Cancer Epidemiology

IV.3

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3.1 Introduction

Cancer encompasses a family of several hundreds of diseases which are distinguished in humans by site, morphology, clinical behaviour and response to therapy. Whether considered from a biological, a clinical or a public health point of view, it is the malignant and invasive nature of many of these diseases that is of dominant importance.

Although the words 'cancer' and 'carcinoma' refer to malignant tumours arising from epithelial tissues, they are often used to include all malignant neoplasms. These are characterized by progressive and variable growth of tissue with structural and functional changes with respect to the normal tissue. In many cases, the alterations can be so important that it becomes difficult to identify the tissue of origin.

Knowledge about the causes of and the possible preventive strategies for malignant neoplasms has greatly advanced during the last century. This was largely due to the findings from cancer epidemiology. In parallel to the identification of the causes of cancer, primary preventive strategies have been developed. Secondary preventive approaches have also been proposed and, in some cases, they have been shown to be effective. A careful consideration of the achievements of cancer research, however, suggests that the advancements in knowledge about the causes of cancer have not been followed by an equally important reduction in the burden of cancer. Part of this paradox is explained by the long latency occurring between exposure to carcinogens and development of the clinical disease. Changes in exposure to risk factors are therefore not followed immediately by changes in disease occurrence. The main reason for the gap between knowledge and public health action, however, rests with the cultural, societal and economic aspects of exposure to most carcinogens.

3.2 Scope and Approaches in Cancer Epidemiology

Cancer epidemiology investigates the distribution and determinants of the incidence, mortality and prevalence of cancer in human populations (Adami and Trichopoulos 2002). Many approaches have been used in cancer epidemiology which can be classified according to different dimensions, as shown in Table 3.1. Although most studies in cancer epidemiology are observational in nature, intervention (experimental) studies are conducted to evaluate the efficacy of prevention strategies, such as screening programmes and chemoprevention trials (clinical trials are usually considered to be outside the scope of cancer epidemiology). Observational studies are traditionally classified in descriptive, analytical (or etiological) and ecological studies (for a detailed description of the different types of epidemiological studies see Chaps. I.3–I.8 of this handbook).

Table 3.1. Approaches used in cancer epidemiology

Dimension	Approaches	Examples
Nature of observation	Experimental	Chemoprevention trial
	Observational	Cohort study
Purpose of investigation	Description	Time-trend analysis
	Etiological research	Case-control study
	Evaluation	Community trial of screening modalities
Unit of observation	Grouped data	Ecological study of environmental exposure
	Individual data	Case-control study with questionnaire data
Sampling strategy*	Census-based	Cohort study
	Sample-based	Case-control study
Source of information on exposure	Routine collection	Record-linkage study
	Ad-hoc collection	Questionnaire-based study

* In studies based on individual data

Descriptive cancer epidemiology is a particularly flourishing branch of the discipline, thanks to the availability of high-quality population-based cancer registries in many areas of the world and to the possibility to use mortality data to estimate the incidence of highly lethal cancers. As an illustration, Fig. 3.1 shows the estimated incidence of cancer among women in all countries of the world: these estimates are derived mainly from data from cancer registries and mortality statistics. Although subject to various sources of error, such estimates are more precise than those available for any other chronic disease. An additional useful distinction of etiological studies concerns the nature of the information on exposure: while some studies use data routinely collected for other purposes, such as census records and hospital files, in other circumstances ad-hoc information on exposure is collected following a variety of approaches, including record abstraction, questionnaires, pedigree reconstruction, environmental monitoring and measurement of biological markers.

Given the importance of cancer in developed countries and the efforts to prevent it, cancer epidemiology has acquired a recognized status in medicine and has developed into a separate profession. For this reason, and thanks to the availability of high-quality data on the outcomes of interest, it has played an important role in the development of modern epidemiology. The criteria for causal inference in observational research (with the corollary of methodological studies on bias, confounding and statistical power) have been largely shaped following the discovery of the important role of tobacco smoking as a human carcinogen (Doll 1998); modern statistical approaches such as multivariable logistic and Poisson regressions have originally been proposed for use in cancer studies (Breslow and

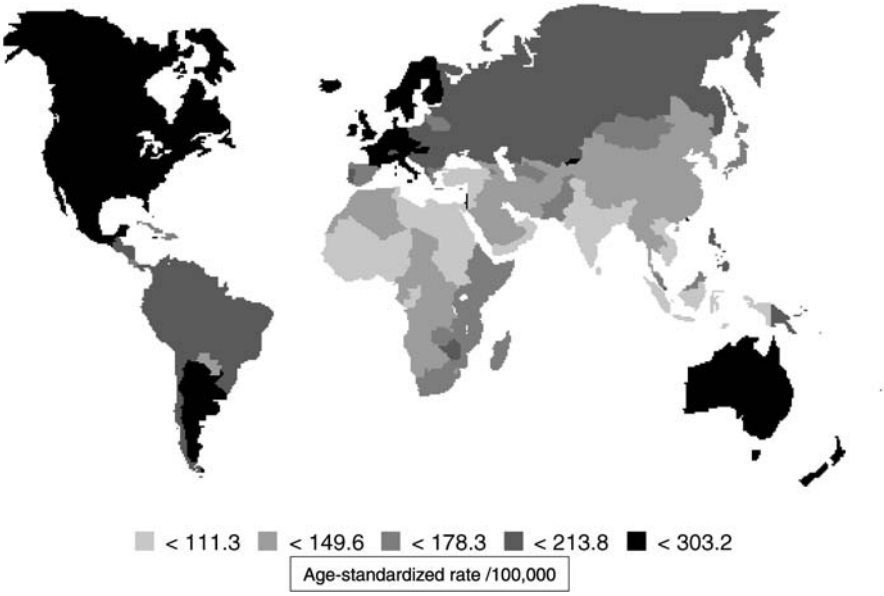

Figure 3.1. Estimated incidence rate of cancer in women, by country (year 2000). From (Ferlay et al. 2001)

Day 1980, 1987; see also Chap. II.3 of this handbook); molecular epidemiology has developed as a discipline bridging different areas of cancer research (Perera 2000; see also Chap. III.6 of this handbook); and methodological advances in genetic epidemiology have stemmed from familial studies of cancer (Thomas 2000; see also Chap. III.7 of this handbook).

3.3 The Global Burden of Cancer

The number of new cases of cancer that occurred worldwide in 2000 has been estimated at about 10 million (Table 3.2) (Ferlay et al. 2001), including 5.3 million in men and 4.7 million in women. About 4.7 million cases occurred in developed countries (North America, Japan, Europe including Russia, Australia and New Zealand) and 5.3 million in developing countries. Among men, lung, stomach, colorectal, prostate and liver cancers are the most common malignant neoplasms (Fig. 3.2), while breast, cervical, colorectal, lung and ovarian cancers are the most common neoplasms among women (Fig. 3.3).

Such global statistics are of limited interest, given the complexity of the factors affecting the risk of each neoplasm and the reader is referred to specialized publications for a more detailed review (Ferlay et al. 2001; Parkin et al. 1997). Some general trends can however be identified:

Table 3.2. Estimated number of new cases of cancer (incidence) and of cancer deaths (mortality) in 2000, by gender and geographical area (Ferlay et al. 2001)

	Men	Women	Total
Incidence:			
Developed countries	2,503,700	2,176,000	4,679,700
Developing countries	2,814,100	2,561,700	5,375,800
Total	5,317,800	4,737,700	10,055,500
Mortality:			
Developed countries	1,488,200	1,157,600	2,645,800
Developing countries	2,034,200	1,528,700	3,562,900
Total	3,522,400	2,686,300	6,208,700

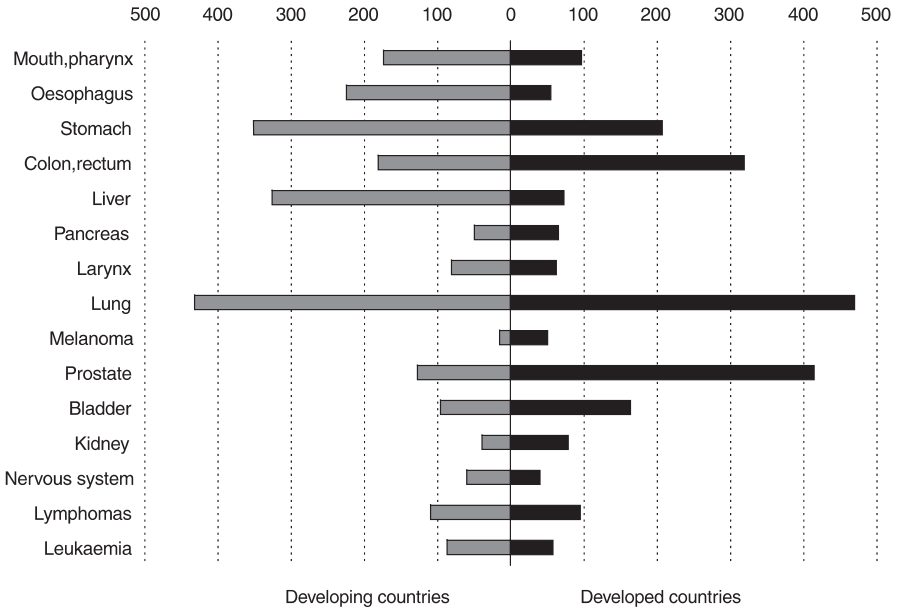

Figure 3.2. Estimated number of new cancer cases (×1000) in men, (year 2000). From Ferlay et al. (2001)

- A decrease in stomach cancer incidence in most countries;
- a plateau or decrease in the incidence of lung cancer and, to some extent, other tobacco-related cancers among men from developed countries, and a corresponding increase among men in developing countries and women in developed countries;
- a very modest improvement in survival, in particular for highly lethal cancers.

The number of deaths from cancer was estimated at about 6.2 million in 2000 (Table 3.2) (Ferlay et al. 2001). No global estimates of survival from cancer are

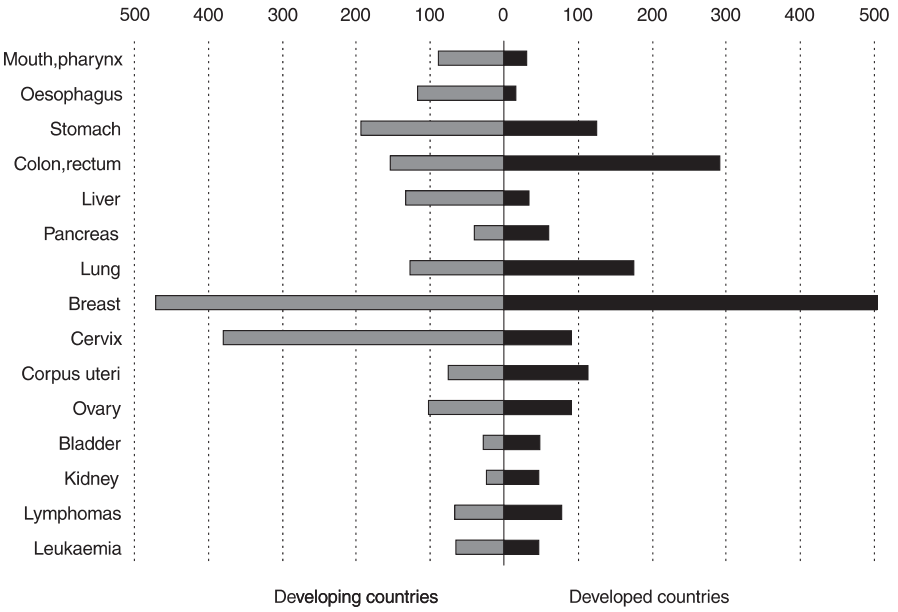

Figure 3.3. Estimated number of new cancer cases (×1000) in women, (year 2000). From Ferlay et al. (2001)

available: data from selected registries suggest wide disparities between developed and developing countries for neoplasms with effective but expensive treatment, such as leukaemia, while the gap is narrow for neoplasms without an effective therapy, such as lung cancer (Berrino et al. 1999; Kosary et al. 1995; Sankaranarayanan et al. 1998) (Fig. 3.4). The overall five-year survival of cases diagnosed during 1985–1989 in European Union countries was 41% (Berrino et al. 1999).

3.4 Causes and Prevention of Human Cancer

In the following sections, the current knowledge about the risk factors and the strategies for primary and secondary prevention of cancer is summarized. For more details, the reader is referred to systematic reviews (Adami et al. 2002; Boffetta et al. 2002; Peto 2001).

Table 3.3 shows the results of reviews of the contribution of known causes of cancer in developed countries (Doll and Peto 1981; HCCP 1996; Peto 2001). Such estimates are subject to assumptions and uncertainties and should be interpreted as approximations. However, it is worth noting that the estimate of the relative importance of the major causes of cancer is fairly consistent. No systematic estimate has been proposed for developing countries, where the contribution of infectious agents is likely to be very important.

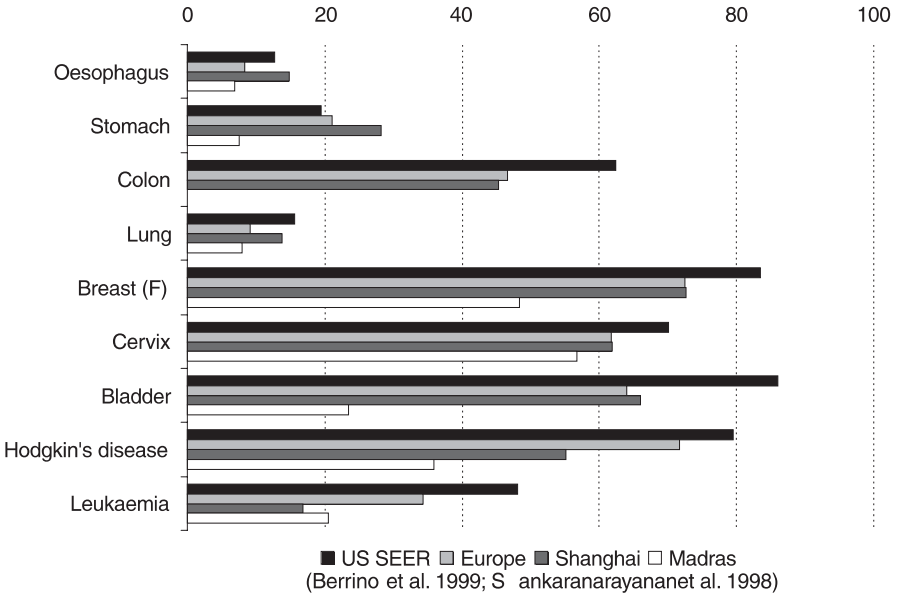

Figure 3.4. Five-year relative survival from cancer in selected populations. From Berrino et al. (1999) and Sankaranarayanan et al. (1998)

Table 3.3. Quantifications of contribution of major causes to human cancer burden (attributable fractions in percent)

Cause	Peto 2001*		HCCP 1996	Doll and Peto 1981
	Smokers	Non-smokers		
Tobacco	60	0	30	30
Dietary factors	4–12?	10–30?	30	35
Obesity	4	10	30	N/A**
Sedentary life	0.4	1	5	N/A
Biological agents	2	5	5	10?
Occupation	0.4	1	5	4
Alcohol	0.4	1	3	3
Environmental factors	0.4	1	2	2
UV/ionizing radiation	0.4	1	2	3***
Reproductive factors	N/A	N/A	3	7
Medical factors	N/A	N/A	1	1
Food additives	N/A	N/A	1	< 1
Perinatal factors	N/A	N/A	5	N/A
Socio-economic factors	N/A	N/A	3	N/A
Genetic factors	N/A	N/A	5	N/A

* Avoidable causes
** Not available *** Geophysical factors

3.4.1 Tobacco Smoking

Tobacco smoking is the main single cause of human cancer worldwide. It is a cause of cancers of the oral cavity, pharynx, oesophagus, stomach, liver, pancreas, nasal cavity, larynx, lung, cervix, kidney and bladder, and of myeloid leukaemia (IARC 2004). It is commonly considered that tobacco smoking causes up to one third of human cancers (Table 3.3); a detailed review of the number of cancers attributable to tobacco smoking in 1985, which was based on very strict criteria for attribution of cases, resulted in the estimate of at least 15% (Parkin et al. 1994), corresponding to about 1.5 million new cases per year. The estimates were 25% in men and 4% in women and, in both genders, they were 16% in developed countries and 10% in developing countries. The low attributable risk in women (and, to a lesser extent, in developing countries) is due to the low consumption of tobacco in past decades: the recent upward trend that has taken place among women and in many developing countries will obviously result in a much greater number of cancers in the future.

The risk of tobacco-related cancers among smokers relative to non-smokers depends on the different characteristics of the habit; in Table 3.4 are reported

Table 3.4. Relative risk of ever smoking and proportion of cancer attributable to tobacco smoking

Cancer	Relative risk for ever smoking*	Attributable risk**	
		Men	Women
Oral cavity, pharynx	2–3	41%	11%
Oesophagus	2-5 (squamous cell carcinoma) < 2 (adenocarcinoma)	45%	11%
Stomach	1.5	13%***	7%***
Liver	2	N/A****	N/A
Pancreas	2–4	27%	11%
Nasal cavity and sinuses	2 (squamous cell carcinoma)	N/A	N/A
Larynx	10–15	67%	28%
Lung	10–15 (small cell and squamous cell carcinoma) 3–5 (adenocarcinoma)	85%	46%
Cervix	2	N/A	N/A
Kidney	2 (renal cell carcinoma) 3 (cancer of the renal pelvis)	38%	4%
Bladder	3	37%	14%
Leukaemia	1.2 (myeloid)	N/A	N/A

* Derived from IARC (2004) and Kuper et al. (2002)
** Derived from Parkin et al. (1994) unless stated otherwise
*** Derived from Tredaniel et al. (1997) **** Not available

relative risks found for ever-smokers in Europe and North America. In different populations, risk estimates have been produced for increasing levels of duration and amount of tobacco smoking: in general, a separate effect has been shown for both dimensions of smoking, with a stronger role of the former (IARC 2004). The effect of duration of smoking on the risk of smoking-related cancers, and of lung cancer in particular, is so strong that it is difficult to determine whether there is an independent contribution of other factors, such as age and age at starting smoking. Smoking of filtered cigarettes and cigarettes with reduced tar content results in a lower risk of lung and other cancers than smoking of cigarettes without filter and with high tar content, although by no means the former products should be seen as 'risk-free' (IARC 2004). Smoking of black tobacco cigarettes entails a higher risk of most smoking-related cancers than smoking of blond tobacco cigarettes (IARC 2004). A carcinogenic effect of cigar and pipe smoking has been demonstrated for cancers of the oral cavity, pharynx, larynx, lung and bladder (IARC 2004). Similarly, smoking of local tobacco products, such as papirossi in Russia, bidis in India and yaa muan in Thailand, entails an increased risk of cancer of the lung and other organs.

A benefit of quitting tobacco smoking in adulthood has been shown for most cancers causally associated with the habit (Table 3.5). This result emphasizes the need to devise anti-smoking strategies that address avoidance of the habit among the young as well as reduction of smoking and quitting among adults. There is strong evidence of a protective effect of quitting smoking at any age (Peto et al. 2000). The decline in tobacco consumption that has taken place during the last 20 years among men in North America and several European countries, and which has resulted in decreased incidence of and mortality from lung cancer, has resulted primarily from the increase in the number of smokers quitting at middle age.

With the identification of tobacco as a carcinogen for the lung, the causal nature of an association between a chronic disease and a risk factor was for the first time established beyond doubt, representing an important contribution to the development of epidemiology. The association was replicated in various populations, using different approaches, namely cohort and case-control studies. This discovery was facilitated by several aspects of tobacco smoking: firstly, it is a potent carcinogen, containing – at high concentrations – several agents

Table 3.5. Effect of quitting tobacco smoking on risk of selected cancers (Kuper et al. 2002)

Cancer	Effect of quitting
Oral cavity, pharynx	Long-term quitters have risk close to that of never-smokers
Oesophagus	Risk decreases, but significant increase persists
Pancreas	Up to 50% risk reduction in long-term quitters
Larynx	Long-term quitters have risk close to that of never-smokers
Lung	Sharp decline in risk, some excess risk persists
Kidney	Up to 25% risk reduction in long-term quitters
Bladder	Up to 60% risk reduction in long-term quitters

acting on different stages of the carcinogenic process; secondly, a sizable group in most populations is composed of heavy smokers, exposing themselves to high doses; and thirdly, exposure is easier to quantify compared to most other agents, since smokers can report with a good degree of precision their present and past consumption.

3.4.2 Use of Smokeless Tobacco Products

There is conclusive epidemiological evidence that use of smokeless tobacco products is associated with an increased risk of head and neck cancer (IARC 1985). Chewing of tobacco-containing products is particularly prevalent in southern Asia, where it represents a major cause of cancer of the oral cavity, pharynx, oesophagus and larynx, either alone or in combination with smoking.

3.4.3 Dietary Factors

Despite considerable research efforts in cancer epidemiology, the exact role of dietary factors in causing human cancer remains largely obscure. The World Cancer Research Fund (WCRF 1997) has published a systematic review of the evidence of an association between intake of foods, food groups and nutrients and different cancers. Their evaluations are summarized in Table 3.6 and, with one exception, are valid today. The evidence of a protective role of vegetable and, to a lesser degree, fruit intake has been evaluated as convincing for a number of important human tumours. However, a formal IARC evaluation which has taken place in March 2003 concluded that there is no definite evidence for a cancer protective effect of high intake of fruits and vegetables, although such an effect is probable for cancer of the esophagus, stomach, colon/rectum and lung (IARC 2003). For the remaining dietary factors, few evaluations of convincing or probable associations have been made by WCRF, and in most cases the conclusion was a possible increase or decrease in risk. This is namely the case for high intake of total and saturated fat, and of micronutrients such as carotenoids, vitamin E and selenium. In addition, the International Agency for Research on Cancer (IARC) has concluded that there is evidence suggesting lack of cancer-preventive activity for preformed vitamin A (IARC 1998a) and for β-carotene when used at high doses (IARC 1998b). In recent years the evidence has grown for a carcinogenic role of excess caloric intake, disregarding the source of calories, resulting in overweight and obesity (see Sect. 3.4.4).

The mechanisms of dietary-related carcinogenesis are not well understood. Dietary factors are likely to play a role in most if not all steps of the process, including genotoxicity, interference in the metabolism of other carcinogens, methylation of cancer genes, alteration of DNA repair and apoptotic mechanisms, alteration of DNA and cell replication, and cell proliferation (for a review see WCRF 1997). In particular, it is plausible that fresh fruits and vegetables act at least in part via

control of endogenously formed radical oxygen species. In addition, insulin and insulin-like Growth Factor-I (IGF-I), which are produced as a result of caloric intake, stimulate anabolic processes resulting in inhibition of apoptosis, and cell proliferation (see Sect. 3.4.4).

Several suspected dietary carcinogens have been widely studied in cancer epidemiology. Grilled and barbecued meat and fish contain carcinogenic polycyclic aromatic hydrocarbons and heterocyclic amines: high intake of these foods has been suggested to increase the risk of stomach and colorectal cancer. Similarly, high intake of cured and processed meat is a probable cause of digestive tract cancer: nitrosamines might be among the relevant carcinogens. High intake of salt probably increases the risk of stomach cancer (WCRF 1997). Intake of Chinese-style salted fish increases the risk of cancer of the nasopharynx (IARC 1993) and consumption of other types of salted fish might represent a risk factor in South-East Asia and the Arctic. Other preserved foods used as weaning food in different areas of China have also been associated to nasopharyngeal cancer: chung choi (a salted root), salted shrimp paste, salted eggs and preserved fruits. The high rates of this tumour in Northern Africa might be due to consumption of dried mutton, touklia (a spiced mixture of peppers) or harissa (a hot sauce).

In several areas of Asia and Africa, high incidence of liver cancer is due to food contamination by mycotoxins, including aflatoxins (Stuver and Trichopoulos 2002). A role of another group of mycotoxins – fumonisins – in oesophageal cancer risk is suspected (IARC 2002a). The application of exposure biomarkers to the study of aflatoxin-related liver cancer represented a major success of molecular cancer epidemiology and has allowed to elucidate the role of this important group of carcinogens (Ross et al. 1992). In Japan, eating bracken fern has been associated with an elevated oesophageal cancer risk (Alonso-Amelot and Avendano 2002). In Central Europe, a chronic renal disease called Balkan Endemic Nephropathy has been described, which is associated with an increased risk of kidney cancer and is likely to be due to ochratoxin contamination of foodstuff (IARC 1993).

Intake of large amounts (more than one litre per day) of hot maté, a herbal tea, is a risk factor for oesophageal cancer in Southern Brazil, Uruguay and Northern Argentina (Castellsague et al. 2000). It is unclear, however, whether the effect is due to components of maté or to the high temperature: studies from other regions suggest that intake of hot beverages (e.g., hot tea in Iran, Singapore and Japan, hot coffee in Puerto Rico, and hot drinks or soups in Hong Kong) increases the risk of oesophagitis and oesophageal cancer, although the evidence is less consistent than in the case of maté (Nyren and Adami 2002a).

The investigation of dietary carcinogens presents major challenges because of the difficulties to assess precisely the relevant carcinogenic (or preventive) factors. In most populations, diet varies greatly during the life of an individual, because of changes in personal choices and in societal aspects (availability of different food items, modification of eating patterns, etc.). Furthermore, many nutritional factors are strongly correlated, making it difficult to disentangle the effect of each factor, and variability in exposure within relatively homogeneous

Table 3.6. Assessment of associations between dietary factors and human cancer (WCRF 1997)

Factor (high intake)	Oral cavity and pharynx	Oeso-phagus	Sto-mach	Colon and rectum	Liver	Pan-creas	Lung	Breast	Cervix	Endo-metrium	Ovary	Pros-tate	Kidney	Bladder
Starch			[−]	[+]										
Fibres			{−}	[−]		[−]		[−]						
Sugar				[+]		{+}								
Total fat				[+]			[+]	[+]		{+}	{+}	[+]		{+}
Saturated fat				[+]			[+]	[+]		[+]	{+}	[+]		
Cholesterol						[+]	[+]	(=)		{+}				
Animal protein								{+}						
Carotenoids		[−]	[−]	[−]			(−)	[−]	[−]	{−}	{−}			{−}
Vitamin C	[−]	[−]	(−)	{−}		[−]	[−]	{−}	[−]			[=]		{−}
Retinol			[=]				[=]	[=]	[=]					{−}
Vitamin E			[=]	{−}			[−]	[=]	[−]					
Folate				{−}					[=]					
Selenium			{−}	[=]	{−}		[−]							
Iron				{+}	{+}									
Vitamin D				{−}										
Calcium				[=]										
Allium compounds			[−]											

table to be continued

Table 3.6. (continued)

Factor (high intake)	Oral cavity and pharynx	Oeso-phagus	Sto-mach	Colon and rectum	Liver	Pan-creas	Lung	Breast	Cervix	Endo-metrium	Ovary	Pros-tate	Kidney	Bladder
Cereals				{−}										
Whole grain cereals			[−]											
Refined cereals		[+]												
Vegetables	−	−	−	−	[−]	(−)	−	(−)	[−]	[−]	[−]	[−]	[−]	(−)
Fruits	−	−	−			(−)	−	(−)	[−]	[−]	[−]			(−)
Meat				(+)		[+]		[+]				[+]	[+]	
Eggs				[+]		{+}					{+}		[=]	[=]
Fish				[=]				{−}			{−}			
Milk & dairy products												[+]	[+]	
Coffee			(+)	{−}		(=)		=				[=]	(=)	[+]
Maté	[+]	[+]												
Black tea			(=)					[=]					(=)	(=)
Green tea			[−]											

Direction of the effect: + increased risk; − decreased risk; = no relationship
Strength of the evidence: no brackets: convincing evidence of an association
round brackets: probable association
squared brackets: possible association
curly brackets: insufficient evidence to fully assess the association

populations might not be large enough to allow the detection of carcinogenic effects. Dietary retrospective exposure assessment is complicated by recall bias and unavailability of valid biomarkers, making the case-control approach particularly unsuitable. Even the evidence derived from prospective (e.g., cohort) studies, however, is far from being unequivocal: as an example, the fairly established notion that high intake of fat, mainly of saturated fat from animal foods, might be a risk factor for breast cancer was recently challenged by the results of prospective studies based on detailed dietary assessment (Holmes et al. 1999). The equivocal evidence, however, might depend on a different effect of fat intake on the risk of premenopausal and postmenopausal breast cancer (Cho et al. 2003). For a general discussion of nutritional epidemiology see Chap. III.4 of this handbook.

3.4.4 Overweight and Obesity

Overweight, defined as body mass index (BMI) over 25 kg/m^2, increases the risk of colon, breast (post-menopausal), endometrial and kidney cancer and of adenocarcinoma of the oesophagus (IARC 2002b). The risk of these cancers is linearly related to severity of overweight and obesity, where obesity is defined as BMI over 30 kg/m^2; adult weight gain is a strong and consistent predictor of risk. In the case of colon cancer, body fat distribution expressed as waist to hip circumference ratio, might have an effect independent from that of body mass. It is likely that obesity exerts a carcinogenic effect via alteration of endogenous hormone metabolism, involving in particular insulin resistance and chronic hyperinsulinaemia, modulation of adrenal cortical hormones, and increased bioavailability of estrogens. Other possible mechanisms include interference with carcinogen metabolism, accumulation of reactive oxygen species and alteration of mechanisms regulating cell proliferation, resulting in enhanced proliferation and reduced apoptosis, as well as induction of angiogenesis in tissues other than the fat. The magnitude of the excess risk is not very high (for most cancers the relative risk ranges between 1.1 and 1.5 for overweight and between 1.3 and 2 for obesity), however, the attributable risk in industrialized countries is large because of the high prevalence of overweight people: estimates for Europe suggest that about 6% of all cancers in women and 3% in men are attributable to overweight and obesity (Table 3.7).

3.4.5 Physical Activity

Regular sustained workplace or recreational physical activity (e.g., at least 30 minutes/day) decrease the risk of colon and breast cancer; a protective effect is also likely for endometrial and prostate cancer (IARC 2002b). The magnitude of risk reduction for colon and breast cancer is in the order of 40%, and a dose-response relationship has been shown for both neoplasms. Up to 13% of cases of colon cancer in the USA can be attributed to physical inactivity (Slattery 1997). Although

Table 3.7. Cancer risk attributable to overweight and obesity in European Union countries (Bergström et al. 2001)

Cancer	Relative risk		Attributable fraction (%)		Attributable cases
	Overweight	Obesity	Women	Men	
Breast	1.12	1.25	8.5	–	12,870
Colon	1.15	1.33	10.7	11.1	21,610
Endometrium	1.59	2.52	39.2	–	14,230
Prostate*	1.06	1.12	–	4.4	4990
Kidney	1.36	1.84	24.5	25.5	10,380
Gallbladder*	1.34	1.78	23.7	24.8	6460
Total	–	–	6.4	3.4	70,540

* Evidence of a causal role of overweight considered less than conclusive by IARC (2002b)

regular physical activity contributes to weight control, the epidemiological evidence suggests that two factors also act independently. The mechanisms through which physical activity contributes to cancer prevention are not fully understood, but they may include enhancement of immune function, interference with sex steroids, and insulin and IGF-I pathways (IARC 2002b).

Alcohol Drinking

3.4.6

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity and pharynx, oesophagus, and larynx. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident; an interaction has been shown between alcohol drinking and tobacco smoking (Fig. 3.5). The evidence of differences in carcinogenicity among alcoholic beverages is inconclusive. Alcohol might act as co-carcinogen, enhancing the effect of tobacco and dietary carcinogens; in addition, a direct carcinogenic effect of acetaldehyde, the main metabolite of ethanol cannot be excluded. An increased risk has also been reported for colorectal cancer and liver cancer, although the effect on the latter might be mediated by development of liver cirrhosis. Breast cancer risk is also increased among drinkers (CGHFBC 2002a): although weak (relative risk in the order of 1.07 for each 10 g/day increase in alcohol intake), the association is of importance because of the apparent lack of a threshold, the large number of women drinking large amounts of alcohol, and the high incidence of the disease.

The carcinogenic effect of alcohol should be considered in the light of other health effects, notably the increased mortality from chronic digestive diseases and accidents and the reduced mortality from cardiovascular diseases among moderate drinkers (Vogel 2002). In middle-aged and old people, the benefit on cardiovascular disease is likely to offset the increased cancer risk, up to a level of approximately 20 g/day among men and 10 g/day among women.

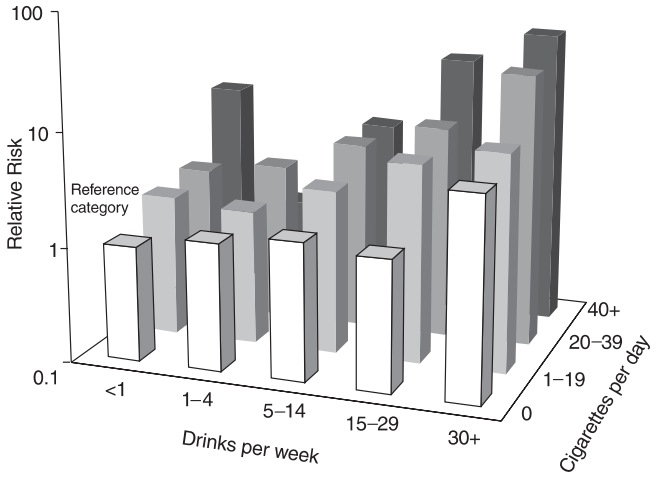

Figure 3.5. Risk of oral cancer, tobacco smoking and alcohol drinking. From Blot et al. (1988)

3.4.7 Infectious Agents

There is growing epidemiological evidence that chronic infection with some viruses, bacteria and parasites represents a major cause of human cancer, in particular in developing countries. A number of infectious agents have been evaluated within the IARC Monograph Programme (Table 3.8), and the evidence of a causal association has been classified as sufficient for several of them. Human Papilloma virus (HPV) is detected in almost all cases of cervical cancer: several oncogenic HPV types have been identified, with HPV 16 and 18 being the most prevalent ones (Munoz et al. 2003). Chronic infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) is a major cause of liver cancer worldwide; an interaction has been shown between HBV infection and other causes of liver cancer such as aflatoxin exposure. Additional carcinogenic viruses include Epstein-Barr virus, a major cause of Hodgkin's disease and of some types of non-Hodgkin lymphoma, Human Herpes virus 8 (HHV8), which causes Kaposi sarcoma, Human Immunodeficiency virus I, which causes various types of non-Hodgkin lymphoma, and Human T-cell leukaemia/lymphoma virus I. In addition, childhood leukaemia is likely linked to one or more viruses that have not yet been identified.

Infection with Helicobacter pylori is associated with an approximately six-fold increased risk of non-cardia gastric cancer, after controlling for other risk factors of the disease (Nyren and Adami 2002a). Unplanned control of Helicobacter infection via widespread antibiotic use and improved living conditions is likely to be an important component of the decline in stomach cancer incidence, which occurred in many countries during recent decades. Infestation with several parasites has been linked with occurrence of human cancer in tropical countries: the evidence is particularly strong for Schistosoma haematobium, causing bladder

Table 3.8. Assessment of associations between infections and human cancer (IARC 1994a,b, 1995, 1996a, 1997a)

	Evidence*	Target organs**
Viruses:		
Hepatitis B virus	S	Liver
Hepatitis C virus	S	Liver, (lymphoma)
Hepatitis D virus	I	Liver
Human papilloma virus types 16, 18	S	Cervix, anus, penis, (oral cavity)
Human papilloma virus types 31, 33	L***	(Cervix)
Human papilloma virus, other types	I***	
Human immunodeficiency virus 1	S	Kaposi's sarcoma, non-Hodgkin's lymphoma
Human immunodeficiency virus 2	I	
Human T-cell lymphotrophic virus I	S	Adult T-cell leukaemia/lymphoma
Human T-cell lymphotrophic virus II	I	
Epstein-Barr virus	S	Burkitt's lymphoma, Hodgkin's disease, nasopharynx
Human herpes virus 8	L***	(Kaposi's sarcoma)
Bacterium:		
Helicobacter pylori	S	Stomach cancer, gastric lymphoma
Parasites:		
Schistosoma haematobium	S	Bladder
Schistosoma japonicum	L	(Liver, stomach)
Schistosoma mansoni	I	
Opistorchis viverrini	S	Liver
Opistorchis felineus	I	
Clonorchis sinensis	L	Liver

* I, inadequate; L, limited; S, sufficient
** Established target organs without brackets; suspected target organs in brackets
*** The evidence of a causal role of these agents has become stronger since the IARC evaluation

cancer in North Africa and the Middle East, and Chlonorchis siniensis, causing cholangiocarcinoma in South East Asia (IARC 1994a,b).

Global estimates of the number of cases of cancer attributable to biological agents suggest that at least 16% of all neoplasms worldwide are due to infection (Table 3.9) (Pisani et al. 1997). HBV- and HCV-related liver cancer, HPV-related cervical cancer and Helicobacter-related stomach cancer each account for approximately 30% of the total. Because of the high prevalence of most carcinogenic agents in developing countries, the estimate of the attributable risk is higher in this part of the world.

More than for other causes of cancer, a carcinogenic role of infectious agents is strongly suggested by extreme variability in cancer risk observed among populations in descriptive epidemiological studies. Thus, an infectious agent had

Table 3.9. Cancer risk attributable to infectious agents (Pisani et al. 1997)

Cancer	Agent	Developing countries		Developed countries	
		AF%	N cases	AF%	N cases
Liver	HBV, HCV	91	352,644*	51	46,762
Stomach	H. pylori	54	299,636	60	205,292
Cervix	HPV	91	335,946	82	80,420
Female genital	HPV	91	20,816	82	10,219
Lymphoma**	HIV, EBV	33	57,987	27	32,316
Leukaemia	HTLV-I	1.4	2200	0.5	500
Bladder	S. haematobium	7.7	10,249	0	0
Total		21	1,079,443	9.1	375,509

AF attributable fraction
* Including 808 cases of cholangiocarcinoma attributable to infestation with 0. viverrini
** Including Kaposi sarcoma (no cases attributed to HHV8)

been suspected for a long time for a number of human neoplasms (e.g., Kaposi sarcoma), before sensitive and specific assays became available for the identification of the responsible agent. In addition, the investigation of infectious causes of cancer poses special problems of reverse causality: the detection of an agent in a tumour, as compared to the normal tissue of the patients or controls, does not imply an etiological role, since the altered environment resulting from the neoplasm might favour the growth of the micro-organism above detection levels. Cohort studies with repeated samples of the target tissue or surrogate material (typically serum) represent the strongest approach to establish causality.

3.4.8 Occupational Exposures

Twenty-nine occupational agents, groups of agents and mixtures, as well as 12 exposure circumstances, are classified as carcinogenic by IARC (Table 3.10) (IARC 1972–2004). An additional 31 compounds and 3 exposure circumstances are classified as probable carcinogens (Table 3.11). While some (e.g., mustard gas) are mainly of historical interest, exposure is still widespread for important carcinogens such as asbestos, coal tar and other mixtures of polycyclic aromatic hydrocarbons, heavy metals and silica. Although the overall burden of occupational cancer is relatively small, these cancers concentrate among exposed subjects (mainly male blue-collar workers), among whom they may represent a sizeable proportion of total cancers (Boffetta et al. 1995). Furthermore, unlike lifestyle factors, exposure is involuntary and can be, to a large extent, avoided. In fact, reduction of exposure to occupational and environmental carcinogens has taken place in industrialized countries during recent decades and represents one of the successes of cancer epidemiology.

The epidemiological approach to study occupational causes of cancer was traditionally based on the historical cohort design. Groups of workers were identified

Table 3.10. Occupational agents, classified by the IARC Monographs programme as carcinogenic to humans

Agents, mixture, circumstance	Main industry, use
Agents, groups of agents:	
4-Aminobiphenyl	Pigment
Arsenic and arsenic compounds	Glass, metal, pesticide
Asbestos	Insulation, filter, textile
Benzene	Chemical, solvent
Benzidine	Pigment
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
Dioxin	Chemical
Ethylene oxide	Sterilant
Mustard gas*	War gas
2-Naphthylamine	Pigment
Nickel compounds	Metallurgy, alloy, catalyst
Plutonium-239 and its decay products	Nuclear industry
Radium-226 and its decay products*	Luminizing industry
Radium-228 and its decay products*	Luminizing industry
Radon-222 and its decay products	Mining
Silica, crystalline	Stone cutting, mining, glass
Solar radiation	Agriculture
Talc containing asbestiform fibres	Paper, paints
Vinyl chloride	Plastics
X- and γ-radiation	Medical
Mixtures:	
Coal-tar pitches	Construction, electrode
Coal-tars	Fuel, construction, chemical
Mineral oils, untreated	Metal
Shale-oils	Fuel
Soots	Pigment
Wood dust	Wood
Exposure circumstances:	
Aluminium production	
Auramine, manufacture of*	Pigment
Boot and shoe manufacture and repair	
Coal gasification	
Coke production	

* Agent mainly of historical interest

table to be continued

Table 3.10. (continued)

Agents, mixture, circumstance	Main industry, use
Furniture and cabinet making	
Haematite mining (underground) with exposure to radon	
Iron and steel founding	
Magenta, manufacture of *	Pigment
Painter (occupational exposure as a)	
Rubber industry	
Strong inorganic-acid mists containing sulphuric acid	Metallurgy

* Agent mainly of historical interest

via company or union records, and their cancer mortality or incidence was compared with that of a reference population, most commonly that of the country or the region, leading to the estimate of indirectly standardized mortality (or incidence) ratios. In recent decades, alternative approaches gained popularity, including: (1) community-based case-control studies, leading to the simultaneous estimate of the risk from exposure to a large number of agents (see for example the multi-site study conducted in Montreal by Siemiatycki (1995)); and (2) comparisons within subgroups of cohort members, based on reconstructed (often model-based) estimates of exposure to one or more agents of interest. Occupational cancer research has also been a field of successful application of biomarkers of exposure, as in the case of the identification of ethylene oxide as a human carcinogen following the detection of protein adducts in exposed workers and in animals showing an increased incidence of neoplasms (IARC 1994c).

The main reasons for the success of the application of epidemiology to the field of occupational cancer are the possibility to identify clearly defined groups of exposed individuals and the availability of historical measures of exposure. For more details on occupational epidemiology see Chap. III.2 of this handbook.

3.4.9 Environmental Agents

Exposure to many occupational carcinogens listed in Tables 3.10 and 3.11 also occurs in the general environment; for two additional agents, the naturally-occurring fibre erionite and short-lived radioiodine isotopes, the main source of exposure is the general environment. Overall, the available evidence suggests, in most populations, a small role of purely environmental sources of exposure to carcinogens (air, water, soil pollution): global estimates are in the order of 1% or less of total cancers. This is in contrast with public perception, which often identifies environmental pollution as a major cause of human cancer. It should be stressed, however, that in selected areas (e.g., residence near asbestos processing plants or in areas with drinking water contaminated by arsenic) environmental exposure to carcinogens may represent an important cancer hazard (Armstrong and Boffetta 1998).

Table 3.11. Occupational agents, classified by the IARC Monographs programme as probably carcinogenic to humans

Agents, mixture, circumstance	Main industry, use
Agents, groups of agents:	
Acrylamide	Chemical, construction
Benz[a]anthracene	Combustion fumes
Benzidine-based dyes	Paper, leather, textile dyes
Benzo[a]pyrene	Combustion fumes
1,3-Butadiene	Plastics, rubber
Captafol	Fungicide
α-Chlorinated toluenes	Chemical intermediate
4-Chloro-ortho-toluidine	Dye/pigment manufacture, textiles
Dibenz[a,h]anthracene	Combustion fumes
Diethyl sulfate	Chemical intermediate
Dimethylcarbamoyl chloride	Chemical intermediate
Dimethyl sulfate	Chemical intermediate
Epichlorohydrin	Plastics/resins monomer
Ethylene dibromide	Chemical intermediate, fumigant
Formaldehyde	Plastics, textiles, laboratory agent
Glycidol	Chemical intermediate
4,4′-Methylene bis(2-chloroaniline) (MOCA)*	Rubber manufacture
N-Nitrosodimethylamine*	Chemical intermediate
Styrene-7,8-oxide	Plastics, chemical intermediate
Tetrachloroethylene	Solvent, dry cleaning
ortho-Toluidine	Dyestuff, rubber
Trichloroethylene	Solvent, dry cleaning, metal
1,2,3-Trichloropropane	Solvent, chemical intermediate
Tris(2,3-dibromopropyl)phosphate	Plastics, textiles, flame retardant
Vinyl bromide	Plastics, textiles, monomer
Vinyl fluoride	Chemical intermediate
Mixtures:	
Creosotes	Wood preservation
Diesel engine exhaust	Transport
Non-arsenical insecticides (spraying and application)	Agriculture
Polychlorinated biphenyls	Electrical components
Exposure circumstances:	
Art glass, glass container and pressed ware (manufacturing of)	
Hairdresser and barber	
Petroleum refining	

* Agent mainly of historical interest

The search for environmental causes of cancer has been particularly elusive to the epidemiological approach. The main reason for such relative lack of success lies in several biases affecting the assessment of exposure to most environmental carcinogens and leading to false negative results: low-level exposure is often widespread and the range of dose is limited; exposure levels vary with time and most available measurements refer to the present or recent past; individuals are unable to validly and precisely reconstruct their past exposure. For more details on these problems please refer to Chap. III.3 of this handbook.

3.4.10 Reproductive Factors

The epidemiological evidence of a carcinogenic effect of reproductive factors is strongest for breast cancer: early age at menarche, low parity, late age at first pregnancy and late age at menopause are all associated with an increased risk, while spontaneous and induced abortions are not (Hankinson and Hunter 2002). In addition, breastfeeding protects from breast cancer. A large pooled analysis resulted in an estimated 4.3% (95% confidence interval (CI) 2.9–5.8) decrease in risk for every 12 months of breastfeeding, in addition to a decrease of 7.0% (95% CI 5.0–9.0) for each birth (CGHFBC 2002b). The same reproductive factors seem to exert an effect on endometrial cancer risk similar to that played on breast cancer, while the evidence of an effect on other cancers is inadequate, although there is limited evidence that nulliparity increases the risk of ovarian cancer. No detailed estimates are available on the contribution of reproductive factors to the global burden of cancer. Some authors have, however, proposed figures in the order of 3% (HCCP 1996). An extensive discussion of methodological problems in reproductive epidemiology can be found in Chap. III.5 of this handbook.

3.4.11 Other Lifestyle Factors

A number of other lifestyle factors have been shown or suggested in epidemiological studies to cause cancer in humans. Poor oral hygiene and ill-fitting dentures are likely to represent additional risk factors for oral cancer. The use of mouthwash with high alcohol content has also been associated with oral cancer (Mucci and Adami 2002). Herbs of the *Aristolochia* genus, used in traditional Chinese medicine as anti-rheumatics and diuretics and included in weight-loss regimens, cause a rapidly progressive renal disease called Chinese Herb Nephropathy, as well as cancer of the urinary tract (IARC 2002a).

3.4.12 Hormones

Increased levels of endogenous estrogens are associated with an increased risk of breast and endometrial cancers, and a similar effect is likely to be played by endogenous androgens (Hankinson and Hunter 2002; Persson and Adami 2002). The role of other hormones, such as progesterone and prolactin, in these can-

cers is not clearly known, nor is the role of endogenous androgens in prostate cancer.

There is growing evidence that growth hormones, in particular IGF-I, have a strong effect on the risk of breast, colon, prostate and possibly other cancers (Furstenberg and Senn 2002), and that chronic hyperinsulinaemia is a cause of cancers of the colon, pancreas, breast and endometrium (Kaaks et al. 2002).

There is a large body of epidemiological studies on cancer risk following exposure to exogenous hormones. Current and recent (up to 10 years) use of oral contraceptives entails a small increase in breast cancer risk, but no excess risk is apparent 10 or more years after cessation of use (CGHFBC 1996). Long-term use of oral contraceptives is associated with an increased risk of liver cancer, while the risk of endometrial and ovarian cancer is decreased following oral contraceptive use (IARC 1999a).

Post-menopausal hormonal therapy increases the risk of breast and endometrial cancer (CGHFBC 1997; IARC 1999a). In the case of breast cancer, the effect is stronger for combined estrogen-progestagen combinations than for other types of hormonal therapy (Beral et al. 2003). The evidence for other organs is inconclusive.

Tamoxifen is widely used for treatment of breast cancer: beyond its therapeutic effects, it decreases the risk of contralateral breast cancer but it increases the risk of endometrial cancer (IARC 1996b).

Perinatal Factors 3.4.13

Excess energy intake early in life is possibly associated with breast and colon cancer (IARC 2002b). The role of attained height, growth factors, and other factors such as insulin resistance or sensitivity in this association is unclear. In addition, high birth weight is possibly linked with an increased risk of breast cancer. Perinatal factors have been proposed to cause up to 5% of human cancers, but this estimate is subject to uncertainty. The implications of these findings for preventive strategies will be clarified by a more detailed understanding of the underlying carcinogenic mechanisms (HCCP 1996).

Ionizing and Non-ionizing Radiation 3.4.14

The available epidemiological studies of populations exposed to ionizing radiation following military actions, accidents, occupational exposure and medical treatments represent a very comprehensive database, which has been used beyond the assessment of radiation carcinogenicity, notably to elaborate models of carcinogenesis in humans and of quantitative risk assessment (Moolgavkar et al. 1999). Ionizing radiation causes acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia and breast, lung and thyroid cancers (IARC 2000). Bone, rectal and brain cancers may develop following prolonged therapeutic exposure. There is evidence of a linear dose-response relationship between radiation dose and cancer risk. However, levels at which people are commonly

exposed to man-made radiation in most countries carry little risk and the main exposure comes from natural radiation, including indoor radon (IARC 2000). The estimates of the global contribution of ionizing radiation to human cancer range from 1% to 3% (Table 3.3).

The study of cancer risk following exposure to ionizing radiation represented one of the main paradigms of chronic disease epidemiology. In most exposure circumstances, doses – including those in the past – are known with great precision. In addition, they are characterized by different intensity and dose rates, allowing the separate investigation of different components of the carcinogenic effect.

Solar (ultraviolet) radiation is carcinogenic to the skin and the lip, and it might increase the risk of other neoplasms such as non-Hodgkin lymphoma (IARC 1992). Over 90% of skin neoplasms are attributable to sunlight; however, because of the low fatality of non-melanocytic skin cancer, solar radiation is responsible for only 1% to 2% of total cancer deaths (Table 3.3). Epidemiological studies have contributed to elucidate the contribution of dose rate and time of exposure in ultraviolet-related carcinogenesis. The evidence of a carcinogenic effect of other types of non-ionizing radiation, in particular electric and magnetic fields, is inconclusive (IARC 2002c).

3.4.15 Medical Procedures and Drugs

In addition to post-menopausal hormonal therapy, oral contraceptives and tamoxifen, other drugs may cause cancer. Many cancer chemotherapy drugs are active on the DNA, in order to block the replication of cancer cells. This, however, might result in damage to normal cells, including cancer transformation. The main neoplasm associated with chemotherapy treatment is leukaemia, although the risk of solid tumours is also increased (Boffetta and Kaldor 1994). A second group of carcinogenic drugs includes immunosuppressive agents, which have been studied in particular in transplanted patients (Kinlen 1996). Non-Hodgkin lymphoma is the main neoplasm caused by these drugs. Phenacetin-containing analgesics increase the risk of cancer of the renal pelvis (Lindblad and Adami 2002).

There is strong evidence from observational studies that aspirin reduces the risk of colorectal cancer (IARC 1997b), an effect probably shared by other non-steroidal anti-inflammatory drugs.

No precise estimates are available for the global contribution of drug use to human cancer. It is unlikely, however, that drugs represent more than 1% in developed countries (Table 3.3). Furthermore, the benefits of such therapies are usually much greater than the potential cancer risk.

Use of ionizing radiation for diagnostic purposes is likely to carry a small risk of cancer, which has been demonstrated only for childhood leukaemia following intrauterine exposure (IARC 2000). Radiotherapy increases the risk of cancer in the irradiated organs. There is no clear evidence of an increased cancer risk following other medical procedures, including surgical implants (IARC 1999b).

The epidemiological investigation of the carcinogenicity of drugs and medical procedures shares several characteristics of occupational cancer research: well-

defined groups of exposed individuals and valid records of exposure, often in the form of prescription or hospital discharge databases, in addition to the strong potency of several medical agents. These factors explain the relatively large number of drugs identified as human carcinogens.

Medical Conditions 3.4.16

Changes in immunological function are likely to play an important role in human cancer, but epidemiological studies have been largely unable to identify specific factors determining an increased or a decreased risk. Both severe immunosuppression and immunostimulation are associated with an elevated risk of cancer (Kinlen 1996). On the one hand, individuals infected with the Human Immunodeficiency Virus (HIV) and patients undergoing immunosuppressive treatments, such as transplant recipients, are at increased risk of lymphoma and skin cancer (Kinlen 1996). On the other hand, patients suffering from systemic autoimmune diseases are also at increased risk of lymphoma and possibly other neoplasms (Kinlen 1996). The significance of less severe disturbances of the immunological competence is poorly known.

Several chronic inflammatory conditions represent a risk factor for cancer: the epidemiological evidence is particularly strong in the case of colorectal cancer following inflammatory bowel disease and of lymphoma following chronic infectious diseases such as tuberculosis, malaria and herpes zoster (Melbye and Trichopoulos 2002; Potter and Hunter 2002).

Recent epidemiological studies have clearly shown that gastro-oesophageal reflux is an important cause of adenocarcinoma of the lower oesophagus, a neoplasm whose incidence is increasing in developed countries (Nyren and Adami 2002b).

Genetic Factors 3.4.17

The notion that genetic susceptibility plays an important role in human cancer is well-established, and early studies have demonstrated an increased risk of several types of cancer in individuals with a familial history of the same or related cancers. Several familial conditions entailing a very high risk of cancer have been identified, such as the Li-Fraumeni syndrome and familial polyposis of the colon (Haiman and Hunter 2002). It is only recently that, thanks to the development of molecular tools in human genetics, specific high-risk cancer genes have been identified. Inherited mutations of such high-penetrance cancer genes increase dramatically the risk of some neoplasms (Table 3.12). However, these are rare conditions in most populations and the number of cases globally attributable to them is rather small.

A familial aggregation has been shown for most types of cancers, in non-carriers of known high-penetrance genes. This is notably the case for cancers of the breast, colon, prostate and lung. The relative risk is in the order of 2 to 4, and is higher for cases diagnosed at young age. Although some of the aggregation can be explained by shared risk factors among family members, it is plausible

Table 3.12. High penetrance cancer predisposition genes (Haiman and Hunter 2002)

Gene	Syndrome	Main targets
RET	Multiple endocrine neoplasia 2	Medullary thyroid carcinoma, pheochromocytoma, parathyroid adenoma
MET	Familial papillary renal cancer syndrome	Papillary renal cancer
APC	Familial adenomatous polyposis	Colorectal cancer
VHL	von Hippel-Lindau syndrome	Clear-cell renal carcinoma, hemangioblastoma, retinal angioma, pheochromocytoma
WT1	Wilms' tumour syndrome	Bilateral Wilms' tumour
RB1	Hereditary retinoblastoma	Retinoblastoma
NF1	Neurofibromatosis 1	Neurofibroma, neurofibrosarcoma, optic glioma
NF2	Neurofibromatosis 2	Vestibular schwannoma, meningioma
p53	Li-Fraumeni syndrome	Sarcoma, leukaemia, breast, brain, lung, pancreas and skin cancers, others
p16/DCK4	Hereditary melanoma syndrome	Melanoma
PTCH	Nevoid basal cell carcinoma syndrome	Basal cell carcinoma
MEN1	Multiple endocrine syndrome 1	Tumours of parathyroids, gastrointestinal endocrine tissues and anterior pituitary
BRCA1	Hereditary breast-ovarian cancer syndrome	Breast, ovary, prostate and colon cancer
BRCA2	Hereditary breast-ovarian cancer syndrome	Breast (also male) and ovary cancer
PTEN	Cowden syndrome	Hamartoma, breast and thyroid cancer
hMSH2, hMLH1, hPMS1, hPMS2	Hereditary nonpolyposis colon	Colon, endometrium, ovary, stomach cancers, others
ATM	Ataxia-telangiectasia	Leukaemia, lymphoma, breast cancer
XP(A-G)	Xeroderma pigmentosum	Skin cancer
BLM	Bloom syndrome	Leukaemia, lymphoma, most cancers
FAC, FAA	Fancomi anaemia	Acute myeloid leukaemia, others
WRN	Werner syndrome	Sarcoma, melanoma, thyroid carcinoma

that a true genetic component exists for most human cancers. This takes the form of an increased susceptibility to exogenous carcinogens. The knowledge of low-penetrance genes responsible for such susceptibility is still very limited, although research has currently focused on genes encoding for metabolic enzymes, DNA repair, cell cycle control and hormone receptors (Haiman and Hunter 2002). Current estimates of the global contribution of genetic factors to human cancer are in the range of 5% to 10%, of which less than 1% is attributable to high-penetrance genes.

The investigation of high- and medium-penetrance genetic cancer risk factors relies mostly on specific methodological approaches whose discussion goes beyond the scope of this chapter (please refer to Chap. III.7 of this handbook for more details). In the case of low-penetrance genes, however, association studies have been successful in identifying genetic susceptibility factors. Given the lack of dependence of genetic markers of time and disease development, the case-control approach is particularly suitable for this type of investigation.

Screening for Cancer 3.5

Screening is considered to be an effective approach to reduce cancer mortality, because human neoplasms go through several pre-neoplastic stages before they become biologically relevant and clinically detectable. For most cancers, this process takes years or even decades. The possibility to detect preclinical lesions with the potential to develop to a full cancer is highly appealing and is an area of very active research. The slow evolution of cancer, however, is a strong argument to avoid intervention on lesions that do not have the potential to develop to a full cancer during the lifespan of the individual, in order to avoid undue medical procedures such as surgery or chemotherapy. Furthermore, any screening technique has to be carefully evaluated in terms of efficacy to reduce mortality, compliance and costs. Carefully conducted trials with mortality as main outcome are needed to demonstrate the effectiveness of screening. In practice, however, the available evidence is often restricted to observational data.

Oral inspection aimed at identifying pre-neoplastic lesions might be an effective approach for secondary prevention of oral cancer. The inspection can be performed by medically certified professionals, but also, in particular in high-risk areas in developing countries such as India, by specifically trained health workers. Large-scale preventive trials are on-going, which should provide evidence in favour or against this approach (Sankaranarayanan et al. 2000).

Surveillance via flexible sigmoidoscopy, involving removal of adenomas, is a recommended measure for secondary prevention of colorectal cancer. An additional approach consists of the detection of occult blood in the faeces. The method suffers from low specificity and, to a lesser extent, low sensitivity, in particular in the ability to detect adenomas. However, trials have shown a reduced mortality from colorectal cancer after annual tests, although this is achieved at a high cost

due to an elevated number of false positive cases. Current recommendations for individuals aged 50 and over include either annual faecal occult blood testing or flexible sigmoidoscopy every five years (Cuzick 1999).

The most suitable approach for secondary prevention of breast cancer is mammography. The effectiveness of screening by mammography in women older than 50 years has been demonstrated, and programmes have been established in various countries (IARC 2002d). The effectiveness of mammography in women younger than 50 is not demonstrated. The benefit of other screening approaches, such as physical examination and self-examination, is not known (Moss 1999).

Cytological examination of exfoliated cervical cells (the Papanicolaou smear test) is effective in identifying precursor lesions, resulting in a decrease in incidence of and mortality from invasive cervical cancer. The benefit is in the order of a two- to four-fold decreased incidence. There is no conclusive evidence, however, regarding the optimal timing of the test (Miller 1999). Cytological smears are not applicable, however, in countries with limited availability of cytologists and pathologists, and alternative approaches for secondary prevention have therefore been proposed, including visual inspection of the cervix with possible enhancement of precursor lesions by acetic acid (Sankaranarayanan et al. 1999). Use of HPV testing as a screening method, either as a first choice for general application or as the triage method of inconclusive cytological diagnoses, is also under trial (Kulasingam et al. 2002).

Secondary prevention has been proposed for prostate cancer, based on digital rectal examination and measurement of prostate-specific antigen. There is no evidence from controlled trials that either procedure decreases the mortality from prostate cancer (Schröder 1999). Despite this lack of evidence, these procedures, in particular the prostate-specific antigen testing, have gained popularity in many countries.

Despite a large body of research since the 1970s, no effective screening method has yet been identified for lung cancer (Black 1999). Spiral computerized tomography scanning has been shown to be able to identify small, subclinical lesions in the lung of high-risk individuals (Henschke et al. 1999), and the effectiveness of this method to reduce mortality is currently under investigation. For a general discussion of the methodological problems of screening see Chap. III.10 of this handbook.

3.6 Conclusions

The application of principles of modern epidemiology to cancer research leads to some methodological considerations of a more general nature. Cancer epidemiology is relatively young, yet it has gained an important status in medicine and is practiced by many professionals around the world. In many respects, cancer epidemiology exemplifies the strengths and the weaknesses of the discipline at large.

On the one hand, cancer epidemiology has the privilege of complete and good-quality disease registries in many populations, covering a broad spectrum of rates and exposures. The network of cancer registries not only provides important clues in terms of etiological and clinical research, for example via the analysis of geographical and temporal differences in incidence, mortality and prevalence of different neoplasms, but also allows in many countries the conduct of large-scale, high-quality (and relatively low-cost) record linkage studies (cf. Chap. I.4 of this handbook). Examples of such studies include the analysis of cancer risk in migrants by region of origin and length of stay in the host country, the linkage between census and cancer registry data to assess risk from employment in specific occupations, the analysis of second primary neoplasms in cancer patients, and the risk of cancer following diagnosis of (or hospitalization for) non-neoplastic conditions.

On several occasions, cancer epidemiology has been the key tool to demonstrate the causal role of important cancer risk factors. The best example is the association between tobacco smoking and lung cancer, which led in the early 1960s to the establishment of criteria for causality in observational research (Doll 1998). Other contributions of epidemiology to the elucidation of important causes of human cancer include the demonstration of the role of HPV in cervical cancer, the role of Helicobacter pylori in stomach cancer, and that of solar radiation exposure in skin cancer, as well as the growing body of evidence for a major role of overweight and obesity in the aetiology of several important neoplasms. These findings have brought important regulatory and public health initiatives as well as lifestyle changes in many countries of the world. For example, Box 1 shows the European Code Against Cancer, which adequately summarizes the current evidence for cancer prevention: these recommendations are mainly based on evidence accumulated via epidemiological studies.

These epidemiological 'discoveries' share two important characteristics: they involve potent carcinogens, and methods are available to reduce misclassification of exposure to the risk factor of interest and to major possible confounders. It has therefore been possible to consistently demonstrate an association in different human populations. It should be noted that it is not necessary for the prevalence of exposure to be high (although this obviously has an impact on the population attributable risk): examples are the many occupational exposures and medical treatments for which conclusive evidence of carcinogenicity has been established on the basis of epidemiological studies conducted in small populations of individuals with well-characterized high exposure.

On the other hand, when these conditions are not met, the evidence accumulated from epidemiological studies is typically inconsistent and difficult to interpret (Taubes 1995). The history of cancer epidemiology presents many examples of premature conclusions, which have not been confirmed by subsequent investigations and have damaged the reputation of the discipline. Misclassification of the relevant exposure (cf. Chap. I.11 of this handbook), uncontrolled confounding (cf. Chaps. I.1 and I.9) and inadequate statistical power (cf. Chap. II.1) are the most common limitations encountered in cancer epidemiology. Two solutions have been proposed to overcome these problems. First, epidemiological studies

Box 1. European Code Against Cancer (Boyle et al. 2003)

Many aspects of general health can be improved, and many cancer deaths prevented, if we adopt healthier lifestyles:

1. Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.
2. Avoid obesity.
3. Undertake some brisk, physical activity every day.
4. Increase your daily intake and variety of vegetables and fruits: eat at least five servings daily. Limit your intake of foods containing fats from animal sources.
5. If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman.
6. Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun active protective measures must be taken throughout life.
7. Apply strictly regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and safety instructions on substances which may cause cancer. Follow advice of National Radiation Protection Offices.

There are public health programmes that could prevent cancers developing or increase the probability that a cancer may be cured:

8. Women from 25 years of age should participate in cervical screening. This should be within programmes with quality control procedures in compliance with *European Guidelines for Quality Assurance in Cervical Screening*.
9. Women from 50 years of age should participate in breast screening. This should be within programmes with quality control procedures in compliance with *European Guidelines for Quality Assurance in Mammography Screening*.
10. Men and women from 50 years of age should participate in colorectal screening. This should be within programmes with built-in quality assurance procedures.
11. Participate in vaccination programmes against hepatitis B virus infection.

should be very large in size. This is achieved either by conducting multicentre studies including thousands of cases of cancer (see for example the analysis of pure cigar and pipe smokers in a study based on 5621 cases of lung cancer and 7255 controls (Boffetta et al. 1999)) or by performing pooled and meta-analyses of independent investigations (see the pooled analyses of risk factors for breast can-

Table 3.13. Examples of important contributions of molecular epidemiology

Class of biomarkers	Agent, exposure	Reference
Dose marker	Aflatoxin	Ross et al. 1992
Viral infection	HPV	Munoz et al. 1992
Adducts	Ethylene oxide	Schulte et al. 1992
Acquired p53 mutations	Tobacco	Hernandez-Boussard and Hainaut 1998
Chromosomal aberrations	Individual susceptibility	Hagmar et al. 1998
Metabolic polymorphisms	NAT2*	Marcus et al. 2000

* N-acetyltransferase 2

cer including more than 50,000 cases (CGHFBC 1996, 1997, 2002a,b)). Second, the use of biological markers of exposure and early effect has been proposed to reduce exposure misclassification, increase the prevalence of the relevant outcomes, and shed light on the mechanism of action of the carcinogen under study (Boffetta and Trichopoulos 2002). In a few cases, biomarker-based studies have led to important advances in cancer epidemiology (Table 3.13). Assessment of exposure to aflatoxins, enhanced sensitivity and specificity of assessment of past viral infection, detection of protein and DNA adducts in workers exposed to reactive chemicals such as ethylene oxide, are among the examples in which molecular epidemiology has greatly contributed to the understanding of human cancer (cf. Chap. III.6). In many other cases, however, initial, promising results have not been confirmed by subsequent, usually methodologically sounder, investigations. They include in particular the search for susceptibility to environmental carcinogens by looking at polymorphism for metabolic enzymes (Vineis et al. 1999). If biomarkers offer new opportunities to overcome some of the limitations of epidemiology, their added value over traditional approaches should be systematically assessed. Biomarkers should be validated; consideration of sources of bias and confounding in molecular epidemiology studies should be no less stringent than in other types of epidemiological studies. Similarly, other aspects of the study (e.g., determination of required sample size, statistical analysis, reporting and interpretation of results) should be approached with the same rigour used in other areas of cancer epidemiology.

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