chosen are compatible with the population of concern regarding exposures, confounders, etc.; a lack of separate risk estimates in some cases for women and/or cancer incidence; methodological issues such as the use of Levin's equation with adjusted risk estimates and employment turnover methodology. Credibility intervals exploring the relative contributions of important sources of uncertainty have shown that the choice of relative risk and the employment turnover estimates contribute most to overall estimate uncertainty with bias from using an incorrect estimator making a much lower contribution [49].

A key decision at the start of any burden estimation is to decide which diseases and exposures are to be included. A common starting point is to use, for cancers, the classification developed and implemented by IARC which is well respected worldwide. The British and Australian studies chose to assess only those agents classified by IARC as Group I and 2A carcinogens.

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 between 10 and 50 years before the estimation year for solid tumors and for up to 20 years 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 of all the studies highlight 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 and 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 [50]. 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 be easily 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). This is clearly illustrated in the British estimation of the future burden of occupational cancers [39]. 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.

The studies described in this chapter have had a range of impacts aimed at reduction of occupational ill health. The results have been used, for example, by the funders of the British study, the UK Health and Safety Executive, to inform guidance documents and to inform the development of programmes to identify practical interventions together with stakeholders. Of particular note is the use of the findings together with those from other projects in the successful Institution for Occupational Safety and Health (IOSH) "No time to lose" campaigns [51]. These campaigns raise awareness of significant health issues from occupational cancer facing employees and provide free practical, original materials to businesses to help them deliver effective prevention programmes. The results from the European project to inform changes to the EU carcinogen directive were considered, together with other information such as socioeconomic (cost–benefit) impact analysis and feasibility issues, by a number of committees during a lengthy and complex process required to provide a consensus opinion on OEL values changes. This included scientific evaluation of the exposure–risk relationship for each chemical by the Scientific Committee on Occupational Exposure Limits (SCOEL) and production of draft recommendations/opinion on limits; Directorate General Employment consultation of the SCOEL report with the Advisory Committee on Safety and Heath (ACSH) via the tripartite Working Party on Chemicals (WPC); preparation of an impact assessment by the Commission; consultation with other DGs; initiation of the legislative procedure. At the start of this procedure, and at intervals during the process, consultation takes place with stakeholders and "social partners" (employers and employees).

The final choice of OELs by the EU will for the first time provide a level playing field by providing binding OELs for 25 important workplace carcinogens across 28 member states. The final choice of the proposed OELs is often the same as that based on scientific evidence. However, the use of formal cost/benefit analyses adds to decision-making processes and may result in higher limits, for example, (1) if a lower value is shown to give no further reduction in DALYs and no lower compliance costs than a higher value, (2) a lower value is estimated to only increase health benefits by a small amount but to increase compliance costs by a much large amount, and (3) there is thought to be a disproportionate cost to industry especially small and medium sized enterprises (SMEs).

In summary, this chapter has outlined different methods for estimating the burden of occupational cancer. The methods described have the potential to be adapted for use in other countries and extended to include social and economic impact evaluation. 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.

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Occupational Carcinogens and Cancer in Children

33

Mana Mann and Philip J. Landrigan

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 part 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 part 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 the 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 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

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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 overrepresented 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 and Blair [5] and Savitz and Chen [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 and Blair 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 ratio for childhood brain tumor for mothers employed during any of these periods in textile/garment industry was 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 Wijngaarden 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-Cowdin 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 1218 cases of childhood brain tumors and 2223 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 6.4–2569) [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 years, 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 and Blair 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 the 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 toward 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 years 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 9022 young men and women who were between the ages of 12 and 17 years 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 years. 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 years 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 years 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.

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Strategies for Primary Prevention of Occupational Cancer

34

Per Gustavsson

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 14 million cancers are diagnosed globally, and 8.2 millions of deaths are due to cancer [1]. 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 [2].

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% [3]. 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 [4]. This figure is probably an underestimation, and more recent estimations have arrived at higher proportions (see Chap. 20). Rushton et al. [5] estimated that 5.3% of all cancer deaths in the UK were attributable to occupational exposures. This can be considered as a conservative estimate taking only 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 [6].

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 [7].

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. [5]. 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 [5].

Much of the research on occupational cancer has been focused on men despite women since long have entered the labor market. A probable association between shift work that disrupts the circadian rhythm and female breast cancer was identified relatively recently and has been classified as group 2a (probably carcinogenic to humans) by the IARC [8].

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.

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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 described 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 [9]. 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 [10]. No cases of scrotal cancer were found in over 5000 Swedish chimney sweeps active since 1918 [11], and there was no excess of skin cancer among Nordic chimney sweeps in a recent record linkage study [12]. 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 [13].

Skin cancer of the scrotum is a very rare disease in the general male population (the incidence is one in one million men per year) [14]. For so rare diseases, 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 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 [15]. Ramazzini could not explain this phenomenon, which today is known to be caused by hormonal factors related to the absence of pregnancies among nuns [16]. This disease is still today the leading cancer form among women [1], 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 clinical 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 bladder cancer patients had worked at 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 [17]. It was not until about 1950 when an excess of bladder cancer was reported from the British dye industry [18], and aromatic amines (specifically 2-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 [19]. Abandoning of 2-naphtylamine in the British rubber industry eliminated the earlier excess of bladder cancer in that industry [20].

Sinonasal Cancer and Wood Dust

The first scientific report of a cluster of 20 cases of sinonasal cancer in association with furniture making came from England in 1965. It was based on an unpublished report by the otolaryngologist Esme Hadfield, cited by her colleague Ronald MacBeth [21]:

> "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."

A large number of subsequent epidemiological studies have confirmed an association between exposure to wood dust and sinonasal cancer [22]. The association is particularly strong for exposure to hardwood dust and adenocarcinoma, although there is also some evidence for the carcinogenicity of soft wood dust, and the IARC has classified wood dust as carcinogenic to humans (Group 1) [23]. 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 the UK. Animal experimental data indicating that asbestos could produce tumors came in 1943 but was suppressed by the industry sponsoring the study [24]. 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 [25]. The study was sponsored by the asbestos industry which tried to stop publication, although the journal decided to publish it anyway [24]. Numerous later publications have confirmed that asbestos causes lung cancer [23]. Asbestos was banned for insulation in Denmark in 1972 and has subsequently been banned in a large number of states including all European Union states (in 2005) until today (July 2017) (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 [26].

That asbestos causes mesothelioma was accepted much quicker than that it causes lung cancer. The first case reports came in the 1940s [27] and the first epidemiological study in 1960 [28]. There is a very long latency from start of asbestos exposure and development of mesothelioma. The upgoing rate of mesothelioma during the second half of the twentieth century in Germany can be related to the increased use of asbestos 3–4 decades earlier [29]. Despite that asbestos exposure was dramatically reduced in Sweden in 1976, mesothelioma rates are still high, have started to level off, but not to decrease [30].

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 in the USA alarmed its employees and authorities about three cases of this very rare tumor among its employees [31]. Animal experiments were started and confirmed within short time 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 the OSHA, and authorities from other parts of the world followed soon [33]. Numerous case reports confirming the association followed, and the first epidemiological study was published in 1981 [34].

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 [35]. 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 leukemogenic effect [35]. When IARC Vol 7 was published in 1974, there were no animal data supporting that benzene caused cancer, and a leukemogenic effect was based on several systematic case reports with supportive evidence from a single epidemiological study [35]. 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. 34.1).

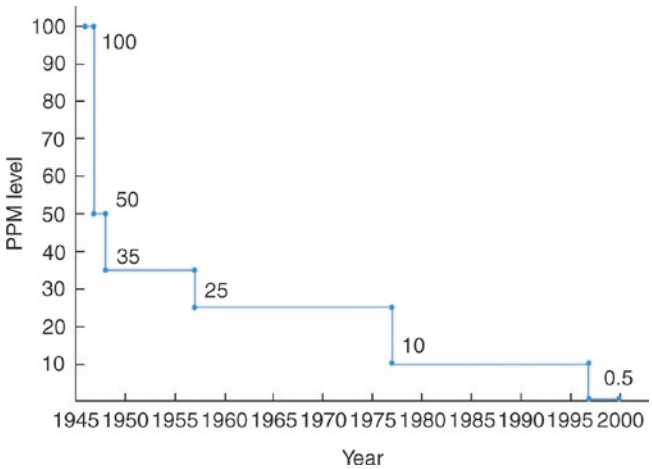

Fig. 34.1 Chronology of ACGIH-adopted exposure limits for benzene. (Reproduced from Verma et al. [33] with permission from BMJ Publishing Group Ltd)

In 1978, the OSHA decided on a reduction of the permissible occupational exposure standard for benzene from 10 to 1 ppm. By action from the industry, this lowering was overruled and postponed until 1987. It has been estimated that between 30 and 490 leukemia cases were induced by this delay [36].

Risk Identification

It is noteworthy from the brief review above that nearly all of today's established occupational cancer hazards 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 more recent examples [7, 33]. Cancer hazard identification from clinical clusters is a failure in the sense that cancers have already been induced when the hazard is identified. Premarket screening by short-term methods is necessary for effective surveillance in the introduction of new chemicals.

Cancer development is a multistage process in which clinical cancer develops several decades after first exposure. This multistage process involves many molecular events which may be monitored by biomarkers for early detection of a potential cancer hazard. There are biomarkers of exposure, markers of early effects, markers of clinical disease, as well as markers indicating an increased susceptibility. Biomarker can include proteins, nucleic acids, antibodies, and peptides, and a biomarker can also be a group of alterations, such as gene expression, and proteomic as well as metabolomic signatures. Biomarkers can be detected in the circulation or excretions, which are accessed non-invasively, or can be tissue-derived and require biopsy [37].

Commonly used markers of genotoxic effects include micronuclei frequency, chromosomal aberrations, sister chromatid exchanging, and comet assay [38]. There is also a huge literature on the alterations of specific genes, proto-oncogenes, and tumor suppressing genes, for the prediction of cancer risk.

For the identification of a cancer hazard and effective prevention, a synthesis of epidemiological, animal experimental, and other relevant data is necessary. There are several systems for such synthesis, and systematic identification of cancer risk is performed by a number of national and international organizations. Most well-known is the monograph series from the International Agency for Research on Cancer (IARC) [39]. IARC is a WHO organization producing evaluations of carcinogenicity to humans from both environmental and occupational exposure and naturally occurring substances (see Chap. 1 for the description of the IARC evaluation process). The IARC process incorporates epidemiological, experimental, mechanistic, as well as occupational hygiene data in the evaluation process, which is based on a qualitative evaluation of weight of the evidence. IARC evaluates carcinogenicity but does not perform risk quantification. IARC has until today (July 2017) evaluated 1003 substances or exposure circumstances for carcinogenicity, classifying 120 of them as carcinogenic to humans, 81 as probably carcinogenic, 299 as possibly carcinogenic, 502 as not classifiable, and 1 as probably not carcinogenic to humans. Considering the very large number of chemical substances and exposure circumstances worldwide, this is a small fraction, and many substances are unevaluated.

A procedure for systematic review, incorporating the GRADE scale for classification of evidence, is used by the National Toxicological Program at National Institute of Environmental Health Sciences (NIEHS) in the US [40]. The GRADE system was initially developed for evaluation of studies of randomized designs, and this poses special challenges in application for evaluation of observational studies. Such adaptions are under development [41].

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 1000 metric tons, REACH will not require data for classification of carcinogenicity, and the criteria vary for substances used or imported in higher amounts [42]. It remains to be evaluated to what extent REACH will improve the early detection of new chemical carcinogens. It is not known how many substances that have been discarded from industrial use due to positive findings in premarket tests.

Future identification of carcinogenic substances must be based on premarket testing—in case this does not work, clinical observations and epidemiological studies may still be necessary although not desirable as a 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. For effective exposure assessment, preferably based on a lifetime history of occupations, access to exposure data from occupational hygiene studies and individual data on important confounders are 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 not often used

in risk quantification since the difference in sensitivity between species often precludes valid risk quantification for humans. Epidemiological and occupational hygiene data are required to investigate dose–response relationships in exposed populations. Information on the prevalence of exposure and exposure levels in the population are needed for assessment of population attributable risk.

Since clinical cancer develops over decades, exposure circumstances may change during that time. While the assessment of population attributable fraction (PAF) aims to assess how large fraction of currently diagnosed cancers that could have been 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 only for a small part [5]. 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) was 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) [43].

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 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 [44]. The matrix has recently been extended to cover all Scandinavian countries [45].

Information on cancer risks in relation to occupational exposure and dose-response must mainly be derived from epidemiological studies. 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 is rarely 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 extrapolate the findings to the general population, provided that the sample of controls is representative for the population. There is often access to a lifetime smoking history and a lifetime history of occupations. The drawback is that exposure information may be derived from the individuals themselves, with a potential for so called 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 zero exposure, whereas cancer developed by other modes of action may have a threshold. The latter has been discussed in association with carcinogens acting via irritation on the cellular level, e.g., strong inorganic acid mist [46].

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 in epidemiological studies due to low numbers. Gender differences in sensitivity to toxic substances and carcinogens 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) [47]. Later research and meta-analyses have shown a large heterogeneity in risk excess per fiber-year between studies and that the often used estimate of 1% increase in SMR per fiber-year is likely to underestimate the risk at low doses [48].

Evaluating the cancer risk from several combined exposures poses specific problems and involves investigation of various types of interaction [49]. This problem is addressed

in an ongoing multicenter epidemiological study of lung cancer, SYNERGY (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 the USA and Europe. They found an average annual decline in exposure levels typically ranging from 4% to 14% over a 30-year period [50, 51]. 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 difficult to discern. There are at least three interchanging components driving this process: (a) formal regulatory action by national legislative authorities; (b) local workplace action by companies, trade unions, and 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 the form of threshold limit values (TLVs) defining the maximum allowable airborne concentration of a substance, or for a smaller set of substances, the maximum allowable concentration in blood or urine. 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 [52]. 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 a legally binding TLV is typically slower, results in a higher TLV, and covers fewer substances than the list published by the ACGIH [52]. 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 seem simple but has turned out to be rather 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 a 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). Second, 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 [53]. Due to this variation, increasing the number of measurements will lead to a larger number of samples showing exposure above a certain level.

Most occupational epidemiological studies report relative risks, sometimes in relation to a dose measure like cumulative dose. In environmental epidemiology, it is more common to calculate the number of excess cases per 10,000 or 100,000 persons per year or per lifetime. This method has recently been adopted for occupational exposure to diesel exhaust and lung cancer, demonstrating risks that were considerably larger than those accepted for the general environment [54].

A legislative TLV is a product considering not only health hazards but also economic and industrial aspects [52]. 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.

The role of screening for lung cancer in persons exposed to carcinogens is not clear. While it is recognized that screening with low-dose computer tomography (LCDT) reduces mortality among heavy smokers, it is currently not clear what should be recommended for persons exposed to asbestos. On the negative side is the number of false-positive findings and the extra radiation exposure. Currently, the role of LCDT in preventing asbestos-related deaths remains to be determined [55].

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. 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 the 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.

The process from the 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 are both rare in the general population and 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 [56]. New substances are continuously introduced, and effective methods for early identification of new cancer hazards are necessary. The following factors will all contribute:

- 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.

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Screening for Occupational Cancer

35

Douglas B. Trout and David N. Weissman

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 [3]. Medical screening can also detect breakdowns in protection of worker populations that might otherwise go unnoticed. Screening is among the tools available to complement exposure control for the 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 the 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 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 using biomarkers of exposure or response. Biomarkers of exposure measure workplace agents or metabolites in biological specimens. Biomonitoring using these

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tests may allow for assessment of exposure via all routes of exposure and absorption [12]. Biomarkers of response are objective measures of normal physiologic processes, pathologic processes, or pharmacologic responses to a therapeutic intervention [13]. The two types of 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]. 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]. For example, the efficacy of a multimodal screening strategy has been investigated for ovarian cancer mortality reduction [20] but remains investigational [21, 22].

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 epidemiologic and laboratory studies and have been among the most informative biomarkers of exposure to genotoxic agents [23–25]. Fibulin and high mobility group box protein 1 (HMGB1) are examples of biomarkers currently being investigated related to asbestos exposure and mesothelioma [26, 27]. 1-Hydroxypyrene and adducts of N-nitroso compounds are among biomarkers of genotoxicity being investigated for research and regulatory applications [18, 28, 29]. Although a number of biomarkers remain important research tools for investigations at the population level [18], poor specificity and positive predictive value (PPV) (among other issues) currently preclude their routine use as workplace screening tools for early detection of cancer in individuals. Ongoing research to augment available data concerning biomarkers of exposure with data related to biomarkers of effect will greatly enhance risk assessment efforts [23]. Research into biomarkers of genetic susceptibility is an emerging field; the evolving science is prompting important considerations related to ethical and social concerns [30–32].

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 8.2 million cancer deaths in 2012 [33]. Twelve million cancer deaths have been predicted for 2030, making primary and secondary prevention of great importance [6, 34]. In the United States, more than 1.6 million people were expected to be diagnosed with cancer in 2016; more than 590,000 people in the United States were expected to die from cancer in that year [35]. Estimates of the burden of occupational cancer have been published, recently summarized for Great Britain in 2012 [36], 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, 37].

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 [38]. If the health condition of concern is cancer, an additional factor important to realizing benefits from screening is that identification at an early stage may improve treatment outcomes. 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 [22, 39, 40]; 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 [41].

Experts have proposed different levels of evidence, including expert opinion [42], 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 [22]. 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 [41]. 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 beneficially modify the clinical course and ideally to cure the illness. In addition to being practical and feasible [43], 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 prevalence of 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, 44], and such concerns have contributed to current recommendations for caution in the use of genetic screening [30, 32]. 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) [45].

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 [46, 47]. 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 [22]. In the United States, elements of screening are included in many standards and recommendations related to agents known or suspected to cause cancer [48–50].

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 symptom questionnaires, medical histories, 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, 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 [30, 32].

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* [51] 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, 52].

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 [33] and an important cancer in working populations [1, 3]. The prognosis of lung cancer is markedly improved by diagnosis at an early stage, so there has been great interest in early detection [53]. The National Lung Screening Trial (NLST) showed that annual low-dose computed tomography (LDCT) screening reduced lung cancer mortality in high-risk individuals followed up for up to 5 years after their last annual screen by 20% relative to a control group receiving chest X-ray (CXR) [54]. The NLST is a national randomized controlled trial launched by the US National Cancer Institute in 2002 which used the following risk criteria for entry—age 55–74 years, 30 or more pack-years of cigarette smoking history, and former smokers had to have quit smoking within the previous 15 years [54]. In 2013 the American Cancer Society (ACS) revised its lung cancer screening guidelines,

recommending that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients with the same risk profile as used for the NLST [55]. The ACS emphasized that (a) a process of informed and shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with LDCT should occur before any decision is made to initiate lung cancer screening; (b) smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer; and (c) screening should not be viewed as an alternative to smoking cessation [55]. The US Preventive Services Task Force (USPSTF) has similar recommendations, differing primarily in the age at which to discontinue screening [22, 56].

In order to provide evidence-based guidance for LDCT screening for early detection of lung cancer in populations that have been exposed to lung carcinogens, it is important to document that such screening will achieve a favorable balance between benefits and harms. In order to assure that potential benefits of early detection exceed potential harms such as causing radiation-induced lung cancer or related to false positive studies, it is important to assure that the screened population is at sufficiently high risk for lung cancer. Studies are ongoing in the attempt to refine screening protocols to improve the efficiency and cost-effectiveness of population-based lung cancer screening programs [57].

Lung cancer risk related to smoking is an important consideration in lung cancer screening. Workers with combined exposures to tobacco smoking and an occupational carcinogen such as asbestos are at greater risk for lung cancer than nonsmokers with the same occupational exposure [58, 59]. Thus, in potential future guidance for LDCT screening, it will be important to identify and consider different thresholds for level of exposure to an occupational carcinogen that triggers screening among nonsmokers as compared to smokers. A recent report by the Finnish Institute of Occupational Health (FIOH) on LDCT screening for lung cancer in asbestos-exposed workers provides guidance on a potential risk threshold. The FIOH recommended LDCT screening of workers "… with any asbestos exposure and a smoking history equal to the entry criteria of the {NLST} study; and workers with asbestos exposure, with or without a smoking history, which alone or together would yield an estimated risk level of lung cancer equal to that in the entry criteria of the NLST study" [58]. The reason for this recommendation was that LDCT screening of the NLST population, which had a high risk for lung cancer, was documented to result in a favorable balance of benefits and harms. Quantitatively, the absolute risk for lung cancer in the NLST study population (and thus the threshold absolute risk for lung cancer proposed by FIOH as a trigger for LDCT screening for early detection of lung cancer) was 1.34% over 6 years [60]. If it is documented that a working population has this high level of risk (or greater) for lung cancer, it will be possible to justify an evidence-based requirement for LDCT screening.

Dissemination of LDCT technology that allows chest scans to be completed using less radiation is changing the risk–benefit calculation in a way that favors screening requirements. For example, it is now feasible to screen with ultralow-dose CT using amounts of radiation similar to a conventional CXR [61]. Widespread availability of this technology would reduce risks from radiation and improve the balance between benefits and risks.

There are several additional aspects of LDCT screening for lung cancer to consider as guidance is refined in the future. Access to appropriate counseling is a very important part of an LDCT screening program—just being identified as being at sufficiently high risk for lung cancer to be eligible for LDCT screening can lead to a need for counseling. Counseling may also be needed to help patients through the screening process as screening results often lead to follow-up tests (often repeat chest CT scans) to assess changes in nodules over a period of many months. It is important that those being screened be fully informed about the process, including the significance of screening findings and the approach to follow-up. Also, since follow-up is so frequently necessary and so critical to the success of an LDCT screening program, future guidance should take into account the provision of appropriate clinical care in follow-up to LDCT screening [62].

Bladder Cancer

It has been estimated that more than 429,800 new cases and 165,100 deaths from bladder cancer occurred worldwide in 2012 [33]. Although occupational exposures rank behind smoking as important risk factors for bladder cancer, a number of occupational agents are known bladder carcinogens [63–65]. Issues related to screening of higher-risk persons, such as those with occupational exposures associated with bladder cancer, have been an important topic for many years [66] and remain an area of active work [67, 68].

Clinical evaluation by cystoscopy, an invasive test, is commonly used as the diagnostic test for bladder cancer among the screened population. Individually, urinalysis for hematuria may have adequate sensitivity (particularly with repeated testing) but specificity is low. Urine cytology has been the primary test employed for bladder cancer screening among workers exposed to agents raising the risk for bladder cancer [63], but has been shown to have low sensitivity, even among those with high-grade cancers [69]. 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, 70], and research continues in developing cell- and urine-based bladder cancer tests [71, 72]. The unique clinical characteristics of transitional cell bladder cancer and inadequate test characteristics of current screening tests, along with inability to demonstrate reduced mortality among the screened groups, all contribute to the current determination that further research on bladder cancer markers is needed to inform screening programs for occupational bladder cancer [73–76]. Further research is underway to identify appropriate target populations (thereby increasing the PPV of subsequent screening tests) for bladder cancer screening [68, 73, 75]. 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 [71–73, 77–79]. While models have been developed incorporating known factors such as smoking and selected tests (such as urinalysis) to identify high-risk populations likely to benefit from screening, clinical judgment remains an important factor which considering screening of populations who may be at risk from occupational exposures [68]. Recent studies of bladder cancer screening programs among specific occupational groups are informative and can help guide future work [75, 80], but further research is needed before bladder cancer screening can be recommended in any systematic manner. The USPSTF concluded that additional research is needed to determine whether screening for bladder cancer improves clinical outcomes [81].

Skin Cancer

Skin cancers are the most common cancers [82] 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 [83, 84]. Environmental and occupational exposures are known to be associated with several types of skin cancer, with exposure to ultraviolet radiation an important occupational risk factor [83, 85]. Examination of the skin is an established prevention activity for clinicians [86, 87]. However, limited evidence that skin cancer screening in the general population, particularly with regard to benefits of skin cancer screening on melanoma mortality, has led to calls for future research on the effectiveness of targeted screening in those considered to be at higher risk for skin cancer [88–90]. New approaches to screening for skin cancer, such as tele-dermatology, are being studied [91, 92]. The substantial burden of morbidity and mortality associated with melanoma have particularly focused calls for improvements in melanoma prevention activities which can include screening programs [83, 84].

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 [93]. Investigations continue into the molecular mechanism of benzene toxicity and into potential biomarkers for early diagnosis of toxic effects [94, 95]. 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 [96]. 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. Recent studies have investigated blood biomarkers such as fibulin-3 and N-ERC/mesothelin [26, 97]. To date, the use of biomarkers as screening tools for persons at risk of mesothelioma remains investigational, and future work to improve their diagnostic performance may help increase their clinical usefulness for this indication [96].

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 [50]. 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 [98]. 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 for established cohorts [99, 100]. Issues concerning cancer endpoints related to potential occupational exposure during the WTC attack and subsequent work may become of increasing

importance in the future [101]. 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 [102, 103]. 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 [104, 105].

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Occupational Cancer in the Practice of Occupational Medicine

36

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Introduction

Occupational cancer is a malignant neoplasm caused by exposure to carcinogenic agents at the workplace. It represents an important challenge for the occupational medicine because of the impact on the individual patients, the burden on society, the difficulties in conducting risk assessment, and the implementation of effective preventive measures.

Estimates of the proportion of cancer deaths attributable to exposure occupational agents are in the order of 2–5% [1, 2]. At the level of individual patients, however, the identification of cases of cancer with occupational etiology is based on the recognition of exposure to the patient to one or more occupational carcinogens. Cancer is a multifactorial disease, and most cancers that may be caused by occupational agents also occur in the absence of such exposure. The identification of occupational carcinogens, as well as other causes of human cancer, is based on epidemiological studies: these studies have identified a large number of substances, groups of substances, and occupational circumstances with different levels of probability to cause cancer.

Regulation of Occupational Carcinogens: The Example of the European Commission

Evidence-based risk assessment is needed to develop effective strategies for the prevention of occupational cancer. Risk assessment is based on valid estimates of the dose–risk relationship and on realistic estimates of exposure levels in different occupational settings. One particular complicated issue is whether the linear, non-threshold (LNT) model is appropriate or a different relationship should be applied. In particular, the concept of threshold applies to different domains (Table 36.1) and is related to the possible mechanism of action of the carcinogen (genotoxic, epigenetic, receptor-based, etc.). As an example, the approach adopted by the European Commission (EC) can lead to defining admissible thresholds for carcinogens which are acting through epigenetic mechanisms or for which genotoxic effects have not been clearly defined. In particular, the Scientific Committee on Occupational Exposure Limits (SCOEL) of the EC defined four hazard categories for carcinogens (Table 36.2) and mutagens (Table 36.3) and classified these agents into four groups, based on their mechanism of action [4]:

Table 36.1 Different definitions of threshold [3]

Absolute threshold: The concentration of an agent not sufficient to produce an adverse effect, in analogy to the concept of general toxicology; a dose that does not produce any observable alteration. The carcinogen is present but cannot interact with the molecular or cellular target(s)
Real threshold: The concentration of an agent that, even if present at the target in defined quantities, at least in theory does not produce any damage due to the inability to induce, below a given concentration, the biochemical reactions required to manifest the adverse effect: the agent is present and can interact with the target, but fails to induce any negative effect
Practical threshold: The concentration of an agent that does not cause the toxic event due to a noncritical concentration at the target. An apparent threshold could be attributed to agent's own toxokinetics or to other factors that limit the adverse effect at the target (e.g., DNA repair, apoptosis, immunological surveillance)
Statistical threshold: The lowest concentration of an agent that manages to induce a statistically significant increase in the effect under study. It depends on the validity (protection from bias) and precision (sample size) of the available study/ies

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Table 36.2 Hazard categories for carcinogens [4]

Category	Criteria
Category 1	Manifested or suspected carcinogenic substances for humans. Classification is based on epidemiological data and/or data obtained with animal experiments
Category 1A	If the human carcinogenic effects are known on the basis of human studies
Category 1B	Carcinogenic effects for humans are presumed on the basis of animal studies The classification of a substance in categories 1A and 1B is based on weight-of-evidence approach and other considerations. Data may come from: – Studies conducted on humans showing a causal relationship between exposure to a substance and the onset of cancer (substances whose human carcinogenic effects are ascertained) – Animal experiments whose results allow to demonstrate carcinogenic effects for animals (substances presumed to be carcinogenic to humans) Moreover, from case to case, on the basis of a scientific evaluation, it may be decided to consider a substance as a presumed carcinogenic substance if there are studies showing the presence of limited carcinogenic effects for humans and animals
Category 2	Substances suspected of having carcinogenic effects on humans The classification of a substance in category 2 is based on the results of human and/or animal studies not sufficiently convincing to justify the classification of the substance in category 1A or 1B, based on weight-of-evidence approach and other considerations. These data may be taken from studies that demonstrate the presence of limited carcinogenic effects for humans or animals

Table 36.3 Hazard categories for germ cell mutagenic substances [4]

Category	Criteria
Category 1	Substances whose ability to cause hereditary mutations or to be considered capable of causing hereditary mutation in human germ cells is ascertained Substances whose ability to cause hereditary mutations in human germ cells is ascertained
Category 1A	The classification in category 1A is based on positive results of epidemiological studies on humans. Substances to be considered as capable of causing hereditary mutations in human germ cells
Category 1B	The classification in category 1B is based on: – Positive results of in vivo mutagenicity testing on mammalian germ cells, or – Positive results of in vivo mutagenicity tests on mammalian somatic cells, associated with data demonstrating that the substance can cause mutations in germ cells. These additional data may come from germ cell mutagenicity/genotoxicity tests or demonstrate the ability of the substance or its metabolites to interact with germ cell genetic material, or – Positive results of tests showing mutagenic effects in human germ cells, but not transmission of mutations to offspring: for example, an increase in the frequency of spermatozoa aneuploidy of the exposed subjects
Category 2	Substances of concern due to the fact that they could cause hereditary mutations in human germ cells: The classification in category 2 is based on positive results of experiments on mammals and/or in some cases of in vitro experiments, obtained by means of: – In vivo tests of mutagenicity on mammalian somatic cells – Other genotoxicity in vivo tests on somatic cells confirmed by the positive results of in vitro mutagenicity tests Note: The substances which give positive results in in vitro mutagenicity tests on mammals and which have an analogy in the chemical structure–activity relationship with substances that are proven to be germ cell mutagenicity shall be considered for classification as category 2 mutagenic substances

- Group A: no-threshold genotoxic carcinogens, for which an LNT model appears appropriate).
- Group B: genotoxic carcinogens, for which the hypothesis of a threshold is not adequately supported; in these cases, considering the scientific uncertainty, the LNT model can be used.
- Group C: genotoxic carcinogens, for which a practical limit can be identified.
- Group D: non-genotoxic and non-DNA-reactive carcinogens, for which no observed adverse effect level (NOAEL) can be identified.

SCOEL accepts occupational exposure limits (OELs) for carcinogens in group C and D; for example, cadmium is classified as a group C carcinogen with a TLV-TWA 8 h of 0.004 mg/m^3 [5]. SCOEL can perform a risk assessment for carcinogens and mutagens in group A and B when data are available; the SCOEL evaluation will clearly state the results of the carcinogenic risk assessment, and it will include results for data on all the concentrations considered and the calculated risk associated to these concentrations.

REACH Regulation and Safety Data Sheets

The Regulation of the European Parliament and Council of December n. 1907/2006 (Registration, Evaluation, Authorization of Chemicals, REACH), concerning the registration, evaluation, authorization, and restriction of chemical substances produced or imported by EU introduced

new elements for the management of occupational carcinogens [6].

The Safety Data Sheet (SDS) is the most complete tool for transferring and obtaining the hazard information of substances and mixtures as well as for the assessment and management of the chemical and carcinogenic risk at the workplace. SDSs are governed by Regulation no. 453/2010 (which updates Annex II of REACH) and are structured in 16 sections. The Extended Safety Data Sheet (eSDS) indicated by the European Chemicals Agency (ECHA) Guideline on Chemical Safety Assessment regards the substances produced/or imported in quantities of more than 10 tons/year and contains along with the SDS also the Chemical Safety Report (which outlines the relevant and relevant exposure scenarios for the use of substances to be included). The eSDS is needed for the REACH registration. The deadline for the registration was set by the REACH Regulation on May 30, 2018. The exposure scenarios, when available, offer useful information that should be included in the risk assessment. When specific uses or workplace scenarios are not included in the eSDS, the employer is required to communicate the use in those specific working scenarios to the importer or to ECHA in order to obtain the authorization to continue to use the agent.

Diagnosis of Occupational Cancer

Occupational tumors do not differ clinically or pathologically from those of other origins. The diagnosis of occupational cancer in individual cases is therefore purely etiological and is based on the biological plausibility, that is, on the evidence that the previous exposure to a carcinogen was sufficient to induce the neoplasm.

Tumors attributable to work environment can be broadly divided into two categories. The first group includes the neoplasms with a clearly identified cause linked to employment; classic examples in this group are pleural and peritoneal mesothelioma (asbestos), liver angiosarcoma (vinyl chloride monomer), and adenocarcinoma of paranasal sinuses (wood and leather dust). The association between exposure to the relevant carcinogen and these cancer is very strong (relative risks among the exposed in the excess of 20 or even 100), while nonoccupational risk factors are likely to account for a small proportion of tumors. Those cases with a confirmed occupational exposure to a known agent and a diagnosis based on strict criteria are recognized as occupational cancers. However, these tumors represent a small proportion of the global cancer burden in the population.

The second group is larger and comprises tumors for which both occupational and nonoccupational causes are known. Those are typically common cancers such as lung and bladder cancer. It is more difficult to establish the occupational origin of these cases, especially when the nonoccupational factors play a major etiologic role, as in the case of tobacco smoking for lung cancer. The etiologic diagnostic procedure for these cases should include:

- The anamnestic assessment of previous occupational exposures
- The definition of the carcinogenic potential of the agents identified during anamnesis
- The estimate of the dose based on the historical reconstruction of exposure circumstances, which can be carried out with historical company data
- Coherence with the need for a reasonable latency period, according to the type of tumor
- The presence of other occupational and nonoccupational risk factors

In some cases, the diagnosis of occupational cancer is important not only from the clinical perspective but also from a legal and compensation point of view. The best example of such situation is probably malignant mesothelioma. This tumor presents complex aspects, in particular with respect to the need for a diagnostic definition based on highly sensitive and specific criteria and to the interpretation of temporal aspects and levels of exposure to asbestos.

The onset of mesothelioma and the initial clinical course are mostly without symptoms. In the pleural localization, the symptoms are represented by increasing chest pain or dyspnea in case of conspicuous pleural effusion. With the evolution of the disease, there is complete involvement of the thoracic wall with signs of invasion and compression of lung parenchyma and adjacent organs. Recurrences of pleural effusion require repeated thoracentesis to control dyspnea. Other possible symptoms are cough, fever, asthenia, weight loss, and dysphagia. In the peritoneal localization, the onset is more nuanced, with ill-defined symptoms of heaviness and abdominal distension, and poor presence of pain. In more advanced stages, the subjective and objective picture becomes more imposing with the presence of ascites and occlusion syndrome due to the involvement of visceral organs.

The radiological picture in the pleural location is characterized by the lobulated profile, due to the tumor mass where it has reached appreciable size. Computed tomography (CT) is a useful aid, able to provide a better imaging definition compared to the standard radiogram, but it is not decisive in terms of differential diagnosis with pleural metastases from other neoplasms. In the peritoneal localization, the CT scan may show ascites of varying severity, diffuse peritoneal thickening and nodules affecting omentum and mesentery. For the evaluation of local extension of the tumor it is useful to perform nuclear magnetic resonance imaging (nMRI), with and without contrast. Valid information regarding the volume and the extent of tumor mass will be obtained before proceeding with a surgical resection. Although some

mesotheliomas can metastasize, the tumor is generally locally invasive, and death is usually caused by local tumor extension.

The main diagnostic question for pleural mesothelioma is the differentiation between mesothelioma and peripheral pulmonary adenocarcinoma, primary extrathoracic tumors with pleural metastases, or tumors of unknown primary. For the peritoneal localization, the main problem is represented by the differential diagnosis with ovarian adenocarcinoma, primary tumors of the gastrointestinal tract, and peritoneal inflammatory reactions. Liquid-based cytology can provide elements for the diagnosis, but it is not decisive, for the aptitude of the metastatic cells of tumors from other sites to assume mesothelioma features. Paracentesis- and thoracentesis-based fluid analysis has nowadays a greater diagnostic value, because of the development of immunohistochemistry, which allows, based on the presence of specific antigens, to direct the diagnosis toward mesothelioma or metastatic lesions. The basis for the diagnosis of malignant mesothelioma is, by widespread consensus, the histological examination of either a targeted biopsy obtained through pleuroscopy or video-assisted laparoscopy, or a specimen obtained after surgical resection via thoracotomy or laparotomy, or during autopsy [7]. In the case of pleural mesothelioma—the most frequent location—it must be remembered that the pleura hosts a limited number of primitive neoplasms and a significantly greater number of secondary tumors that may originate from different organs and systems, with a ratio of at least 50:1 between metastatic and primary lesions [8].

A clear diagnostic distinction must therefore be made between mesothelioma and benign pleural conditions, other primary pleural tumors, or metastatic localizations from primary tumors of different organs. Since secondary lesions largely outnumber mesotheliomas, there is a high probability that the clinical onset, which is undistinguishable between the two, is related to a metastasis rather than to a mesothelioma. In fact, with the exception of brain tumors, all primitive neoplasms can metastasize to the pleura. In the peritoneal area, the primary tumors most frequently responsible for dissemination are gastrointestinal tract cancers and, in women, reproductive tract cancers.

The diagnosis of mesothelioma is complex, since the neoplasm presents an unspecific symptomatological and clinical picture, common to that of other primitive or metastatic pleuro-pulmonary neoplasms. From a histological point of view, malignant mesothelioma can occur in three different histotypes [9]:

- Malignant epithelioid mesothelioma;
- Malignant sarcomatoid mesothelioma,
- Biphasic malignant mesothelioma, in which epithelioid and sarcomatoid aspects coexist.

The majority of mesothelioma cases display the epithelioid form. There are no imaging features that are sufficiently specific for the disease, and the histological examination of biopsies or surgical samples can't be decisive, if it is not complemented by appropriate immunohistochemical analyses. The histological pattern obtained with the traditional staining techniques, such as hematoxylin-eosin, does not discriminate between malignant mesothelioma and metastasis from other tumors. It is therefore essential to complete the histological examination with an appropriate immunohistochemical investigation. The most recent international guidelines assume that there is a direct relationship between the diagnostic yield of a panel of immunohistochemical markers and the number of the markers included in the panel and recommend using not less than four markers, of which two with a positive and two with a negative diagnostic value, with the indication to use further markers in ambiguous cases [10]. The selection of markers should be guided, according to the international guidelines, by their discriminating ability between the diseases compared. The panel of the most widely used markers to distinguish between pleural mesothelioma and lung adenocarcinoma comprises markers that are positive for mesothelioma, including calretinin, D2–40 (podoplanin), cytokeratin 5/6, and WT1, as well as markers that are positive in lung adenocarcinoma, including MOC-31, BG8, CEA, B72.3, Ber-EP4, and TTF1 (Table 36.4) [7, 10].

The fundamental investigation for the diagnosis of malignant mesothelioma is therefore the histological examination,

Table 36.4 Panel of immunohistochemical markers used in the differential diagnosis between MM of the epithelioid pleura and lung adenocarcinoma [7, 10]

Markers positive in mesothelioma
WT1: Very useful. Up to 95% of mesotheliomas are positive at nuclear level. Squamous carcinomas are negative
Calretinin: Partially useful. Theoretically all mesotheliomas are positive, particularly if aggressive and widespread, with nuclear and cytoplasmic expression
D2–40 (podoplanin): Not useful. Approximately 80–100% of mesotheliomas are positive, as well as 50% of the squamous carcinomas of the lung
Cytokeratin 5/6: Not useful. Positive in 75–100% of mesotheliomas and in 100% of pulmonary squamous carcinomas
Markers positive in lung adenocarcinoma
MOC-31: Very useful. 95–100% of lung adenocarcinomas are positive. 2–10% of mesotheliomas are focally positive
BG8: Very useful. 90–100% of the lung adenocarcinomas are positive. 3–7% of mesotheliomas express focal positivity
CEA: Very useful. 80–100% of lung adenocarcinomas are positive. Less than 5% of mesotheliomas are focally positive
B72.3: Very useful. 75–85% of lung adenocarcinomas are positive. Only rare mesotheliomas are positive
Ber-EP4: Very useful. 95–100% of lung adenocarcinomas are positive. Up to 20% of mesotheliomas show focal positivity
TTF1: Very useful. 75–85% of lung adenocarcinomas show unclear positivity (normally all lung adenocarcinomas not mucinous ones are positive); not expressed in mesotheliomas

which must be performed either on targeted biopsies, preferably collected from multiple sites during thoracoscopy or laparoscopy, or on a surgical specimen, in the case of thoracotomy or laparotomy, paired by adequate immunohistochemical stains. Moreover, in the formulation of the immunohistochemical report, it is appropriate to quantify the degree of positivity of the markers used; among those considered positive for mesothelioma [11], the degree of positivity of the immunohistochemical stain should be indicated using a four-category scale, corresponding to the quartiles of the proportion of reactive cells over total cells. The first quartile, indicating a proportion up to 25% of reactive cells, or the mere indication of positivity, may not provide sufficient information for the diagnostic decision.

Prevention of Occupational Cancer

Prevention of occupational cancer comprises primary interventions aimed at the elimination or containment of risk, as well as secondary and tertiary interventions aimed at the early identification of conditions that could outbreak in illnesses or, once the disease has been verified, to contain its effects with early interventions that limit its progression and improve prognosis. The role of the occupational physician is crucial in these interventions.

Laws and regulations established in many Countries have provisions for eliminating and replacing carcinogens and mutagens in the workplace, if technically possible, or, if elimination is not possible, either for processing the agents in closed systems, or, if this second hypothesis is also not technically feasible, for containing them in order to reduce the exposure of workers to the minimum possible level.

The crucial step in the preventive approach is the assessment of carcinogenic risk, and employers are required to assess exposure circumstances aiming at:

- Evaluating whether the concentration of carcinogens at the workplace is reduced to the minimum technically achievable level
- Identifying exposed workers, and, in some Countries, include them in specialized registers

The evaluation should take into account:

- The characteristics of the working processes
- The amount of carcinogens produced or used
- Their state of aggregation and the potential of release
- Their concentration in air or other media
- The duration and frequency of exposure
- The ability to enter the body through different absorption routes

In this framework the activities necessary to quantify and manage carcinogenic risk include, where technically possible, environmental and biological monitoring of exposure, health surveillance and, in well-defined situations, monitoring of biological effects. About this, it is important to note the difference between health surveillance and monitoring of biological effects. Health surveillance consists of one or multiple repeated health visits and aims at reaching a judgment on the suitability for the individual worker to perform the required tasks, taking into account preexisting or acquired conditions that make the individual particularly susceptible to the effects of tasks or exposures deemed acceptable for workers in general. The object of biological monitoring is the worker or group of workers exposed to a hazard and its purpose is the evaluation, through indicators of dose, effects, and susceptibility, of the actual or potential ability of the work environment to cause irreversible stochastic events in workers exposed with higher frequency compared to that expected in an unexposed population.

Measurement and assessment activities should not be confused with prevention measures and should be modulated according to the extent of exposure and risk. The classification of workers in predefined categories (e.g., unexposed, exposed to moderate concentrations, and exposed to high concentrations) is useful to identify the most appropriate actions (environmental monitoring, biological monitoring, health surveillance) at each level of exposure and sets the methodological basis to provide the occupational physician with a fundamental role in risk assessment, especially in the case of serious and complex events such as cancer.

Information and Training

Information and training are among the cornerstones of prevention strategies, and a critical aspect of their implementation lies in the difficult balance between the need to communicate precise notions and the risk of creating alarm situations, which may deteriorate the quality of life of the worker or to push them to a negative attitude toward the information.

Information and training on carcinogenic risk should be based on counseling, similar to what is done for other occupational risks [12, 13]. Counseling can be seen in general as a support intervention aimed at providing advice to workers exposed to a carcinogenic hazard, and guide them to adopt the best decisions to protect their health. Such suggestions include, for example, indications to change personal behavior that could contribute to the risk, to encourage preventive measures, or to promote participation in early diagnosis and treatment programs, in addition to those foreseen within the framework of health surveillance for the specific risk.

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The Use of Register Data in Occupational Cancer Control

37

Tom K. Grimsrud, Eero Pukkala, and Elisabete Weiderpass

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 the contrast between the lives in two occupational groups: housewives and nuns. Nuns avoided the risk of death associated with pregnancy and labor, leaving them with a greater chance of reaching old age and developing cancer.

Ramazzini's observation was confirmed 260 years later, when Dr. Fraumeni reported that nuns had a 40–60% higher probability of dying from breast cancer before the age of 75 compared to other US women [3]. In the non-Catholic Nordic societies, women with higher education—often seen to postpone their first childbirth—have an incidence of breast cancer 20–30% above the general female population [4]. The use of mortality data and cancer registry information was instrumental for evidencing these associations and for a precise quantification of risk.

Register-based studies of morbidity and mortality connected with occupations started being documented around 1840 in the UK when William Farr identified hazardous work from British death records [5]. In the last several decades, the practice in the Nordic countries includes the assignment of unique personal identity codes for all citizens in continuously updated population registers, and nationwide compulsory cancer registration. A combination of the two, along with census data on occupation, was utilized in 2009 for a long-term follow-up study on the incidence of cancers among 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.

We will restrict the following discussion to the 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, administrative, or fiscal purposes. Registers help to assure quality and assist in planning of health-care services. A registry is the place or work unit where such data are aggregated. Some kind of register data are almost indispensable for the enumeration of a study population, and they may provide the denominator for estimates of absolute risk or disease rate. Throughout the last decades, it has been considered essential in epidemiology to define the study group in order to secure a correct interpretation of the results and for assessment of the study's validity and generalizability [6].

For follow-up studies, registers on date of death are essential in defining end of observation and thereby time at risk. Together with the increasing migration, it has also become more important to have access to information on dates of immigration and emigration to know exactly when an individual is under follow-up or not in a specific country.

In addition to cohort definition, modern etiologic epidemiological research rests the precise definition of the study's outcome (disease or cause-specific death), and the exposure(s) of interest, which both may be acquired in several ways. For outcome measures, data from a register are often preferred, as opposed to self-reported information or

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individually collected data from the health-care system. Registers provide independent and unbiased data and may offer appropriate age- and gender-specific background rates for comparisons with different population groups. When quality is satisfactory in terms of completeness, reliability, and linkage possibilities, registers may add relevant and valuable data on trends and absolute risks for almost any study group or reference group.

The detrimental effects of strong carcinogens have often been discovered as a clustering of cancers. In 1975, at a marking the 200th anniversary of Percival Pott's classic report of scrotal skin cancer among chimney sweeps, Sir Richard Doll elaborated on clusters and development of knowledge [7]. In fact, clusters observed in *occupational* groups have been particularly useful in providing leads for the identification of human carcinogens. Clusters may occur in time or place, or among workers of the same kind. In a clinical setting, medical personnel may also identify strikingly similar exposures in a uniform group of patients.

Strong risk factors are more likely to be recognized by cluster observations than weak or moderate risk factors. For rare diseases, such as most cancer forms, the use of medical records from a register, hospital, or physicians' files may be indispensable. The benefit of a cross-sectional study, or repeated cross-sectional surveys, may be limited, especially if they rely on recollection and reporting of exposures or outcomes by study participants. Thus, data from registries have become increasingly 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 development or death may very well approach, or even surpass, the quality of a good register-based study. Examples may be found in studies from China and from a number of large consortia [8, 9]. Diagnostic data from hospital records may contain important details on the disease that remain unreported in many registers.

In the following, a register designates a set of data on disease, death, or demographic characteristics collected with the ambition to cover completely the population of a defined region in an updated and continuous way. For an optimal use, register data should include personal identifiers which allow linkage with information from other sources.

Occupational Cancer Control

The identification of occupational hazards 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 started to be implemented 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 the event of workers dying in occupational accidents or by occupationally related diseases, and the family losing its breadwinner. The identification of the causes of occupationally related cancers has been important regarding the employers liability. Primary prevention of occupational cancers must rely on knowledge about cancer etiology and occupational exposures.

Thus, 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. 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 observed in South Wales (UK) in the 1920s [10]. A decade later, observed and expected cancer mortality rates were evaluated in an unpublished report to the company, based on national mortality statistics (Bradford Hill, 1939—cited in Ref. [11]). By 1949, lung cancer and sinonasal cancer were considered industrial diseases giving rise to economical compensation in nickel workers [12]. Another decade passed before the first epidemiologic nickel study was published in a medical journal, in the form of a proportional cancer mortality study, based on information from death records [12].

The emergence of modern epidemiology after World War II [6] has led to great advances in the characterization of already recognized occupational cancer risks, as well as better opportunities for the identification of new ones. Access to large sets of data from disease registers and additional details on exposure and background conditions from other sources have been indispensable for much of this progress. Such information has been used to determine acceptable occupational exposure limits, and it has served as an incentive to reduce occupational exposures in workplaces.

An example of the benefits from cancer registration, along with modern epidemiologic methods, can be found in Norwegian studies on cancer caused by occupational exposure, starting with nickel compounds. Before the first published study in 1973 [13], Norwegian studies of occupational cancer were largely case reports [14, 15], published with no data on background or expected rates. When the suspicion of a nickel-related excess risk reappeared in the late 1960s, the Cancer Registry of Norway was able to offer reference rates, technical solutions, and statistical expertise for the evaluation of cancer incidence in a cohort of refinery workers, providing convincing evidence of elevated risks [13]. A similar study design was used throughout the subsequent decades to

cover a large part of trades and industries in Norway [16] and other Nordic countries.

The term register-based epidemiology has been used by Nordic epidemiologists to mark the difference from researcher-collected data [17]. We will discuss the use of registers and its relation to occupational cancer control in the form of surveillance, etiologic research, prevention, and economical compensation.

Occupational Hazards and Exposures

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 established carcinogens [18]. In Finland, a national register on occupational exposure to carcinogens was established in 1979 [19], while Sweden, Denmark, and Norway instruct all employers to keep such registers within their undertaking [20–22]. 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 cancer is likely largely underreported worldwide [23–29]. A number of reasons may exist for this incompleteness, 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 related. A better recording of relevant exposures could potentially improve the basis for epidemiologic studies and for the evaluation of compensation claims. The underreporting of occupational cancers illustrates the universal challenge associated with obtaining completeness and high-quality record keeping in a registry. A good register needs clear criteria for reporting and precise definitions for classification. It will also profit from networking between institutions and from alertness and dedication among the employees.

The acquisition of reliable data on occupational exposures is a great challenge in the evaluation of occupational cancer, both in research and in economical compensation claims. 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 [30]. Still, exposure assessment is often found to be challenging in occupational cancer studies.

In the absence of exposure registers, 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 advances in the understanding of occupational cancer disease. For population- or hospital-based studies, the assessment of occupational risk often relies on work history obtained by interviews or by questionnaires. Although job-specific exposure estimates of sufficient quality 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 exposure. Duration of work is often used as a proxy metric for degree of exposure, relying on the assumption that exposure levels are fairly constant. Duration of work may be one of the parameters that can be estimated with least misclassification.

Disease Outcome

Cancer registration, in terms of continuous notification of new diagnoses of cancer cases (incident cancers) at state or national level, has taken place in a number of countries since the 1940s (Denmark) or 1950s. The main aims of cancer registration have been to improve the etiologic understanding of the occurrence of cancer and to provide long-term surveillance of cancer distribution and time trends. Such information is useful to facilitate organization of cancer care and prevention [31]. Registration of deaths has a substantially longer history, with provision of data for demographic statistics, disease surveillance, and research.

For highly lethal cancers such as lung or pancreas cancers, the number of incident cases and deaths within a given time interval—for example 1 year—is approximately the same. In such cases cause-of-death registers may offer almost equally good opportunities for surveillance and research as do cancer registers. However, this is only possible in countries with high-quality cause of death registration. There are some known problems in the accuracy of the causes of death, such as erroneously coding the site of a metastasis (such as liver and brain) as the topography of the primary cancer. Incidence registers are considered superior for the study of less lethal cancers and for studies that address details in cancer histology, diagnoses, and therapy. Alternatively, hospital-based cancer registers or discharge lists can serve as the source of outcome data in a study, although some uncertainty may then remain as to the representativeness and the outline of the underlying study population.

Some cancer registries do not include as incident cases those that are notified only from death certificates. 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 [32, 33]. This phenomenon

calls for attentiveness when trends or cancer incidence rates are compared within nations or across borders [34].

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 data may contribute high-quality information, both for case identification and—if no better options are available—for selection of reference or comparison groups. For case–control studies, controls should preferably be sampled from the study population from which the cases were identified. Combined hospital- and population-based studies in Canada have contributed importantly to the knowledge of cancer risk and numerous occupational exposures [35, 36]. 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 [37].

Strengths and Limitations of Register-Based Studies

Occupational cancer studies are mostly observational in design. Intervention studies to access the efficacy or effectiveness of cancer prevention measures or cancer treatment modalities may, under certain circumstances, be based on 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 false explanations. Register-based research has several strengths that may improve the control of these biases.

Studies based on register linkage may provide a complete enumeration of citizens, workers, or cancer cases. Register data may help to avoid potential problems with low response rate, self-selection, disease outcome, or exposure-related factors, which can be influenced for example by socioeconomic status. Studies performed on data from registers with good coverage are very valuable in terms of generalizability.

Bias induced by an economical support from an industry, company, or other organization with direct or indirect vested interests may be difficult to recognize and should always be kept in mind when reading the literature on occupational cancer. Industrial cooperation can still be useful or even *necessary* in occupational cancer studies, for access to cohorts and to exposure data, while potential pitfalls may exist. Paper-based historical lists of employees or pay-rolls can easily be a more reliable source of data than electronic files that can be kept continuously "updated" by removing workers who die or terminate their employment.

The risk of introducing errors or being subject to fraud may increase if requirements for the protection of personal data include removal of all identifiers from the data set. Quality control of de-identified data can vary from challenging to impossible. Data from complete and independent registers may help to assess validity in such situations.

When cohort enumeration, exposure information, and disease or mortality data are recorded in this order—or, even better—if they come from independent historical sources such as registers, many problems associated with retrospective collection of information can be avoided. An information bias, such as a recall bias or attribution, can potentially be strong and difficult to measure.

Issues involving occupational cancer often attract substantial attention from the media, claims of economical compensation, or pressure from interest groups. A situation may arise where it is difficult to obtain unbiased information by interviews or questionnaires. Important issues may become *out of reach* for common retrospective research methods. A scientific clarification may then ultimately rely on the availability of historically registered data for the outline of a study group, for exposure information, and for the disease outcome.

Challenges in Occupational Hygiene and Epidemiology

Through the last 50 years, industrial hygiene has reduced the risk of cancer associated with many industries and trades. New or remaining unrecognized hazards—if we do not count factors such as lack of physical activity at work, obesity, postponed age at first birth due to long education, etc.—are not expected to compare in severity with those revealed in studies from the twentieth century. The identification of low-risk exposures requires more detailed data and larger studies to obtain necessary statistical power. Data from registers may then provide a rapid, economic, and secure access to complete data sets with more cases than those seen in most epidemiologic studies.

Scientific benefit of the use of registers in occupational cancer research 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 such as smoking history may be inferior compared to data collected for a specific study. It may still be possible to improve register-based studies at these points if there are available data on exposure measurements, good procedures for exposure assessment, or representative biological samples for the analysis of biomarkers.

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, on the other hand, can have lifestyle characteristics contrasting those of the exposed group. Differences in smoking habits, alcohol consumption, diet, or leisure time activities may then confound the risks otherwise ascribed to occupations. For low-grade occupa-

tional risks, the lack of confounder control may represent an annoying uncertainty. Rarely, data on lifestyle characteristics are available at an aggregated level [38], and even methods to obtain confounder control in the absence of actual behavioral data have been suggested [39].

Nordic Experience and Coordination

In the Nordic countries there are numerous population-based registers which have been used for large occupational cancer studies, within a total population of 25 million people. The rather uniform structure in the national health-care systems of these countries 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, the national population registers are continuously updated, and unique personal identity codes have been used for five decades.

Personal Identity Codes and Linkage

Unique personal identity codes were introduced in the Nordic countries between 1947 and 1968, that is, somewhat later than the start of cancer registration. The codes 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, health care, and in passports; and they are mostly perceived as beneficial by the public. For research, it is highly useful that unique codes facilitate computerized linkage to governmental statistical data and data on cancer incidence and mortality. The codes also allow for linkage between rosters of workers and disease registers, as well as a number of other registers with data that may influence exposure and cancer risk.

The transition from manual linkage—based on name, residence, and date and place of birth—to electronic linkage by personal identity codes constituted a great improvement in study quality [39, 40].

Another advantage of the personal identity codes is the improved possibility of preserving confidentiality. Codes are less recognizable, and they need not follow the data provided for the researcher, for laboratories, or data handlers, since linkage can be performed in a completely mechanical, safe, and computerized way, and the official codes easily may be substituted by a new code or artificial number. The cost is the negative effect this may have on the opportunity for quality control, as commented above.

Approved legislation on protection of personal data has made it more difficult to conduct observational epidemiologic studies even in the Nordic countries. Admittedly, though, there have been improvements in how information is provided to the public, and ethical deliberations are now included in the planning of every new study. In the long run, having a system designed to strengthen the mutual trust between data providers and researchers is likely better than being secured by a regulation only, which easily can be changed.

Registers Providing Background Data

The Nordic countries' 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. Each statistical office may also require that data are analyzed on their servers, allowing no transfer of data to researchers. Data on residence and vital status are continuously updated.

Cause-of-death registries have long traditions for research on occupational cancer and provision of data to studies of other potentially fatal chronic disease. However, death records are usually not subject to the same quality control as those of a cancer registry. The Nordic cancer registries are of high quality, offering good population coverage and completeness of data [33, 41–45]. Despite some historical differences in registration practices, the cancer incidence data between the Nordic countries are largely comparable, and access has been facilitated through a free and interactive website in the NORDCAN database [32].

Repeated Studies on Occupational Cancer

For some forms of cancer, the time between exposure and diagnosis may span several decades. The Nordic model of use of registers in occupational cancer research 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, smaller number of chance findings, and a better understanding of the causal associations. Several study series 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 information of the working population. Nordic registry 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 follow-up for incident cancers using cancer registries [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 were developed [69], with contribution by occupational hygienist experts from each country. This effort was inspired by the Finnish occupational exposure matrix [70–72]. For some of the countries, the Nordic exposure matrix and the linked census and cancer data allow for more detailed studies on occupational exposures and cancer incidence.

The large and homogenous NOCCA database proved its usefulness and ability for rapid mobilization following a 2013 study of Japanese printing workers exposed to organic solvents, in whom a cluster of cholangiocarcinoma was observed [73]. Within the publication year of the Japanese study, a Nordic NOCCA-based study was established, which revealed a similar occupational hazard in Nordic printers [74]. In June 2014, the International Agency for Research on Cancer (IARC, WHO) re-evaluated carcinogenicity for the solvents in question, and upgraded 1,2-dichloropropane from Group 3 (not classifiable as to its carcinogenicity to humans) to Group 1 (carcinogenic to humans), and reclassified dichloromethane from Group 2B (possibly carcinogenic) to Group 2A (probably carcinogenic) [75].

The study of genes, intracellular regulation, and carcinogenic processes has improved our understanding of pathways and causes of cancer. Still, an epidemiologic study design is essential for assessing the relevance in humans of biomolecular observations. For most occupational cancers, there is a long latency time between occupational exposures to carcinogens and the development of cancers. Therefore, studies on animal models, identification of biomarkers of exposure and effect, and mechanistic studies will become increasingly important for an early evaluation of new chemicals and suspected carcinogens.

An important challenge is to combine traditional studies with these new sources of information and to find the best use of biobanks and pathology specimens. For conducting such studies, researchers need to convince the public that the benefit of better knowledge likely outweigh the potential threat against protection of personal data.

Conclusion

Independent registers of cancer incidence, cause-specific mortality, employment data (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. A growing demand of better knowledge and high therapeutic costs may motivate improvements for cancer control and epidemiologic research. The best of existing data sources must be incorporated in studies with additional exposure measurements and biomolecular analyses.

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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 insulation works	
5. Electrical installation works	
6. Other construction works in new buildings	
7. Other renovation works	

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 works 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 works 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	
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:	

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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				

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