2

Etiology of Cancer

2.1 Identifying Human Carcinogens

Summary

- Cancer prevention begins with identifying known and suspected human carcinogens
- Carcinogen identification involves the scientific evaluation of epidemiological studies, animal bioassays, and mechanistic and other relevant data
- Carcinogen identification is an important activity at IARC (the *IARC Monographs*) and at several national health agencies
- National and international health agencies use carcinogen identifications to guide their actions to prevent human exposure to known or suspected human carcinogens
- Carcinogen identification programmes should avoid real or apparent conflicts of interests in order to maintain public confidence in the integrity of their evaluations

The first step in cancer prevention is to identify the causes of human cancer. Carcinogen identification programmes at IARC and several national health agencies provide a scientific basis for government actions and private efforts to control cancer by preventing exposure to known and suspected carcinogens. Individuals, too, can use this information to make more informed choices to reduce their exposure to cancer-causing agents.

Carcinogen identification is the first step in the *risk assessment* of carcinogens. This first step is called *hazard identification* and can be followed by *dose-response assessment* to characterise the relation between the dose of a carcinogen and the incidence of tumours, *exposure assessment* to determine the extent of human exposure to the carcinogen, and *risk characterisation* to describe the nature and magnitude of the human cancer risk. Risk assessment is followed by *risk management*, which is the process of weighing policy alternatives and selecting the most appropriate action [1,2].

Under this paradigm, a cancer *hazard* is an agent that is capable of causing cancer while a cancer *risk* is an estimate of the incidence of cancer expected from exposure to a cancer hazard. Risk depends on both the existence of a hazard and exposure to that hazard. A cancer hazard exists even when current exposures suggest little or no cancer risk, because accidental or unanticipated exposures that are difficult to foresee may pose a risk for cancer.

Studies used to identify carcinogens

The term "carcinogen" generally refers to an agent, mixture or exposure that can increase the age-specific incidence of human cancer. Carcinogen identification is an activity grounded in the scientific evaluation of the results of human epidemiological studies, long-term bioassays in experimental animals, and mechanistic and other relevant data. Each source of data has a distinct role in the overall assessment.

Epidemiological studies provide information about the responses of humans exposed to potential carcinogens. Among these, cohort and case-control studies are especially useful for identifying causal relationships. Criteria for assessing the adequacy of epidemiological studies include selection of exposed and reference groups, characterisation of exposure, identification of confounding factors and possible bias, duration of follow-up in view of cancer's latent period, ascertainment of causes of disease and death, and statistical power to detect specific effects. In evaluating a body of epidemiological evidence, the key scientific questions are whether a causal interpretation is credible and whether chance, bias and confounding can be ruled out with reasonable confidence. Epidemiologists have found useful guidance in a set of factors known as the Hill criteria [3]. These assess:

- Consistency of the observed association
- Strength of the observed association
- Specificity of the observed association
- Temporal relationship of the observed association
- Biological gradient (exposure-response relationship)
- Biological plausibility
- Coherence
- Experimental evidence (from human populations)
- Analogy

There are, however, limitations to what epidemiology can tell us. For example, it is often difficult to attribute causality to a single factor or to rule out small risks below a study's level of sensitivity. In addition, cancer's latent period implies that many years of preventable human exposure could pass before informative epidemiological studies become available.

Some carcinogen identification programmes

International Agency for Research on Cancer *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* http://monographs.iarc.fr/
U.S. National Toxicology Program Report on Carcinogens http://ntp.niehs.nih.gov/
U.S. Environmental Protection Agency Integrated Risk Information System (IRIS) http://cfpub.epa.gov/ncea/iris/
German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) Maximum Allowable Concentrations (Maximale Arbeitsplatzkonzentrationen, MAK) and Biological Tolerance Values (Biologische Arbeitsstofftoleranzwerte, BAT) http://www.dfg.de/
California Environmental Protection Agency List of chemicals known to the State to cause cancer http://www.oehha.ca.gov/prop65.html

For these reasons, *long-term studies in experimental animals* generally provide the means of assessing potential risks to humans. In these studies, exposures can be tightly controlled and confounding factors can be excluded. It is also possible to examine all organs and tissues that may be potential sites of carcinogenic activity. The use of animal studies is based on the physiological similarity that exists across mammalian species and on the plausible scientific assumption that agents causing cancer in animals will have similar effects in humans [4,5]. In evaluating a body of cancer studies in experimental animals, the key scientific question is whether the results can plausibly be generalised to humans, as indicated by replication in independent studies, preferably in different experimental systems and species.

Mechanistic studies and other relevant data are used to assess the correspondence of response between animals and humans. Toxicokinetic studies allow cross-species comparisons of absorption, distribution, metabolism, and elimination. Mechanistic studies attempt to elucidate the multiple cellular processes involved in tumour development. This has the potential to improve the analysis of studies in both humans and experimental animals by giving insight into the biology of cancer and helping to identify susceptible individuals and developmental stages.

In evaluating a body of mechanistic and other relevant data, the key scientific questions are whether the mechanistic data are strong and whether the mechanisms leading to cancer in experimental animals could also operate in humans. Strong support can be obtained from studies that challenge a hypothesised mechanism experimentally, by demonstrating that the suppression of a key mechanistic step leads to the suppression of tumour development. It is important to consider that multiple mechanisms may contribute to tumour development, that different mechanisms may operate in different dose ranges, that separate mechanisms may operate in humans and experimental animals, and that a unique mechanism may operate in a susceptible group. It is also important to keep in mind that an uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating one favoured mechanistic hypothesis [4].

The IARC Monographs

The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* are a series of scientific reviews that identify agents, mixtures or exposures that can increase the risk for cancer in humans. Each *Monograph* includes a critical review of the pertinent scientific literature and an evaluation of the weight of the evidence that the agent can alter the risk for cancer in humans.

The critical reviews and evaluations are developed by an interdisciplinary group of experts who conducted the original scientific research. The experts are selected on the basis of knowledge, experience, and absence of real or apparent conflicts of interests. The *IARC Monographs* are a worldwide scientific endeavour that has involved more than 1000 scientists from more than 50 countries.

IARC Monographs are developed during an 8-day meeting whose objectives are peer review and consensus. Before the meeting, each expert writes a portion of the critical review related to his or her area of expertise. At the meeting, four subgroups (exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) meet to review this text and develop a consensus subgroup draft.

When the subgroup of epidemiologists has reviewed the pertinent studies of cancer in humans, they characterise this evidence with a set of standard descriptors that span a range of levels of evidence [4]:

Sufficient evidence of carcinogenicity: A causal interpretation has been established, and chance, bias, and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A causal interpretation is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies permit no conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: Several adequate studies are mutually consistent in not showing a positive association at any level of exposure.

Similarly, a subgroup of toxicologists and pathologists reviews the pertinent studies of cancer in experimental animals, then characterises that evidence using similar standard descriptors [4]:

Sufficient evidence of carcinogenicity: A causal interpretation has been established through either multiple positive results or a single, highly unusual result.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but positive results come from a single study or there are limitations in the study design or results.

Inadequate evidence of carcinogenicity: The available studies permit no conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: Adequate studies in at least two species show that the agent is not carcinogenic.

Fig. 2.1.1 *The four heads of the IARC Monographs Programme (Harry Vainio, Vincent Cogliano, Lorenzo Tomatis and Jerry Rice)*

At the same time, another subgroup of experimental scientists reviews the mechanistic and other relevant data to characterise this evidence as weak, moderate or strong and to determine whether the mechanisms leading to cancer in experimental animals could also operate in humans. Then the entire Working Group meets in plenary session to review the work of the subgroups and to discuss and develop an overall evaluation of the weight of the evidence. Based on the epidemiological evidence, the evidence in experimental animals, and the mechanistic and other relevant data, the Working Group classifies each agent into one of the following groups [4]:

- Group 1: The agent is ***carcinogenic to humans***.
- Group 2A: The agent is ***probably carcinogenic to humans***.
- Group 2B: The agent is ***possibly carcinogenic to humans***.
- Group 3: The agent is ***not classifiable as to its carcinogenicity to humans***.
- Group 4: The agent is ***probably not carcinogenic to humans***.

The classification of an agent is a matter of scientific judgement. The use of a standard set of descriptors allows the *IARC Monographs* to provide evaluations for a wide variety of carcinogenic agents using comparable terms. These descriptors refer only to the strength of the evidence that an exposure is carcinogenic and not to its carcinogenic potency. The graded nature of the descriptors *(sufficient evidence, limited evidence, . . . ; carcinogenic, probably carcinogenic, . . .)* communicates the level of credibility of a potential cancer hazard in clear terms that can be understood by people who are not cancer specialists.

Similar terminology has been adopted by several national health agencies that identify carcinogens.

After the meeting IARC scientists review the final draft for accuracy and clarity before it is published. In order to communicate the outcomes of these Monograph meetings to the scientific community as quickly as possible, summaries of each meeting are now published in the scientific literature within 6–8 weeks after the meeting [6-18].

The scope of the *IARC Monographs* has expanded beyond an initial focus on single chemicals to also include complex mixtures, occupations, physical and biological agents, and lifestyle factors. As the world cancer burden has shifted from high-income to low- and moderate-income countries, the *IARC Monographs have* also included more agents that are of particular interest in the latter areas. Since the *IARC Monographs* began in 1971, more than 900 agents have been evaluated and more than 400 of these have been classified as *carcinogenic to humans, probably carcinogenic to humans,* or *possibly carcinogenic to humans.*

National and international health agencies use the *IARC Monographs* as a source of scientific information and as support for their actions to reduce or prevent human exposure to known or suspected carcinogens. Decisions about reducing exposure to suspected carcinogens are sometimes controversial, in part because the available data often cannot identify human carcinogens with certainty and because the costs and the benefits of exposure reduction go to different segments of society. For this reason, it is important that carcinogen identification programmes implement strong measures to avoid real or apparent conflicts of interests so that the public can have utmost confidence in the integrity of these classifications [19,20].

Some examples of carcinogenic agents

	Some agents that are *carcinogenic to humans*	**Some agents that are *probably carcinogenic to humans***
Chemicals	Benzene, 1,3-butadiene, formaldehyde, vinyl chloride	Trichloroethylene, styrene oxide
Complex mixtures	Aflatoxins, coal-tar, soots	PCBs, creosote, emissions from high-temperature frying
Occupations	Painting, chimney sweeping, coal gasification, coke production	Petroleum refining, hairdressing
Metals	Arsenic and compounds, beryllium and compounds, cadmium and compounds, chromium [VI]	Inorganic lead compounds, cobalt metal with tungsten carbide
Particles and fibres	Asbestos, crystalline silica, wood dust	Diesel engine exhaust
Pharmaceuticals	DES, estrogen-progestogen menopausal therapy, tamoxifen, phenacetin	Androgenic (anabolic) steroids, chloramphenicol
Radiation	Radon, solar radiation, X- and Gamma-radiation	
Biological agents	Hepatitis B and C, human papillomaviruses (type 16 and several others), *Helicobacter pylori*	
Lifestyle factors	Tobacco smoke (active and passive smoking), areca nut, alcoholic beverages, household combustion of coal	Shiftwork that involves circadian disruption, household combustion of biomass fuel (primarily wood)

Table 2.1.1 *Some examples of carcinogenic agents*
Source: IARC Monographs, http://monographs.iarc.fr/

Dr. Lorenzo Tomatis and the IARC Monographs Programme

The staff of the International Agency for Research on Cancer (IARC) were saddened to hear of the death on 21st September 2007 of Dr. Lorenzo Tomatis, the second Director of IARC and the founder of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. After devoting more than 26 years to the IARC, the last 12 years as director, Lorenzo Tomatis retired in December 1993. Throughout these years he was the tireless embodiment of IARC's mission: to conduct and coordinate research at an international level aimed at cancer prevention through the application of scientific knowledge of the causes of cancer.

Dr. Tomatis joined IARC in November 1967 at the age of 38. He arrived to create and establish the Unit of Chemical Carcinogenesis, and spent his career there developing the field in which he had already established his reputation. One of Tomatis's major contributions to IARC and to global public health was to establish the evidence of animal carcinogenicity in long-term experiments as a valid criterion for evaluating possible carcinogenic risks to humans, alongside or, even more importantly in the absence of, epidemiological evidence. Tomatis worked to establish this balanced perspective in which human epidemiology and experimental results are both seen as essential to the identification of human risks.
The overall objective of IARC is to prevent human cancer, and identifying environmental carcinogens as the prerequisite for their removal or reduction is a major step toward that goal. In 1969, Tomatis initiated what has become in the eyes of many IARC's most important contribution to cancer prevention, *the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. This programme has won an international reputation for its scientific validity, impartiality and integrity, and for its contribution to preventive measures for the benefit of public health.
The first Working Group of internationally recognised experts met in Lyon in December 1970 to prepare the scientific criteria that would be used in the Monographs and to make preliminary evaluations of the data on 5 substances. These 5 evaluations, together with those of 14 more substances, were considered by a Working Group that met in December 1971, and made up the first volume of the *IARC Monographs* Series, published in 1972 and covering organic, inorganic and natural products.
Since then, with the scientific collaboration and financial support of the US National Cancer Institute, the U.S. National Institute of Environmental Health Sciences and the Commission of the European Communities, among others, the programme has undergone considerable expansion. To date, 91 volumes of the Monographs have been published, with more currently in press. It is perhaps for his continuous efforts in publishing the Monographs series that Lorenzo Tomatis was most highly regarded, and for which he will be long remembered by the scientific community.

REFERENCES

1. National Research Council (U.S.) (1983). *Risk assessment in the federal government: managing the process*. Washington, D.C.: National Academy Press.
2. National Research Council (U.S.) (1994). *Science and judgement in risk assessment*. Washington, D.C.: National Academy Press.
3. Hill AB (1965). The environment and disease: association or causation? *Proc R Soc Med* 58: 295-300.
4. IARC. *Preamble to the IARC Monographs*. Available from: http://monographs.iarc.fr Date Accessed: October 12, 2008.
5. National Toxicology Program (2004). *11th Report on Carcinogens (RoC)*. Washington, D.C.: U.S. Department of Health and Human Services.
6. Cogliano V, Grosse Y, Baan R, et al. (2004). Advice on formaldehyde and glycol ethers. *Lancet Oncol* 5: 528.
7. Cogliano V, Straif K, Baan R, et al. (2004). Smokeless tobacco and tobacco-related nitrosamines. *Lancet Oncol* 5: 708.
8. Cogliano V, Baan R, Straif K, et al. (2005). Carcinogenicity of human papillomaviruses. *Lancet Oncol* 6: 204.
9. Cogliano V, Grosse Y, Baan R, et al. (2005). Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. *Lancet Oncol* 6: 552-553.
10. Straif K, Baan R, Grosse Y, et al. (2005). Carcinogenicity of polycyclic aromatic hydrocarbons. *Lancet Oncol* 6: 931-932.
11. Baan R, Straif K, Grosse Y, et al. (2006). Carcinogenicity of carbon black, titanium dioxide, and talc. *Lancet Oncol* 7: 295-296.
12. Grosse Y, Baan R, Straif K, et al. (2006). Carcinogenicity of nitrate, nitrite, and cyanobacterial peptide toxins. *Lancet Oncol* 7: 628-629.
13. Straif K, Baan R, Grosse Y, et al. (2006). Carcinogenicity of household solid fuel combustion and of high-temperature frying. *Lancet Oncol* 7: 977-978.
14. Baan R, Straif K, Grosse Y, et al. (2007). Carcinogenicity of alcoholic beverages. *Lancet Oncol* 8: 292-293.
15. Grosse Y, Baan R, Straif K, et al. (2007). Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. *Lancet Oncol* 8: 679-680.
16. Straif K, Baan R, Grosse Y, et al. (2007). Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol* 8: 1065-1066.
17. Baan R, Straif K, Grosse Y, et al. (2008). Carcinogenicity of some aromatic amines, organic dyes, and related exposures. *Lancet Oncol* 9: 322-323.
18. Cogliano V, Baan R, Straif K, et al. (2008). Future priorities for IARC Monographs. *Lancet Oncol* 9: 708.
19. Cogliano V, Baan R, Straif K, et al. (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect* 112: 1269-1274.
20. Cogliano V, Baan R, Straif K, et al. (2005). Transparency in IARC Monographs. *Lancet Oncol* 6: 747.

2.2 Tobacco Smoking

Summary

- Tobacco smoking causes 13 different cancers: lung, oral cavity, nasal cavity and nasal sinuses, pharynx, larynx, oesophagus, stomach, pancreas, liver, urinary bladder, kidney, uterine cervix and myeloid leukaemia. In high-resource countries, tobacco smoking accounts for approximately 30% of all human cancers
- Lung cancer has the highest smoking attributable fraction among all cancers induced by smoking. Duration of smoking is the strongest determinant of excess lung cancer risk in smokers, with risk increasing proportionally with the number of cigarettes smoked. Tobacco smoking raises the excess risk of all histological types of lung cancer
- Pooled estimates from a recent meta-analysis of smoking and cancer shows, persuasively, very similar risks of cancer associated with smoking in males and females
- Tobacco smoke is the most common source of carcinogens to human, including polycyclic aromatic hydrocarbons (i.e. benzo[a] pyrene) and tobacco specific nitrosamines (i.e. NNK). The chronic presentation of carcinogens to the airway epithelial cells, through sustained smoking, can lead to molecular lesions which, in the presence of reduced metabolic detoxification, can diminish repair capability, overwhelming cellular defences and leading to lung cancer
- About 1.3 billion people smoke globally, making tobacco a major avoidable cause of disease and mortality worldwide. Approximately 150 million deaths from tobacco use are projected worldwide for the period 2000–2024 if current smoking patterns persist; this number of deaths will not be much reduced unless a sizeable proportion of adults who are established smokers quit

Tobacco-related cancer burden

Tobacco smoking is the major cause of cancer in humans, inducing cancer of the lung, oral cavity, nasal cavity and nasal sinuses, pharynx, larynx, oesophagus, stomach, pancreas, liver, urinary bladder, kidney and uterine cervix, and myeloid leukaemia [1]. In addition, involuntary or secondhand smoke (SHS) causes lung cancer [1,2]. Furthermore, the detrimental effects of tobacco use, smoking in particular, are seen in the causation of other important chronic conditions: cardiovascular disease, cerebrovascular disease, peripheral vascular disorders, abdominal aortic aneurysm and chronic obstructive pulmonary diseases [3].

In the year 2000, 1.42 (95% CI 1.27–1.57) million cancer deaths in adults (≥30 years) were reported worldwide due to smoking [4]. This global estimate translated into a proportion of cancer mortality attributable to smoking of 21%, representing 32% and 8% of adult cancer mortality in males and females respectively. In high-resource countries, tobacco smoking has been estimated to cause approximately 30% of all human cancers [5-7]. Table 2.2.1 shows the regional distribution of cancer mortality attributable to smoking, indicating higher values in more developed regions, where widespread consumption of cigarettes had an earlier start in the 20th century. A pronounced disparity in cancer mortality attributable to smoking is seen between males and females, reflecting dissimilar incidence rates caused by the fact that in most countries women took up smoking a few decades after men and never reached their consumption levels.

Lung cancer has the highest smoking-attributable fraction among all neoplasms induced by tobacco smoking, and although not all cancer at this site is caused by smoking, a glance at the lung cancer incidence and mortality rates by country and region reveals the cumulative hazard of smoking and the underlying dimension of the tobacco epidemic in those areas of the world. Table 2.2.2 displays countries and populations with the highest and lowest age-standardised lung cancer incidence rates in males and females by continent. Age-standardised lung cancer incidence and mortality rates (per 100 000), on average, are higher in developed (54.9 and 47.6 respectively) than less-developed regions (25.9 and 22.9 respectively) reflecting past uptake and cessation of smoking in those populations [8]. Countries in these regions are at different stages of the tobacco epidemic and its subsequent effect on lung cancer mortality [9](Figure 2.2.1). In many medium- and low-resource countries, the burden of tobacco-related cancer is lower, given the relatively recent start of the smoking epidemic, which will result in a greater number of cancers in the future. In several low/medium-resource countries, however, the epidemic of tobacco-related lung cancer has already reached its maturity: for example, Kazakhstan with an incidence rate of 77.4 and a mortality rate of 66.8, Armenia (58.9 and 50. 4 respectively) and the Philippines (50. 2 and 46.6 respectively) in South-Central Asia and South

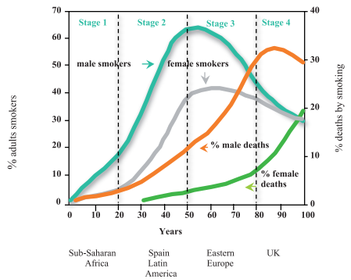


Fig. 2.2.1 *Stages of the tobacco epidemic*
Deaths from tobacco related disease vary markedly from country to country and these differences are determined, to a great extent, by differences in the rates of smoking initiation two to seven decades earlier and the rates of cessation five and more years prior to the year of the death rate. As a result, differences in the prevalence of current smoking for a given year in different countries may not match differences in lung cancer rates in the same year. These differences have been described as falling into four stages of the tobacco epidemic (adapted from Lopez et al., 1994)

east Asia respectively as compared to the USA (61.9 and 48.7 respectively), France (52.6 and 47.5 respectively) and Japan (38.1 and 32.4 respectively) in North America, Western Europe and Eastern Asia [8].

Tobacco use

About 1.3 billion people smoke globally [10], making tobacco a major avoidable cause of disease and mortality worldwide. Gajalakshmi and colleagues [11], using earlier estimates of the global prevalence of smoking (1.1 billion people in 1995) estimated the proportion of daily smokers ≥15 years of age to be 29% of the world population in 1995 (including users of cigarettes and/or bidis in South Asia). The majority of those daily smokers resided in less-developed areas of the world, with wide variations in prevalence across regions in both males and females, but with overall prevalence being higher in males (47%) than in females (11%). However, the proportion of male daily smokers ≥15 years of age can be significantly higher than the above average in many countries: 82% in Indonesia, 78% in the Philippines and 72% in Colombia, to illustrate a few high estimates [11]. The percentage of daily smokers ≥15 years of age is lower in the European Union but with contrasting differences by sex and across countries (Figure 2.2.2). The preceding data suggest that if smoking patterns continue unaltered, the habit will cause approximately 1 000 000 000 deaths this century, representing a tenfold increase over the previous century [12]. These data also highlight how large the population is that would benefit from interventions aimed at reducing tobacco use. Given the number of smokers worldwide, achieving tobacco abstinence is an urgent public health priority with no geographic limits.

World production of tobacco is approximately 6.6 million tonnes annually, with China being the leader in production (41% of total) [13].

WHO Region*	Smoking-Attributable Cancer Mortality					
	Male		Female		Total	
	N	%	N	%	N	%
Europe C	133 000	49	11 000	5	144 000	29
Europe B	72 000	44	9 000	8	81 000	29
Southeast Asia (India and others)	174 000	43	16 000	4	190 000	24
Southeast Asia B	45 000	43	2 000	4	47 000	24
North America	131 000	42	80 000	26	211 000	34
Western Europe	225 000	40	47 000	10	272 000	27
Western Pacific A	69 000	36	18 000	13	87 000	27
Eastern Mediterranean B	12 000	30	2 000	7	14 000	21
Eastern Mediterranean B	26 000	28	3 000	3	29 000	16
Americas B	48 000	27	12 000	6	60 000	17
Western Pacific (China and others)	209 000	20	35 000	5	244 000	14
Africa E	23 000	17	5 000	4	28 000	10
Africa D	5 000	9	400	1	5 400	5
Americas D	2 000	6	300	1	2 300	3

Table 2.2.1 *Estimated cancer mortality attributable to smoking by WHO Region in 2000*
** A, very low child mortality and very low adult mortality; B, low child mortality and low adult mortality; C, low child mortality and high adult mortality; D, high child mortality and high adult mortality; E, high child mortality and very high adult mortality.*
From Ezzati et al., 2005 (WHO estimates reported)

Continent	Country	Males		Country	Females	
		ASR (W)	Std. Error		ASR (W)	Std. Error
Highest rates						
Africa	Tunisia, Centre	37.1	2.05	Zimbabwe, Harare	4.8	0.69
	Algeria, Setif	19.9	1.05	Uganda, Kyadondo	3.8	0.69
America	USA, New Orleans: Black	96.6	3.30	USA, Kentucky	50.3	0.59
North	USA, Kentucky	90.1	0.84	USA, Pennsylvania: Black	46.8	1.09
America	Argentina, Bahia Blanca	45.5	2.42	Brazil, Brasilia	12.5	0.75
Central & South	Brazil, Sao Paolo	33.5	0.42	Brazil, Sao Paolo	11.7	0.21
Asia	Turkey, Izmir	74.5	0.98	China, Nangang District	34.6	1.20
	China, Guangzhou City	71.9	1.19	Thailand, Lampang	27.0	1.09
Europe	Poland, Kielee	76.9	1.39	UK, Scotland	34.9	0.39
	Croatia	72.1	0.67	UK, England: Merseyside	31.9	0.54
Oceania	French Polynesia	62.3	4.06	French Polynesia	23.6	2.45
	Australia, Northern Territory	51.4	4.07	Australia, Northern Territory	22.7	2.87
Lowest rates						
Africa	Zimbabwe, Harare	9.5	0.90	Tunisia, Centre	1.7	0.43
	Uganda, Kyadondo	4.8	0.84	Algeria, Setif	1.7	0.29
America	USA, California, L.A.: Hispanic	23.2	0.66	USA, California, L.A.: Hispanic	12.3	0.41
North	USA, New Mexico: Amer. Indian	12.2	1.91	USA, New Mexico: Amer. Indian	3.9	0.96
America	Ecuador, Quito	7.9	0.56	Costa Rica	4.5	0.24
Central & South	Peru, Trujillo	5.9	0.83	Ecuador, Trujillo	4.1	0.37
Asia	India, Mumbai	9.7	0.23	India, Karunagappally	2.3	0.51
	India, Nagpur	7.5	0.45	India, Trivandrum	1.7	0.24
Europe	Portugal, Porto	30.5	0.56	Spain, Albacete	3.3	0.53
	Sweden	20.9	0.24	Spain, Granada	3.3	0.33
Oceania	Australia, Capital Territory	25.6	1.77	Australia, South	16.7	0.54
	New Zealand	35.3	0.53	Australia, Capital Territory	13.7	1.24

***Table* 2.2.2** *Highest and lowest lung cancer age-standardized (world) incidence rates (per 100 000) in males and females by continent as reported in CI5, Vol IX*

Location	Production (tonnes / annum)	Import** tonnes	Export** tonnes
China	2 688 500	69 404	161 850
Brazil	889 426	7 900	616 468
India	550 000	1 152	231 570
Europe	498 916	126 578	253 177
USA	290 170	261 067	152 978
Russian Federation	80	291 807	1 739
World	6 580 828		

***Table* 2.2.3** *Tobacco production, imports and exports in 2005*
** Data source: http://faostat.fao.org/*
*** Data source: http://unstats.un.org/unsd/comtrade/*

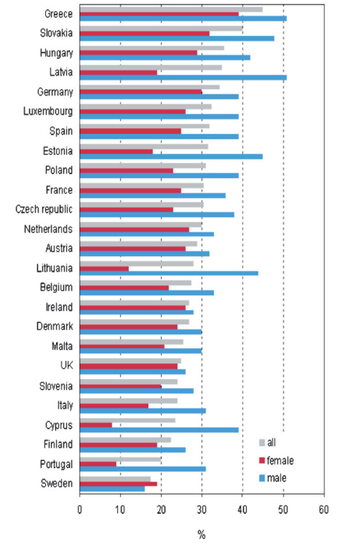


***Fig.* 2.2.2** *Percentage of daily smokers age 15+ in the EU-25 (WHO-HFA, 2005)*
Kaiser S, Gommer AM (RIVM). Percentage of daily smokers age 15+ in the EU-25. In: EUPHIX, ECHI Indicator & EUphact. Bilthoven: RIVM, <http://www.euphix.org> ECHI Indicator & EUphact\ Determinants of health\ Health behaviours\ Smoking, 13 March 2007

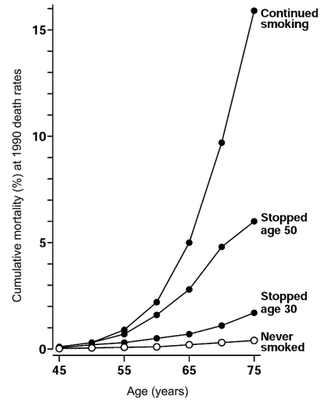


***Fig.* 2.2.3** *Lung cancer mortality in UK current and former male smokers by age at quitting*
Adapted from Peto *et al.*, 2000

Substances	Tobacco smoke	Smokeless tobacco ng / g
Volatile aldehydes		
Formaldehyde	70 - 100 µg	1600 - 7400
Acetaldehyde	500 - 1400 µg	1400 - 27 400
Crotonaldehyde		200 - 2400
N-Nitrosamines		
N-Nitrosodimethylamine	2 - 1000 ng	nd - 270
N-Nitrosodiethylamine	nd - 2.8 ng	
N-Nitrosopyrrolidine	3 - 110 ng	nd - 860
Tobacco specific nitrosamines		
N'Nitrosonornicotine (NNN)	45 - 58 000 ng/g	400 - 3 085 000
4-(Methylnitrosamino)-1-(3-pyrydyl)-1-butanone (NNK)	nd - 10 745 ng/cigarette	0.07 - 22 900
4-(Methylnitrosamino)-1-(3-pyrydyl)-1-butanol (NNAL)		
N'Nitrosoanabasine (NAB)		present - 2 370 000
Metals		
Nickel	nd - 600 ng	180 - 2700
Cadmiun	7 - 350 ng	
Polonium 210	0.03 - 1.0 pCi/g	0.16 - 1.22
Uranium 235 and 238		2.4 and 1.91
Arsenic	40 - 120 µg	500 - 900
Polycyclic aromatic hydrocarbons		
Benzo[a]pyrene	20 - 40 ng	> 0.1 - 90 ng/g
Benzo[a]anthracene	20 - 70 ng	
Benzo[b]fluoranthene	4 - 22 ng	
Chrysene		
Dibenzo[a,l]pyrene	1.7 - 3.2 ng	
Dibenzo[a,h]anthracene	4 ng	

Table 2.2.4 *Concentration of carcinogenic agents in mainstream tobacco smoke of non-filtered cigarettes and in smokeless tobacco*
Numbers in black derived from IARC Monographs volumes 83 and 89; numbers in red from Hoffman, Hoffman and El-Bayoumy, 2001

Brazil, Europe and India are major exporters in tobacco trade (Table 2.2.3). At present, cigarette smoking is by far the most common form of smoking tobacco worldwide, with a few important exceptions where other products prevail (e.g. bidi smoking in India, narghile among men in West Asia and North Africa). The use of cigars and pipe smoking is considerably lower and has declined over time. In India, the third-largest producer and consumer of tobacco in the world, the most common form of tobacco smoking is bidi smoking as opposed to smoking of manufactured cigarettes.

Smoking and cancer risk

All of the above-mentioned forms of tobacco smoking are harmful to health and have been unquestionably found to cause cancer. However, this link was not established until 1950, following the observed dramatic increase in lung cancer incidence in a few countries in Europe, the USA and Australia in the first half of the last century. The seminal large-scale studies of Wynder and Graham [14] and Doll and Hill [15] compared the smoking habits, a proposed possible cause at the time, in lung cancer cases and other individuals without cancer of the lung. Their results confirmed cigarette smoking as a cause of lung cancer: the frequency of smoking and amount smoked were significantly higher in patients with cancer of the lung than in controls. These results were promptly followed by many other studies and led to the 1964 Surgeon General's Report which established the causal link for the first time [16].

Duration of smoking is the strongest determinant of excess lung cancer risk in smokers [1]. The majority of lung cancer cases have smoked for decades. In the original British study and in the study by Wynder and Graham, 43–50% of lung cancer cases had smoked ≥40 years. Doll and Peto (1978) have calculated from the male British doctors' data an annual excess lung cancer incidence of 0.01%, 0.2% and 1% for 15, 30 and 45 years of smoking respectively. The excess risk of lung cancer increases proportionally with the number of cigarettes smoked [1].

Tobacco smoking raises the excess risk of all histological types of lung cancer [1]. However, there has been a shift over time in the frequency distribution of the major histological types observed in smoking-induced lung cancer cases. In more recent studies the proportion of adenocarcinoma of the lung has increased, considerably decreasing the ratio of squamous to adenocarcinoma cases typically reported in early studies. Several explanations have been proposed, including changes in the composition of cigarettes and in the nitrite content of tobacco used in manufactured cigarettes. Lower nitrate content may have caused modifications in the way people smoke by inducing deeper inhalation to compensate for the reduced nicotine content; smoke inhaled in this fashion may reach more peripheral parts of the bronchi. In addition, changes in the nitrate content in US blends of tobacco used to make cigarettes in more recent years may have increased the formation of nitrosamines during tobacco storage, processing and smoking. Nitrosamines, such as NNK, are carcinogens that induce the formation of adenocarcinoma [17,18].

Cigar and/or pipe smoking, with or without inhalation, causes lung cancer, and the risk increases with amount smoked and duration of smoking [1]. Inhalation increases the risk to a greater extent, and smokers who have switched from cigarettes to cigar/pipe have reported a higher risk of lung cancer than exclusive cigar/pipe smokers. Cigar or pipe smoking has also been associated with oral cancer, oropharyngeal, hypopharyngeal, laryngeal and oesophageal cancers [1]. Similarly, bidi smoking is associated with lung, oral, laryngeal, oesophageal and stomach cancer with the risk increasing with amount smoked and duration [1].

Mechanisms of carcinogenesis

Tobacco smoke is the most common source of carcinogens to humans. It includes about 10^{10} particles per ml and 4800 compounds, of which 66 are carcinogens [19,20]. Of these, polycyclic aromatic hydrocarbons and tobacco specific nitrosamines are the most important. In addition, inducers of reactive oxygen species like NO, NO_2, peroxynitrite and nitrosamines initiate, promote or amplify oxidative DNA damage [21-23]. Chemicals such as aromatic amines, benzene and heavy metals, independently established as carcinogenic to humans, are present in tobacco smoke as well (Table 2.2.4). Most carcinogens are oxygenated by cells using cytochrome P54 enzymes to be transformed into excretable forms. Electrophilic oxygenated carcinogens can form covalently bound DNA adducts. Six carcinogens present in tobacco smoke are known to form

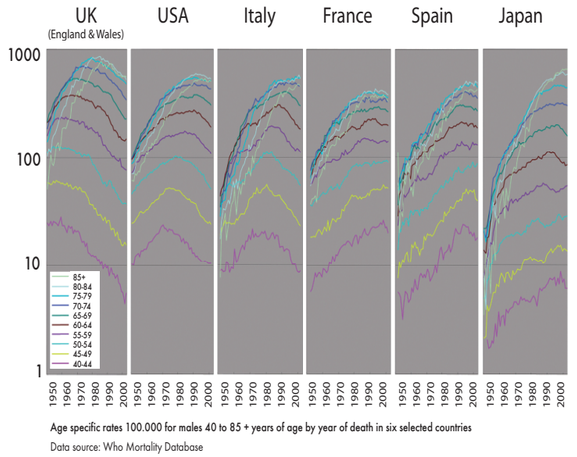


Fig. 2.2.4 *Trends in lung cancer mortality by age group and year of death in males*
Recent trends in lung cancer mortality rates differ by country even among high resource countries. Trends in birth-cohort specific lung cancer mortality rates generally follow trends in smoking behaviour by birth cohort with lag time of approximately 20 years. For several of the countries depicted, rates first began to decrease among younger age groups, and these decreasing trends gradually extended to older age groups (UK, USA, Italy). In France, Spain and Japan, decreasing trends were observed among some older age groups but younger age groups show increasing mortality rates.

DNA adducts in human tissue: benzo[a]pyrene (BaP), NNK, NDMA (N-nitrosodimethylamine), NNN (N'-nitrosonornicotine), ethylene oxide and 4-aminobiphenyl [22]. Cells can remove adducts and repair DNA. The balance between metabolic activation and metabolic detoxification and the efficiency of DNA repair pathways may define cancer risk in individuals exposed to polycyclic aromatic compounds, for example [22]. In summary, the chronic presentation of carcinogens through sustained smoking can lead to molecular lesions which in the presence of reduced metabolic detoxification can diminish repair capability, overwhelming cellular defenses and leading to lung cancer [22].

Pooled estimates of smoking-associated cancer risk

A recent meta-analysis of 177 case-control studies, 75 cohorts and 2 nested case-control studies reported in IARC Monograph 83 [1] has provided pooled estimates of the risk associated with smoking for 13 different cancer sites [24]. Accordingly, the pooled magnitude of the association in current smokers as compared to never smokers was RR = 8.96 (95% CI 6.73–12.11) for lung cancer, RR = 6.98 (95% CI 3.14–15.52) for laryngeal cancer, RR = 6.76 (95% CI 2.86–15.98) for pharyngeal cancer, 3.57 (95% CI 2.63–4.84) for the upper-digestive tract and RR = 3.43 (95% CI 2.37–4.94) for oral cancer. Table 2.2.5 shows pooled estimates from the above-mentioned meta-analysis stratifying results by sex and demonstrating very similar risks of cancer associated with smoking in males and females.

Smoking cessation

A benefit of quitting tobacco smoking in adulthood has been shown for lung cancer and other major cancers causally associated with the habit (Figure 2.2.3; [22]). This result emphasises the need to devise anti-smoking strategies that address avoidance of the habit among the young people as well as reduction of smoking and quitting among adults. In fact, the decline in tobacco consumption 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 occurred primarily by increase in quitting at middle age (Figure 2.2.4). The great challenge for the control of tobacco-related cancer, however, lies today in low-resource countries, in particular in China and the other Asian countries; the largest increase in tobacco-related cancers has been forecast in this region of the world [25]. Despite growing efforts from medical and public health institutions and the growing involvement of non-governmental organisations, the fight against the spread of tobacco smoking among women and in low-resource countries remains the biggest and most difficult challenge of cancer prevention to face in the coming decades.

Cancer site	Sex	Pooled* Relative Risk (RR)	95% Confidence Interval
Lung	M	9.87	6.85, 14.24
(C 34)**	F	7.58	5.36, 10.73
Upper digestive tract	M	3.52	1.94, 6.37
(C10-15)	F	3.80	1.97, 7.33
Esophagus	M	2.52	1.81, 3.52
(C15)	F	2.28	1.51, 3.44
Stomach	M	1.74#	1.46, 2.07
(C16)	F	1.45	1.20, 1.75
Pancreas	M	1.63	1.32, 2.03
(C16)	F	1.73	1.31, 2.30
Liver	M	1.85	1.21, 2.83
(C22)	F	1.49	1.12, 1.98
Lower urinary tract	M	2.80	2.01, 3.92
(C65-67)	F	2.73	1.82, 4.10

Table 2.2.5 *Human cancers associated with smoking*
** Estimates as reported in Gandini et al., 2008 [24]*
*** Cancer site ICD- 10*
 # Statistically significant heterogeneity by sex at this cancer site

REFERENCES

1. IARC. (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking*. Iyon, France: International Agency for Research on Cancer.

2. U.S. Department of Health and Human Services (2006). *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

3. U.S. Department of Health and Human Services (2004). *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

4. Ezzati M, Henley SJ, Lopez AD, et al. (2005). Role of smoking in global and regional cancer epidemiology: current patterns and data needs. *Int J Cancer* 116: 963-971.

5. International Union Against Cancer. *Deaths from smoking*. Available from: http://www.deathsfromsmoking.net/ Date Accessed: November 14, 2007.

6. IARC (2007). *IARC Working Group Reports, Volume 3, Attributable Causes of Cancer in France in the year 2000*. Iyon, France: International Agency for Research on Cancer.

7. Doll R, Peto R, Boreham J, et al. (2005). Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br J Cancer* 92: 426-429.

8. Ferlay J, Bray F, Pisani P, et al. *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide*. Available from: http://www-dep.iarc.fr/

9. Lopez AD, Collishaw NE, Piha T (1994). A descriptive model of the cigarette epidemic in developed countries. *Tob Control* 3: 242-247.

10. World Health Organization Tobacco Free Initiative. *Why is tobacco a public health priority?* Available from: http://www.who.int/tobacco/health_priority/en/index.html Date Accessed: October 14, 2008.

11. Gajalaksmi CK, Jha P, Ranson K, et al. (2000). Global patterns of smoking and smoking attributable mortality. In: Jha P, Chaloupka FJ, eds., *Tobacco control in developing countries*. Oxford: Oxford University Press. 11-39.

12. Peto R, Lopez A (2001). Future worldwide health effects of current smoking patterns. In: C.E.Koop, C.E.Pearson, M.R.Schwartz, eds., *Critical Issues in Global Health*. San Fransisco: Joosey-Bass. 154-161.

13. Food and Agriculture Organization of the United Nations. Available from: http://faostat.fao.org Date Accessed: September 12, 2008.

14. Wynder EL and Graham EA (1950). Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. *J Am Med Assoc* 143: 329-336.

15. Doll R and Hill AB (1950). Smoking and carcinoma of the lung; preliminary report. *Br Med J* 2: 739-748.

16. U.S. Surgeon General's Advisory Committee on Smoking and Health (1964). *Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service*. Washington, DC: U.S. Dept. of Health, Education, and Welfare, Public Health Service.

17. Hecht SS (1999). Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst* 91: 1194-1210.

18. Wynder EL and Hoffmann D (1998). Re: Cigarette smoking and the histopathology of lung cancer. *J Natl Cancer Inst* 90: 1486-1488.

19. Hoffmann D, Hecht SS (1990). Advances in tobacco carcinogenesis. In: Beland FA, Cooper CS, Grover PL, eds., *Chemical carcinogenesis and mutagenesis*. Berlin: Springer-Verlag. 63-1002.

20. Hoffmann D, Hoffmann I, El-Bayoumy K (2001). The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. *Chem Res Toxicol* 14: 767-790.

21. Zhang J, Liu Y, Shi J, et al. (2002). Side-stream cigarette smoke induces dose-response in systemic inflammatory cytokine production and oxidative stress. *Exp Biol Med* 227: 823-829.

22. IARC (2007). *IARC Handbooks of Cancer Prevention, Tobacco Control. Volume 11, Reversal of Risk After Quitting Smoking*. Iyon, France: International Agency for Research on Cancer.

23. Church DF and Pryor WA (1985). Free-radical chemistry of cigarette smoke and its toxicological implications. *Environ Health Perspect* 64: 111-126.

24. Gandini S, Botteri E, Iodice S, et al. (2008). Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* 122: 155-164.

25. Peto R, Chen ZM, Boreham J (1999). Tobacco–the growing epidemic. *Nat Med* 5: 15-17.

2.3 Passive Smoking

SUMMARY

> Passive smoking causes lung cancer and non-neoplastic diseases, such as coronary heart disease, chronic respiratory symptoms, and adverse effects on fetal growth.

> The epidemiological evidence is strongly supported by the chemistry of tobacco smoke, cancer bioassays and mechanisms of tobacco-related carcinogenesis.

> Nearly half of never-smokers are exposed to tobacco smoke at home and at work; bars and restaurants can be particularly polluted. About 10–15% of lung cancers in never-smokers are attributed to passive smoking.

> The WHO Framework Convention on Tobacco Control calls for protection from exposure to tobacco smoke.

> After the introduction of strict national smoking bans, beneficial effects on the respiratory and cardiovascular system have been shown

There is no doubt that passive smoking is carcinogenic to humans. Many national and international scientific expert committees have concluded that passive smoking (also called secondhand smoke, involuntary smoking or environmental tobacco smoke) causes lung cancer in humans. Like active smoking, passive smoking has also been causally associated with a number of non-neoplastic diseases, such as coronary heart disease, chronic respiratory symptoms, and adverse effects on fetal growth [1,2].

Constituents of secondhand tobacco smoke

Secondhand tobacco smoke is a mixture of exhaled mainstream smoke and sidestream smoke diluted with ambient air. Involuntary smoking involves inhaling the same carcinogens that are found in mainstream smoke, including benzo[a]pyrene, tobacco specific nitrosamines (NNN and NNK), and benzene (Table 2.3.1). Secondhand tobacco smoke also contains nicotine and other toxic components.

Measurement of exposure

There are several useful indicators of exposure to secondhand smoke, ranging from surrogate indicators to direct measurements of exposure and of biomarkers that reflect dose (Table 2.3.2). Assessment of exposure to secondhand smoke in epidemiological studies of cancer is often based on questionnaire information, and exposure may be further characterised by source: spousal or parental exposure at home, workplace exposure and exposure in social settings.

The most widely studied components of secondhand smoke in the air have been respirable suspended particles and carbon monoxide; both are nonspecific indicators of secondhand smoke. Nicotine in air, by contrast, is highly specific because smoking is its only source.

Cotinine is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke; it is an integrative measure that reflects recent exposure to secondhand smoke in all environments and has also been used to assess misclassification of smoking status as derived from questionnaire information.

Exposure to passive smoking

Smoking prevalence (see *Tobacco smoking*, Chapter 2.2) can be used as a surrogate measure for exposure to SHS. The Global Youth Tobacco Survey (GYTS) data from 137 countries and territories during 2000–2007 among students aged 13–15 years who had never smoked indicated that nearly half of never-smokers were exposed to SHS at home (46.8%), and a similar percentage were exposed in places other than the home (47.8%) (Table 2.3.3); [3].

An estimated 7.5 million workers in the European Union and 24.6 million indoor workers in the USA are exposed to secondhand smoke at work, and environmental tobacco smoke was the second most prevalent carcinogen at the workplace in the EU [4,5].

Based on large numbers of measurements made in various indoor environments in the USA between 1957 and 1991, the average concentrations of nicotine in air showed about 100-fold variation, i.e. from 0.3–30 μg/m^3. The average concentrations of nicotine in air of homes with one or more smokers typically ranged from 2 to 10 μg/m^3 [6]. A review of exposure to secondhand smoke in bars, bowling alleys, billiard halls, betting establishments and bingo parlours found that nicotine concentrations in these places were 2.4 to 18.5 times higher than in offices or residences, and 1.5 to 11.7 times higher than in restaurants (Table 2.3.4; [7]). Personal exposure to respirable suspended particles associated with secondhand tobacco smoke was determined for workers in 11 countries and the mean concentrations ranged from 24 to 112 μg/m^3 [8].

Epidemiology of passive smoking and cancer

More than 50 studies of involuntary smoking and lung cancer risk in never-smokers, especially spouses of smokers, have been carried out in many countries. A meta-analysis of all the studies available to the IARC Monographs Working Group in 2002 showed that there is a statistically significant and consistent association between exposure to secondhand tobacco smoke from the spouse who smokes and lung cancer risk in spouses of smokers (women, RR, 1.24, 95% CI 1.14–1.34; men RR, 1.37, 95% CI 1.02–1.83), after controlling for some potential sources of bias and confounding. The magnitude of the observed risk is reasonably consistent with predictions based on studies of active smoking.

Case–control and cohort studies published after this comprehensive meta-analysis have further corroborated an increased risk of lung cancer for secondhand tobacco smoke exposure [9,10]. A pooled analysis of the two largest case–control studies with a total of more than 1200 never-smoking lung cancer patients found an increased risk of lung cancer for secondhand tobacco smoke exposure from the three main sources: spousal, workplace and social [9].

A recent meta-analysis of more than twenty studies of workplace exposure to secondhand smoke reported a summary relative risk of 1.24 (95% CI 1.18–1.29) for all studies, and of 1.59 when only the studies that adjusted for other occupational carcinogens were included. The meta-analytic result for the highest exposure in terms of cumulative exposure or intensity of exposure as provided by 7 studies was 2.01 (1.33–2.60) (Table 2.3.5; [11].

In 2002, the IARC Working Group concluded that the evidence linking passive smoking to other cancer sites was inconsistent. Since the US Surgeon General's Report in 1964 [12] established a causal link between cigarette smoking and lung cancer, more and more cancer sites have been causally associated with smoking of different tobacco products (see *Tobacco smoking*, Chapter 2.2). History may repeat itself in terms of causal associations between passive smoking and cancer sites other than lung. Several studies published since 2002 have suggested an association between passive smoking and cancers of the upper aero-digestive tract, the pancreas, urinary bladder, kidney, cervix, and childhood leukaemias. It had been suggested that exposure to secondhand tobacco smoke may also increase the risk of breast cancer. However, a recent prospective study and a meta-analysis including seven additional studies with prospectively recorded exposure information did not observe an increased incidence of breast cancer in never smoking women exposed to secondhand smoke (RR, 0.99, 95% CI 0.93–1.05) [13]. Volume 100 of the *IARC Monographs* (see *Identifying human carcinogens*, Chapter 2.1) will provide an opportunity to revisit the evidence for passive smoking and cancer sites other than lung.

Mechanisms of tobacco-related carcinogenesis

Metabolites of the tobacco specific nitrosamine NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, have been found to be elevated in the urine of involuntary smokers [14], and studies in humans have shown that concentrations of adducts of carcinogens to biological macromolecules are higher in adult involuntary smokers and in the children of smoking mothers than in individuals not exposed to secondhand tobacco smoke. Protein adduct concentrations in fetal cord blood correlate with those in maternal blood [15].

In mice, inhalation of sidestream and mainstream smoke and implants of condensates of sidestream smoke in rat lungs have induced lung tumours; topical application of sidestream condensates has produced skin tumours in mice [1]. Together, these data provide supportive evidence for a causal link between exposure to secondhand tobacco smoke and development of lung cancer.

Burden of passive smoking-related lung cancer

In the US, 3423 annual lung cancer deaths in never-smokers are attributed to spousal smoking [16]. For Europe, Vineis et al [17] estimated the proportion of lung cancers in never- and ex-smokers attributable to secondhand smoke in the EPIC (European Prospective Investigation into Cancer and Nutrition) population to be between 16 and 24%, mainly due to work-related exposure. The proportion of lung cancers attributable to secondhand smoke from spouse and workplace among never-smokers in France was estimated to be 12.2% in men and 15% in women [18]. Work-related exposure to secondhand smoke was calculated to account for 5.7% of lung cancers in never-smokers in the USA [19].

Cancer control

Primary prevention is the only effective tool to decrease the burden of cancer related to passive smoking. General tobacco control interventions will also reduce exposure to secondhand smoke. With the Framework Convention on Tobacco Control (FCTC) the WHO has initiated a process to ban smoking globally ([20]; see Tobacco Control section). Moreover, the FCTC also addresses passive smoking specifically in Article 8, which calls "for protection from exposure to tobacco smoke in indoor workplaces, public transport, indoor public places and, as appropriate, other public places." Since the ratification of this first global treaty on health, several jurisdictions have introduced strict smoking bans (including Ireland, Norway, Italy, Sweden, Scotland, England, Wales and Northern Ireland) and other jurisdictions introduced bans in 2008 (e.g. France, and Bavaria with coverage including the Oktoberfest). The report of the U.S. Surgeon General [2] concluded that the scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke. While eliminating smoking in indoor spaces fully protects non-smokers from exposure to secondhand smoke, separating smokers from non-smokers, cleaning the air and ventilating buildings cannot eliminate exposures of non-smokers to secondhand smoke.

Beneficial effects of workplace bans

Comparing pre- and post-ban exposure to secondhand smoke, several studies have showed substantial decreases in respirable suspended particles, nicotine, PAH, benzene and 1,3-butadiene in air and biomarkers of exposure (cotinine, exhaled carbon monoxide) (e.g. [21]; Figure 2.3.1). One of these studies further demonstrated significant improvements in measured pulmonary function tests and significant reductions in self-reported symptoms in non-smoking barmen after the ban [22]. Recently, studies reported a significant reduction in acute coronary events after the introduction of strict smoking bans in Italy and Scotland [23,24].

In the study from Scotland, persons who had never smoked reported a decrease in the exposure to secondhand smoke that was confirmed by a decrease in their serum cotinine levels, and the largest reduction in the number of hospital admissions for acute coronary syndrome was observed among persons who had never smoked.

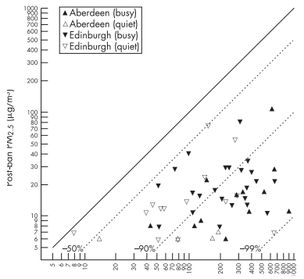


***Fig.* 2.3.1** *Log-log scatter plot comparing particulate matter, 2.5 mm in diameter PM2.5) concentrations at pre- and post-ban visits. Diagonal dotted lines indicate various ratios of reduction*

Compound	Type of Cigarette						
	Regular	Light	Extra light	Ultra light	Regular/ light	Regular/ extra light	Regular/ ultra light
IARC Group 1 carcinogens							
Benzene (µg/cig.)	222.0	250.0	260.0	296.0*	0.9	0.9	0.8*
Cadmium (ng/cig.)	438.0	484.0	502.0*	627.0*	0.9	0.9*	0.7*
2-Naphthylamine (ng/cig.)	157.0	147.0	175.0	186.0	1.1	0.9	0.8
Nickel (ng/cig.)	34.3	45.1	74.4*	73.0*	0.8	0.5*	0.5*
Chromium (ng/cig.)	61.0	62.0	121*	82.9*	1.0	0.5*	0.7*
Arsenic (ng/cig.)	ND	NQ	ND	ND			
4-Aminobiphenyl (ng/cig.)	22.1	19.5	21.0	21.2	1.1	1.1	1.0
Formaldehyde (µg/cig.)	378.0	326.0	414.0	431.0	1.2	0.9	0.9
1,3-Butadiene (µg/cig.)	196.0	185.0	264.0	299.0	1.1	0.7	0.7
Benzo[a]pyrene (ng/cig.)	48.8	98.3	92.2	113.0	0.5	0.5	0.4
NNK (ng/cig.)	95.2	153.4	38.3	34.7	0.6	2.5	2.7
NNN (ng/cig.)	23.3	53.9	43.7	45.2	0.4	0.5	0.5
IARC Group 2A carcinogens							
Lead (ng/cig.)	54.8	39.4	22.3	18.5	1.4	2.5	3.0
IARC Group 2B carcinogens							
Acetaldehyde (µg/cig.)	1416.0	1454.0	1449.0	1492.0	1.0	1.0	0.9
Isoprene (µg/cig.)	1043.0	1164.0	1060.0	1172.0	0.9	1.0	0.9
Catechol (µg/cig.)	130.0	117.0	149.0	148.0	1.1	0.9	0.9
Acrylonitrile (µg/cig.)	78.6	85.6	74.1	81.8	0.9	1.1	1.0
Styrene (µg/cig.)	74.0	84.7	87.5	108.0*	0.9	0.8	0.7*

***Table* 2.3.1** *Yields of IARC carcinogens in sidestream smoke of regular-sized Canadian cigarettes, International Organization for Standardization (ISO)[a] machine-smoking parameters[b]*
Adapted from IARC, 2004. (Source: Government of British Columbia, 2003)
NNN, N1-nitrosonornicotine; NNK, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; ND, not detectable
a ISO smoking parameters: 35 mL puff in 2 sec, interval 60 sec, ventilation holes not blocked
b Reporting period: year 1999

Measure	Indicator
Surrogate measures	Prevalence of smoking in men and women
Indirect measures	Report of secondhand tobacco smoke exposure in the home and in the workplace Smoking in the household Number of smokers Smoking by parent(s) Number of cigarettes smoked Smoking in the workplace Presence of secondhand tobacco smoke Number of smokers
Direct measures	Concentration of secondhand tobacco smoke components Nicotine Respirable particles Other markers Biomarker concentrations Cotinine Carboxyhaemoglobin

***Table* 2.3.2** *Indicators of exposure to secondhand tobacco smoke*
From Samet & Yang [25]

WHO region	All students who never smoked, % (95% CI)	Never smokers	
		Exposed to SHS at home, % (95% CI)	Exposed to SHS in places other than home, % (95% CI)
Africa (n = 103 906)	79.3 (75.5-82.7)	22.6 (19.5-26.1)	38.2 (34.2-42.4)
Americas (n = 236 687)	54.9 (50.8-59.0)	39.1 (31.6-47.2)	41.7 (38.9-46.6)
Eastern Mediterranean (n = 92 075)	84.4 (80.2-87.8)	37.0 (33.7-40.4)	42.9 (39.0-47.0)
Europe (n = 154 759)	69.0 (65.0-70.8)	71.5 (64.6-76.0)	79.4 (73.9-83.7)
South-East Asia (n = 91 459)	87.4 (83.8-90.2)	42.8 (35.2-49.7)	38.8 (35.9-41.7)
Western Pacific (n = 68 717)	69.8 (66.1-73.2)	57.3 (48.5-65.3)	52.6 (49.2-56.1)
Total (N = 747 603)	80.3 (76.7-83.4)	46.8 (39.9-52.5)	47.8 (44.1-51.3)

***Table* 2.3.3** *Exposure* to second-hand smoke (SHS) at home and in places other than home and susceptibility to initiating smoking among students aged 13-15 years who had never smoked cigarettes, by World Health Organization (WHO) region – Global Youth Tobacco Survey, 2000-2007*
**Determined by answers to two questions: "During the past 7 days, on how many days have people smoked in your home, in your presence?" and "During the past 7 days, on how many days have people smoked in your presence, in places other than in your home?" Students who answered 1 or more days were considered exposed to SHS.*
CI= Confidence Interval

Type of Workplace	Number of studies	Number of establishments sampled	Weighted mean*	Range	Ratio†
Offices	22	940	4.1	0.8-22.1	1.0
Residences	7	91	4.3	1.6-21.0	1.0
Restaurants	17	402	6.5	3.4-34.0	1.6
Betting establishments	3	4	9.8	8.0-10.7	2.4
Bowling alleys	2	6	10.5	10.1-10.7	2.6
Billiard halls	2	3	13.0	9.8-19.4	3.2
Bars	10	27	31.1	7.4-105.4	7.6
Bingo parlours	2	3	76.0	65.5-81.2	18.5

Table 2.3.4 *Indoor air concentrations of nicotine (µg/m3) in a variety of workplaces*
**Mean of average nicotine values reported in individual studies weighted by number of establishments sampled in each study.*
†Ratio of weighted mean nicotine concentration in residences, restaurants, bowling alleys, billiard halls, betting establishments, bars, and bingo parlours to weighted mean nicotine concentration in offices.
Adapted from Siegel and Skeer, 2003 [7]

Reference	Sex	Exposure Measure	RR (95% CI)
Boffetta et al.	both	≥89 level x hours/day x years[b]	2.07 (1.33-3.21)
Johnson et al.	women	≥ 64 smokers x years	1.58 (0.6-4.0)
Kabat et al.	men	smokers x hours/week x years[c]	1.21 (0.47- 3.13)
Kabat et al.	women	smokers x hours/week x years[c]	1.35 (0.64-2.84)
Kalandidi et al.	women	duration x number of co-workers[d]	1.08 (0.24-4.87)
Kreuzer et al.	both	>100.6 level x hours/day x years[b]	2.64 (1.07-6.54)[e]
Lee et al.	men	Average to a lot	0.46 [0.05-4.65][f]
Zhong et al.	women	≥ 4 co-workers smoked	3.0 (1.8-4.9)
Meta-analysis Fixed effects Mixed effects			 2.01 (1.55-2.60) 2.01 (1.33-2.60)

Table 2.3.5 *Relative risk (RR) and 95% confidence intervals (95%CI) results for highest cumulative or intensity of exposure groups[a]*
[a]The measure of exposure used to categorize workers varied from study to study. For studies that presented more than one measure, preference was given to exposure measures reflecting both intensity and duration (i.e., cumulative exposures).
[b]The total number of years of exposure weighted for the number of hours of exposure per day and for a subjective index of level of smokiness at the workplace (1=very smoky, 0.5=fairly smoky and 0.2=little smoky).
[c]The highest tertile of exposure was compared with the lowest tertile. The actual values of the tertiles were not presented in the paper.
[d]The results are for a comparison between the highest and lowest quartiles of "the time weighted sum of exposure at work, the exposure being based on the number of smokers among people working in the same closed space". The units of these quartiles are not presented in the paper.
[e]Results are from an analysis excluding cases and controls that were in the analysis by Boffetta et al. 1999, which was not presented in the original analysis.
[f]Crude results not adjusted for any risk factors.
Adapted from Stayner et al, 2007 [11]

REFERENCES

1. IARC. (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking.* Lyon, France: International Agency for Research on Cancer.

2. U.S. Department of Health and Human Services (2006). The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

3. Exposure to secondhand smoke among students aged 13-15 years worldwide, 2000-2007 (2007). *MMWR Morb Mortal Wkly Rep* 56: 497-500.

4. Kauppinen T, Toikkanen J, Pedersen D, et al. (2000). Occupational exposure to carcinogens in the European Union. *Occup Environ Med* 57: 10-18.

5. Ong MK and Glantz SA (2004). Cardiovascular health and economic effects of smoke-free workplaces. *Am J Med* 117: 32-38.

6. U.S. Environmental Protection Agency (1992). *Respiratory health effects of passive smoking: lung cancer and other disorders.* Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, ORD, Report No. EPA/600/6-90/006F.

7. Siegel M and Skeer M (2003). Exposure to secondhand smoke and excess lung cancer mortality risk among workers in the "5 B's": bars, bowling alleys, billiard halls, betting establishments, and bingo parlours. *Tob Control* 12: 333-338.

8. Properties and measure, of environmental tobacco smoke (2000). In: Jenkins RA, Guerin MR, Tomkins BA, eds., *The chemistry of environmental tobacco smoke: composition and measurement.* Boca Raton, FL: Lewis Publishers.

9. Brennan P, Buffler PA, Reynolds P, et al. (2004). Secondhand smoke exposure in adulthood and risk of lung cancer among never smokers: a pooled analysis of two large studies. *Int J Cancer* 109: 125-131.

10. Wen W, Shu XO, Gao YT, et al. (2006). Environmental tobacco smoke and mortality in Chinese women who have never smoked: prospective cohort study. *BMJ* 333: 376.

11. Stayner L, Bena J, Sasco AJ, et al. (2007). Lung cancer risk and workplace exposure to environmental tobacco smoke. *Am J Public Health* 97: 545-551.

12. U.S. Surgeon General's Advisory Committee on Smoking and Health (1964). *Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service.* Washington, DC: U.S. Dept. of Health, Education, and Welfare, Public Health Service.

13. Pirie K, Beral V, Peto R, et al. (2008). Passive smoking and breast cancer in never smokers: prospective study and meta-analysis. *Int J Epidemiol* 37: 1069-1079.

14: Stepanov I, Hecht SS, Duca G, et al. (2006). Uptake of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by Moldovan children. *Cancer Epidemiol Biomarkers Prev* 15: 7-11.

15. Husgafvel-Pursiainen K (2004). Genotoxicity of environmental tobacco smoke: a review. *Mutat Res* 567: 427-445.

16. California Environmental Protection Agency (2005). *Proposed Identification of Environmental Tobacco Smoke as a Toxic air Contaminant. Part B: Health Effects.* Sacramento, CA: California Environmental Protection Agency, Air Resources Board.

17. Vineis P, Hoek G, Krzyzanowski M, et al. (2007). Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health* 6: 7.

18. IARC (2007). *IARC Working Group Reports, Volume 3, Attributable Causes of Cancer in France in the year 2000.* Lyon, France: International Agency for Research on Cancer.

19. Steenland K, Burnett C, Lalich N, et al. (2003). Dying for work: The magnitude of US mortality from selected causes of death associated with occupation. *Am J Ind Med* 43: 461-482.

20. World Health Organization. *WHO Framework Convention on Tobacco Control.* Avaliable from: http://www.who.int/fctc/en/ Date Accessed: October 12,2008.

21. Semple S, Creely KS, Naji A, et al. (2007). Secondhand smoke levels in Scottish pubs: the effect of smoke-free legislation. *Tob Control* 16: 127-132.

22. Goodman P, Agnew M, McCaffrey M, et al. (2007). Effects of the Irish smoking ban on respiratory health of bar workers and air quality in Dublin pubs. *Am J Respir Crit Care Med* 175: 840-845.

23. Cesaroni G, Forastiere F, Agabiti N, et al. (2008). Effect of the Italian smoking ban on population rates of acute coronary events. *Circulation* 117: 1183-1188.

24. Pell JP, Haw S, Cobbe S, et al. (2008). Smoke-free legislation and hospitalizations for acute coronary syndrome. *N Engl J Med* 359: 482-491.

25. Samet JM, Yang G (2001). Passive smoking, women and children. In: Samet JM, Yoon SY, eds., *Women and the tobacco epidemic, challenges for the 21st century.* Geneva: World Health Organization. 17-45.

2.4 Smokeless Tobacco

Summary

> Smokeless tobacco products are widely used in Asia and Africa. These products cause cancers of the oral cavity, the pharynx and the oesophagus

> Use of smokeless tobacco is also common in Nordic European Countries. These products increase the risk of cancers of the oesophagus and pancreas

> Use of smokeless tobacco in Northern America has been associated with oral cancers

> Carcinogenicity is likely to be caused by a high concentration of nitrosamines.

During most of the 20th century, use of oral and nasal smokeless tobacco products has been significant in India and other Asian countries, as well as in some parts of Africa, although it has declined in Northern Europe and North America. However, during the last few decades an increase in use has been observed in the United States and some Northern European countries, in particular among young people.

Smokeless tobacco is consumed without burning the product, and can be used orally or nasally. Globally, a wide variety of different smokeless tobacco products are used. These may be used on their own, mixed with other products, such as slaked lime (khaini) or as ingredients to other products, such as betel quid (Figure 2.4.1).

The prevalence of use of smokeless tobacco varies substantially not only across countries, but also within countries, by gender, age, ethnicity and socioeconomic characteristics. In the United States in 2000, 4.4% of men and 0.3% of women were current users of smokeless tobacco products. Current use was more common among young men, non-Hispanic Whites, people of lower attained level of education, southern states and rural areas [1]. The major form of smokeless tobacco used in Sweden is moist snuff ("snus"). In 2004, 20% of men and 3% of women aged 16–75 years used moist snuff daily; the prevalence of use was higher in young adults, and among manual workers [2].

In India, a large variety of commercial or home-made smokeless tobacco products exist. The use of chewing tobacco (often chewed with betel quid or other preparations including areca nut) is more prevalent than the use of snuff; applying smokeless tobacco products as a dentifrice is also common. According to a 1998–99 survey, 28.1% of adult men and 12.0% of women reported chewing tobacco [3]. Smokeless tobacco products are also widely used in other countries in Southeast Asia. There are many other products used in other regions and countries, including naswar in Central Asia, zarda in Western Asia, maras in Turkey, toombak in Sudan, chimó in Venezuela and iq'mik in Alaska [4].

The available studies from countries in Northern Europe and the United States indicate an increased risk of oral cancer for use of smokeless tobacco in the United States, while results of studies in the Nordic countries do not support such an association [5,6]. In the case of esophageal and pancreatic cancer, the available evidence points toward the presence of a causal association, mainly based on the results of the studies from Nordic countries. Results on lung cancer risk are not conclusive, and data for other cancers are inadequate.

Betel quid without tobacco, as well as areca nut, the common ingredient of betel quid, have been classified as human carcinogens; they cause cancers of the oral cavity, the pharynx and the oesophagus [4]. Several case–control studies from India, Pakistan and Sudan provide strong and consistent evidence of an increased risk of oral cancer (or oral and pharyngeal cancer) for use of smokeless tobacco (or tobacco plus lime) products, with relative risks as high as 10 [6]. Additional evidence comes from ecological studies showing positive correlations between use of smokeless tobacco products and high rates of oral cancer (e.g. in Sudan, Central Asia and Saudi Arabia), as well as from case reports and case series from different regions across the world, in which cases of oral cancer reported high prevalence of use of smokeless tobacco products [6].

A few studies from India and North Africa support the hypothesis of an association between nasal snuff use and risk of cancer of the oral cavity, the esophagus and the lung [6].

In one study in the USA, men who switched from cigarette smoking to use of spit tobacco ("switchers") had a 2.6-fold higher mortality from cancer of the oral cavity and pharynx than men who quit using tobacco entirely ("quitters") [7]. Compared to men who never used any tobacco product, the risk of lung cancer among switchers was increased 5–6 fold.

There are over 30 carcinogens in smokeless tobacco, including volatile and tobacco specific nitrosamines, nitrosamino acids, polycyclic aromatic hydrocarbons, aldehydes, metals [6]. Smokeless tobacco use entails the highest known non-occupational human exposure to the carcinogenic nitrosamines, NNN and NNK (Figure 2.4.2). Exposure levels are 100 to 1000 times greater than in foods and beverages commonly containing nitrosamine carcinogens. The uptake of NNK and NNN by smokeless tobacco users has been demonstrated in many studies by detection of their metabolites in urine. Twenty years of smokeless tobacco use would expose its user to an amount of NNK (75–150 mg, or about 1.5 mg/kg body weight) similar to that which has caused tumours in rats (1.8 mg/kg body weight), in addition to considerable exposure to NNN [8].

There is also consistency among the target tissues for cancer in smokeless tobacco users and in rats treated with NNK or NNN, since a mixture of NNK and NNN swabbed in the rat oral cavity caused oral tumours, and NNK and its metabolite NNAL caused pancreatic tumours in rats upon administration in the drinking water, and NNN given in the drinking water to rats produces esophageal and lung tumours [5]. Tobacco specific nitrosamines and their metabolites have also been quantified in the urine of smokeless tobacco users, and their levels were generally higher than in smokers [9].

There is a spectrum of risk arising from use of tobacco products that is due to the wide variation in the types used, their chemical composition and the way in which they are used, leading to opportunities for harm reduction initiatives within the field. This is compounded by the fact that tobacco is marketed in sophisticated ways in high-resource countries and this practice is migrating to low-resource country markets with some rapidity.

Harm (risk) reduction can be achieved by reduction of dose or change of product. This may involve substitution of one risk for another but may nevertheless lead to a lower overall risk of cancer. A policy concession that switching to smokeless tobacco may benefit cigarette smokers, while certainly true in many cases, has the downside that it may have the side effect of actually increasing the number of continuing smokers. While there are arguments to support the notion that a global switch from smoking to smokeless tobacco would reduce global cancer risk over time [10], comparative risk estimates depend on many assumptions, including in particular the expected effect of the introduction of new smokeless products in populations where the habit has not been prevalent. Data are available on a possible beneficial effect of switching from smoking to smokeless tobacco a few studies and models in the United States and Sweden. Overall, there is not enough evidence to support promotion of such products as substitutes for cigarettes in populations with a high prevalence of smoking and no tradition of use of smokeless tobacco.

Fig. 2.4.1 *Selection of smokeless tobacco products*

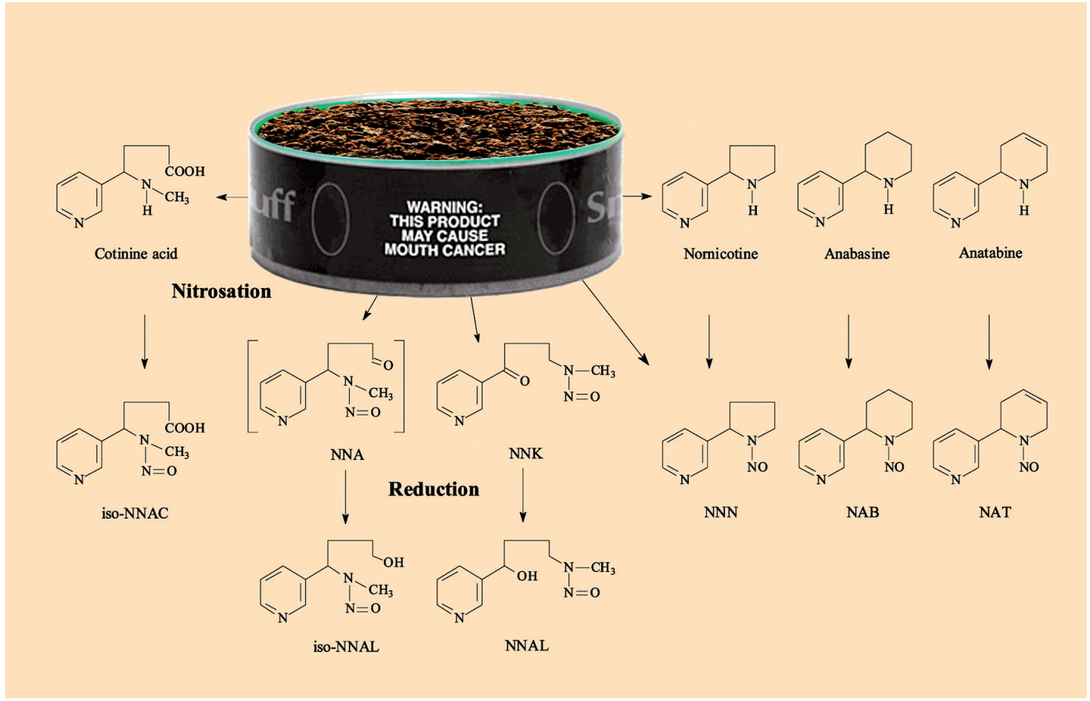


Fig. 2.4.2 *Smokeless tobacco chemistry*

REFERENCES

1. Tomar SL, Connolly GN, Wilkenfeld J, et al. (2003). Declining smoking in Sweden: is Swedish Match getting the credit for Swedish tobacco control's efforts? *Tob Control* 12: 368-371.

2. Wicklin B (2006). *Tobacco Statistics: Sales, Consumption and Lung Cancer*. Hasselby, Sweden: Statistical Bureau VECA.

3. Rani M, Bonu S, Jha P, et al. (2003). Tobacco use in India: prevalence and predictors of smoking and chewing in a national cross sectional household survey. *Tob Control* 12: e4.

4. IARC. (2004). *Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 85, Betel quid and areca nut chewing and some areca-nut-derived nitrosamines*. Lyon, France: International Agency for Research on Cancer.

5. Boffetta P, Hecht S, Gray N, et al. (2008). Smokeless tobacco and cancer. *Lancet Oncol* 9: 667-675.

6. IARC. (2007). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 89, Smokeless tobacco and some tobacco-specific N-nitrosamines*. Lyon, France: International Agency for Research on Cancer.

7. Henley SJ, Thun MJ, Connell C, et al. (2005). Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control* 16: 347-358.

8. Belinsky SA, Foley JF, White CM, et al. (1990). Dose-response relationship between O6-methylguanine formation in Clara cells and induction of pulmonary neoplasia in the rat by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Cancer Res* 50: 3772-3780.

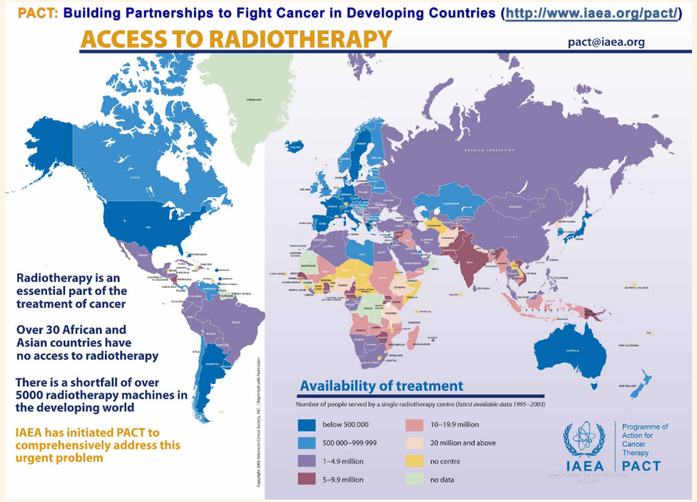
9. Stepanov I and Hecht SS (2005). Tobacco specific nitrosamines and their pyridine-N-glucuronides in the urine of smokers and smokeless tobacco users. *Cancer Epidemiol Biomarkers Prev* 14: 885-891.

10. Gartner CE, Hall WD, Vos T, et al. (2007). Assessment of Swedish snus for tobacco harm reduction: an epidemiological modelling study. *Lancet* 369: 2010-2014.

CANCER INSTITUTE PROFILE: PACT/IAEA

The International Atomic Energy Agency (IAEA) has a long, successful history of assisting cancer treatment programmes in the developing world with the use of radiotherapy. Radiation medicine techniques are indispensable in cancer care, where radiotherapy plays a fundamental role in treating and curing many forms of cancer. The IAEA's assistance has enabled many countries to establish safe and effective radiotherapy capabilities, but with a cancer epidemic looming in developing countries, the existing infrastructure is far from sufficient to respond to the growing demand (see Figure).

The Programme of Action for Cancer Therapy (PACT) was created within the IAEA in 2004 to build upon this experience to enable low- and middle-income countries to introduce, expand and improve their cancer care capacity by integrating radiotherapy into a comprehensive cancer control programme that maximises its therapeutic effectiveness and impact. Such a programme also addresses other challenges such as infrastructure gaps and builds capacity and long-term support for continuous education and training of cancer care professionals, as well as for community-based action.



PACT is working with WHO, IARC, UICC, INCTR and other leading organisations to build a global public-private partnership to assist low- and middle-income countries to develop cancer control programmes that meet the challenges posed by cancer in all its aspects by mobilising new resources from charitable trusts, foundations, and others in the public and private sectors.

To achieve its goals, PACT is being implemented in overlapping stages that raise awareness about cancer, assess cancer control needs, develop demonstration projects and attract donors to establish effective new funding mechanisms beyond those currently available from the IAEA and bilateral or multilateral donors. Through these collaborations, PACT and its partners will place cancer on the global health agenda and comprehensively address cancer control needs in the developing world over the next 10 to 20 years. The IAEA will continue to invest in PACT with personnel and resources as one of its key priorities.

website: www.iaea.org

2.5 Chronic Infections

Summary

> Approximately 15–20% of cancers worldwide have been attributed to infectious agents. However, this proportion is higher in low-resource countries (26%) than in the developed world (8%).

> Common cancers induced by specific infectious agents include hepatocellular carcinoma associated with human hepatitis B virus (HBV) or human hepatitis C virus (HCV), cervical cancer and other malignancies associated with human papillomavirus (HPV), lymphomas and others associated with Epstein-Barr virus (EBV), leukaemia associated with human T cell leukemia virus (HTLV), Kaposi sarcoma associated with human herpes virus 8 (HHV8), gastric cancer with Helicobacter pylori (H. pylori) and cancer of the urinary tract with Schistosoma haematobium

> HPV, EBV, HTLV1 and HHV8 play a direct role in carcinogenesis encoding oncoprotein, which are able to promote cellular transformation by altering the regulation of cell cycle, telomere/telomerase system, apoptosis and other cellular pathways

> Other infectious agents, e.g. HBV, HCV and *H. pylori*, appear to have an indirect role, inducing a chronic inflammation with tissue necrosis and regeneration. HIV also has an indirect role, mediating its effects on cancer risk by lowering host immunity to other oncogenic infections

> In the last two decades several strategies against cancer-associated infectious agents have been developed. These include antibiotic therapy against H. pylori and two prophylactic vaccines against HBV and HPV

The hypothesis of the contagious nature of a given cancer was envisaged in the beginning of the 20th century, when researchers could prove the transmission of cancer in animals using cell-free filtrates of cancer cells. Ellermann and Bang, and a few years later Rous, showed that inoculation of cell-free filtered tumour extracts from ill to healthy chickens could lead to development of cancer [1]. Similar experiments in other animals confirmed the contagious nature of certain types of cancers. These findings led to the discovery of several carcinogenic animal viruses, e.g. Rous-sarcoma virus, Lucké frog renal carcinoma virus, mammary murine tumour virus and many more [1]. However, despite the clear indications that cancer could be transmitted from ill to healthy animals, the idea of involvement of infectious agents in carcinogenesis was only accepted after several decades. This was mainly due to the lack of appropriate detection methods, such as electron microscopy and molecular biology techniques. Despite the isolation of EBV in Burkitt lymphoma cells in 1964, it took several years to completely accept the role of EBV in human cancer [1]. Around 1970, H. zur Hausen suggested the link between HPV and cervical cancer. A few years later, Gissmann and de Villiers, within the group of zur Hausen, isolated and characterised the first mucosal HPV type, HPV6, which then allowed the identification of several other mucosal HPV types, including HPV16, fully supporting their original idea [2]. Nowadays HPV is accepted as a necessary cause of cervical cancer.

Epidemiological and biological studies have now conclusively proved that a variety of infectious agents are among the main causes of cancer worldwide. At least six different viruses have been linked to the development of specific types of human cancers. Other infectious agents involved in human carcinogenesis include four parasites and one bacterium (Table 2.5.1).

Hepatitis B virus and hepatitis C virus

Hepatitis B virus (HBV) is a small partially double stranded hepatotropic DNA virus that belongs to the *Hepadnaviridae*. HBV infection is a major public health problem worldwide. Approximately two billion people are infected worldwide, and more than 400 million are chronic (lifelong) carriers of HBV [3]. However, the geographical distribution of chronic carrier state varies considerably. The majority of chronically infected people live in Southeast Asia and sub-Saharan Africa. HBV infections occur in all age groups; however, most of the chronic infection (70–80%) occurs during the perinatal period, 25–30% in infancy or early childhood, and less than 10% in adults [3]. Infection can be transmitted from mother to child (vertical transmission), child to child (horizontal transmission), through sexual transmission and by contact with infected blood (transfusion, non-sterilized needles and syringes, tattooing and scarification procedures) or blood products.

Hepatitis C virus (HCV), an enveloped single-stranded RNA virus, infects about 80 million people worldwide. The prevalence of HCV varies also from region to another. It is low (<1%) in Australia, Canada and northern Europe, intermediate (1%) in the USA, high (>2%) in the rest of Europe and high (2%) in many African countries, Southeast Asia, Italy and Egypt. HCV is mainly transmitted through unscreened blood transfusions and use of contaminated needles and syringes. Unlike HBV, where about 10% of those infected progress to chronicity, 80% of HCV newly infected people develop a chronic state [4]. Similar to HBV, HCV is clustered into distinct genotypes, probably with a different severity in inducing disease or in response to treatment [5,6]. Chronically infected persons with HBV and/or HCV are at high risk of developing cirrhosis and HCC, diseases that kill about half a million persons each year. The fraction of HCC attributable to HBV and HCV in 2002 have been estimated to be, respectively, 23 and 20% in developed countries and 59 and 33% in developing countries [7].

The molecular mechanisms by which HBV and HCV viruses induce tumours are far from being elucidated. The pathway shared by these viruses in inducing HCC in a multistep process is likely to be chronic injury by viral components and environmental factors resulting in inflammatory responses and apoptosis followed by hepatocellular regeneration. Interactions with other environment factors such as aflatoxins also contribute to carciongenesis. During this process, chromosomal rearrangements, gene mutations and other biological alterations that occur may provide a selective growth advantage to the initiated abnormal cell (Figures 2.5.4 and 2.5.5).

HBV infection is preventable with a safe and effective immunisation programme available since 1982. However, up to now, only a fraction of children in low- and medium-resources countries are vaccinated. No vaccine is currently available to prevent HCV infection. The control of HBV and HCV disease burden requires prevention strategies by reducing the risk of contamination (safe blood transfusion, safe infection practices, etc.).

Human papillomavirus

The family of the epithelio-tropic human papillomaviruses (HPV) comprises approximately 100 different types that have been sub-grouped in different genera according to their genomic DNA sequence [8]. In addition, the different HPVs appear to have a preferential tropism for the mucosa or the skin; therefore, they can be further subdivided into mucosal or cutaneous HPV types. The genus alpha comprises the mucosal HPV types that are preferentially detected in the female reproductive tract and are sexually transmitted. An IARC monograph has recently reported that the mucosal high-risk alpha HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52 56, 58, 59 and 66 are clearly associated with cervical cancer. In addition, HPV16 and HPV18, at much lower extent, have a causal role for a subset of anal cancers (80%) or vulva, vagina, penis and oro-pharynx (approximately 30% in all latter cases) [9]. Another group of mucosal alpha HPVs is termed "low risk" and is normally associated with benign genital lesions. HPV16 is the most frequently high-risk HPV type detected in pre-malignant and malignant cervical lesions [10]. The high frequency of HPV16 in the cervix is most likely linked to its biological properties: e.g. efficiency in promoting cellular proliferation and evading the immune surveillance (see paragraph "Mechanisms of carcinogenicity").

Emerging lines of evidence indicate that another group of HPVs that belongs to the genus beta may be involved in human carcinogenesis, i.e. non-melanoma skin cancer (NMSC) [11]. They were first isolated in skin cancer-prone patients suffering from a rare autosomal recessive genetic disorder called *Epidermodysplasia verruciformis* (EV), but it is now clear that they are very common in the skin of healthy individuals [11]. Although these HPVs are known to be responsible for NMSC development in EV patients, their direct role in skin carcinogenesis in normal population remains to be proven. It is possible that the cutaneous HPV types may promote the formation of malignant lesions acting as co-carcinogens together with UV.

Epstein-Barr virus

Epstein-Barr virus (EBV) is a ubiquitous human Gamma Herpes virus that infects most of human population early in life and usually causes mild disease. EBV was isolated for the first time from a biopsy of Burkitt's lymphoma (childhood B-cell-derived tumour common in sub-Saharan Africa), and was the first virus directly associated with human cancer [12]. EBV has a specific tropism for B-cells through a binding to B-cell surface receptor CD21 leading to the emergence of proliferating B-cell referred as lymphoblastoid cell

Infectious agent	IARC classification[1]	Cancer site/cancer	Number of cancer cases	% of cancer cases worldwide
H. Pylori	1	Stomach	490 000	5.4
HPV	1, 2A	Cervix and other sites	550 000	6.1
HBV, HCV	1	Liver	390 000	4.3
EBV	1	Lymphomas and nasopharyngeal carcinoma	99 000	1.1
HHV-8	2A	Kaposi sarcoma	54 000	0.6
Schistosoma haematobium	1	Bladder	9 000	0.1
HTLV-1	1	Leukaemia	2 700	0.1
Liver flukes Opisthorchis viverrini Clonochis sinensis	1 2A	Cholangiocarcinoma (biliary system)	800	
		Total infection-related cancers	1 600 000	17.7
		Total cancers in 1995	9 000 000	100

Table 2.5.1 *The burden of cancer caused by infectious agents worldwide*
[1]Group 1 = carcinogenic to humans, Group 2A = probably carcinogenic to humans

lines (LCLs). EBV can also infect other cell types, including epithelial, but with much less efficiency. EBV is thought to be transmitted orally, and primary infection is generally asymptomatic. However, when the infection occurs during adolescence, EBV can cause infectious mononucleosis, a benign self-limited disease. After remission, EBV remains in infected individuals for the lifetime, making it among the most persistent viruses that infect humans. In individuals with severe inherited or acquired deficiencies in T-lymphocyte response, EBV-infected B-lymphocytes can proliferate without immune control and cause fatal lymphoproliferative disease. EBV is also strongly associated with the development of several human cancers such as Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin disease, sinonasal angiocentric-T-cell lymphoma, and gastric carcinoma [13]. EBV-induced growth transformation results in a complex interaction between viral encoded proteins and the cellular regulatory machinery, and the EBV latent proteins, particularly the Latent Membrane Protein 1 (LMP1), play an important role in this process (Klein E, Kis LL and Klein G, 2007).

Human T-cell lymphotropic virus

Human T-cell lymphotropic virus type 1 (HTLV-1) is part of the Deltaretrovirus family and is responsible for the development of adult-T-cell leukamia (ATL). Based on the divergence in the nucleotide sequence, HBV is classified into eight different genotypes (A to H) with different geographical distributions. Studies reported mainly from Asia indicate that HBV genotypes may influence the HCC outcome. Patients infected with HBV genotype C being more susceptible to develop HCC. Other types have been identified (HTLV-2-4). HTLV-2 was isolated from a few cases of leukemia and neurological disease, but its pathology is not clear. Little is known about HTLV-3 and HTLV-4. HTLV-1 is endemic in southwestern Japan, Africa, the Caribbean Islands and South America, while it is frequent in Melanesia, Papua New Guinea, the Solomon Islands and in Australia among the aboriginal population. In contrast, HTLV-1 is rarely detected in North American and European populations. All ATL cells contain integrated HTLV-1 provirus, highlighting its key role in leukaemogenesis. Nevertheless, only a small minority of HTLV-1-infected individuals progress to ATL. Indeed, the cumulative risks of developing ATL among virus carriers are estimated to be approximately 6.6% for males and 2.1% for females. As many as 20 million people worldwide may be infected with HTLV-1. Spread of the virus may occur from the mother to the child mainly through breast-feeding beyond six months, via sexual transmission and during blood transfusion.

Cancer	Relative Risk
HHV8-related	
Kaposi Sarcoma	3640 (3326 – 3976)
EBV-related	
Non-Hodgkin Lymphoma	77 (39 – 149)
Hodgkin's Lymphoma	11 (8.4 – 14)
HBV/HCV related	
Liver	5.2 (3.3 – 8.2)
HPV-related	
Cervix	5.8 (3.0 – 11)
Vulva and Vagina	6.5 (4.1 – 10)
Penis	4.4 (2.8 – 7.1)
Anus	29 (22 – 38)
Oral cavity	2.3 (1.7 – 3.3)
Non-melanoma skin	4.1 (1.1 – 17)
Conjunctiva	2.0 (1.0 – 3.8)
H.Pylori related	
Stomach	1.9 (1.5 – 2.4)

Table 2.5.2 *Relative risk for cancers related to chronic infection among more than 400 000 PHIV (adapted from Grulich et al, Lancet, 2007)*

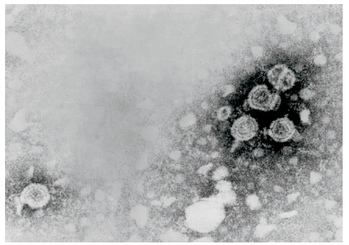


Fig. 2.5.1 *Electron microscopy of hepatitis B virus particles*

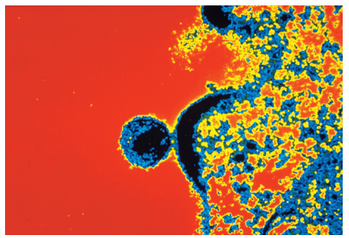


Fig. 2.5.2 *Electron microscopy of the human immunodeficiency virus entering into T-lymphocytes*

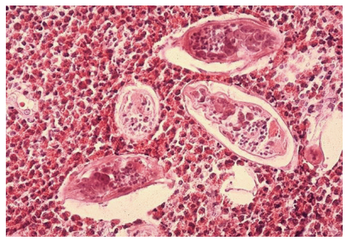


Fig. 2.5.3 *Schistosoma haematoilum chronic infection in the bladder causes inflammatory reaction with dense eosinophilic infiltrates which may promote the development of squamous-cell carcinoma*

KSHV/HHV8

Kaposi's sarcoma associated herpesvirus (KSHV), also termed human herpesvirus 8 (HHV8), is a gamma-2 herpesvirus, related genetically to simian herpesvirus saimiri, the prototype virus of this subgroup of the gammaherpesvirus subfamily. HHV8 is the etiological agent of all forms of Kaposi's sarcoma and primary effusion lymphoma (PEL) and most forms of multicentric Castelman's disease (MCD). HHV8 infection is normally associated with immunocompromised status and is therefore very frequent in geographical regions where HIV is highly prevalent, e.g. Africa. In addition, HHV8 is endemic in normal populations of the Mediterranean regions, such as South Italy and Israel. Horizontal transmission by saliva appears to be the most common route in population of endemic regions as well as in high-risk populations. However, also vertical, sexual, and blood and transplant-related transmission are also considered as additional routes.

HHV8 is able to establish a persistent infection in the host by two alternative genetic life-cycle programmes. The latent programme provides a stable and immunologically silent mode of persistence, while the lytic programme guarantees the release of virions and their propagation to other hosts. Several viral proteins are able to interfere with the immune-system related pathways facilitating the establishment of persistent infection.

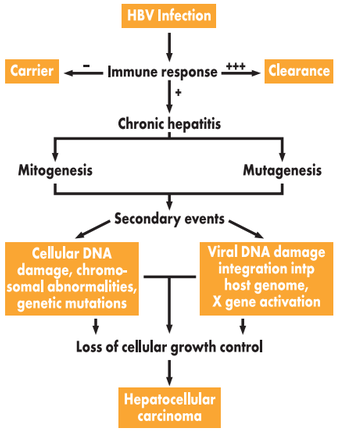


Fig. 2.5.4 *Hepatitis B virus and the chronic injury hypothesis. A strong immune response to hepatitis B virus (+++) leads to clearance of the infection. Lack of immune response (-) results in the "healthy" carrier state, while a weak response (+) produces chronic hepatitis that may eventually progress to Hepatocellular carcinoma*

Helicobacter pylori

Helicobacter pylori (*H. pylori*) is a non-spore forming and spiral-shape gram-negative bacterium that colonises the stomach and is possibly transmitted via the fecal-oral and/or oral-oral route. Epidemiological studies have clearly shown that *H. pylori* infection is associated with peptic ulcer diseases, gastric cancer and mucosa-associated lymphoma tissue (MALT). In 1994, it was classified as a group 1 carcinogen by the International Agency for Research on Cancer. *H. pylori* is one of the most common infections in humans, with an estimated prevalence of 50% worldwide and 90% in developing countries. One striking feature of *H. pylori* biology is its high allelic diversity and genetic variability. To date, an incredibly high number of strains have been described. In addition, the bacteria can undergo genetic alteration *during the infection*, due to an elevated mutation rate and frequent intraspecific recombination. Recent findings support the concept that this genetic variability, which affects both housekeeping and virulence genes, may contribute to host adaptation and persistence of the infection.

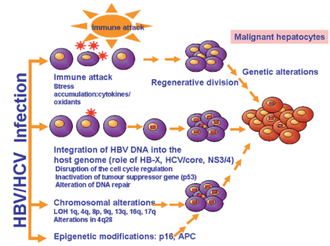


Fig. 2.5.5 *Hepatitis B and hepatitis C-induced liver carcinogenesis. Infection of most of the individuals with hepatitis viruses leads to immune-mediated viral clearance. Viral persistence in few individuals produce chronic hepatitis which may lead to hepatocellular carcinogenesis in a multistep process*

Parasites

Two liver flukes, *Opisthorchis viverrini* and *Clonorchis sinenesis,* have been associated with cholangiocarcinoma in parts of Asia. Infection by these flukes is acquired by eating raw or undercooked freshwater fish containing the infective stage of the fluke; the fluke matures and produces eggs in the small intrahepatic ducts. The evidence for cancer causation by *O. viverrini,* a parasite mainly prevalent in Thailand, is stronger than for *C. sinensis*. The incidence of

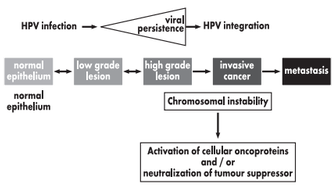


Fig. 2.5.6 *Proposed pathogenesis mechanism by which human papillomavirus infection causes cervical cancer*

cholangiocarcinoma in areas where these liver flukes are non-endemic is very low.

Schistosomes are trematode worms. The cercarial stage infects humans by skin penetration. The worms mature and lay eggs in the bladder or intestine of the host, provoking symptoms of a disease known as bilharzia. *Schistosoma haematobium* infection is prevalent in Africa and the Middle East and has been associated with bladder cancer (Figure 2.5.3). *Schistosoma japonicum* infection is prevalent in Japan and China and has been associated with cancers of the liver, stomach and colorectum, but the evidence is weak and inconsistent.

The impact of HIV on virus-induced cancers

An estimated 40 million people worldwide are infected with HIV, of whom 25 million live in sub-Saharan Africa [14]. HIV is not believed to have any direct carcinogenic effect, but exerts its effects on cancer risk by lowering host immunity. Persons infected with HIV (PHIV) are at increased risk for all those cancers that are known to be associated with chronic infection [15] (Table 2.5.2).

Incidence rates for Kaposi Sarcoma (KS) and Non-Hodgkin Lymphoma (NHL), etiologically linked to HHV8 and EBV, respectively, are the most highly elevated among PHIV compared to the general population. The risk for these cancers increases strongly as immunity declines (as measured by CD4 T-cell count), and can be reversed by the immune reconstitution offered by treatment with highly active antiretroviral therapy (HAART). HAART is also the first-line treatment for KS, often resulting in complete regression. The prognosis of HIV-related NHL remains poor.

For cancers other than KS and NHL, increases in risk among persons infected with HIV are smaller and do not show such strong linear relationships with degree of immune suppression. However, increased access to HAART and improvement in survival after HIV infection means that the consequences of mild but prolonged immune deficiency are being seen on a wide spectrum of infection-related cancers. EBV-related Hodgkin Lymphoma is increased about ten-fold in PHIV. The excess risk for HPV-related cancers of the cervix, vulva, vagina, anus and penis, as well as for HBV/HCV-related liver cancer were suspected to be related to heavy exposure to oncogenic viruses *per se* due to the lifestyle of PHIV, rather than immune impairment. It is known that low CD4 T-cell counts are associated with increased HPV persistence and with risk of development of advanced precancerous lesions of the cervix and anus, and that co-infection with HIV and HCV or HBV leads to higher mortality from liver cancer than does

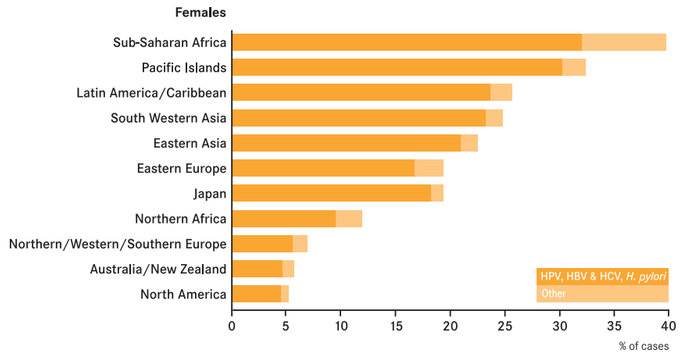


Fig. 2.5.7 *The burden of cancers caused by infections in women*

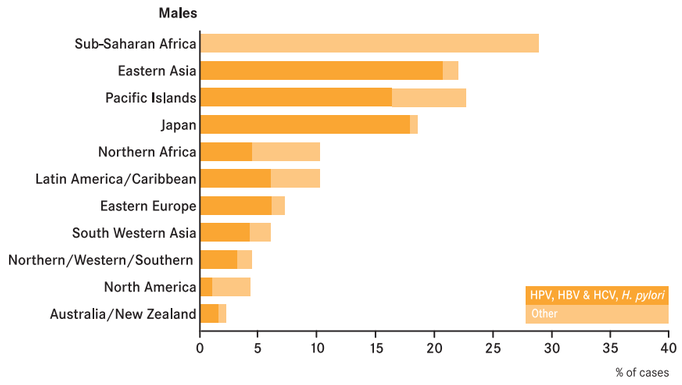


Fig. 2.5.8 *The burden of cancers caused by infections in men*

Global burden of cancer attributed to infectious agents

The total of infection-attributable cancer in the year 2002 has been estimated at 1.9 million cases, or 17.8% of the global cancer burden [7]. The principal agents are Helicobacter pylori (5.5% of all cancer), HPV (5.2%), HBV and HCV (4.9%), EBV (1.0%) and HHV8 (0.9%). The proportion of infection-attributable cancer is higher in developing countries (26%) than in developed countries (8%), reflecting the higher prevalence of infection with the major causative agents (e.g. HBV, HP, HPV and HIV), and lack of screening for HPV-related precancerous cervical lesions.

The calculation of attributable fractions is largely based on two parameters, the population prevalence of infection, and the relative risk for developing cancer given infection. These parameters may remain under-estimated for certain infections. For example, HCV seroprevalence surveys tend to over-sample young individuals at low risk of HCV infection (e.g. blood donors and pregnant women), and a review of liver cancer cases, suggested that the attributable fraction of HCV might be higher, particularly in developing countries [20]. Furthermore, the current estimate of non-cardia gastric cancer attributable to *H. pylori* is 63%, which is based on a relative risk of 5.9 for *H. pylori* strains. However, much higher relative risks observed for certain strains of *H. pylori* suggest that the true attributable fraction may be somewhat higher [21].

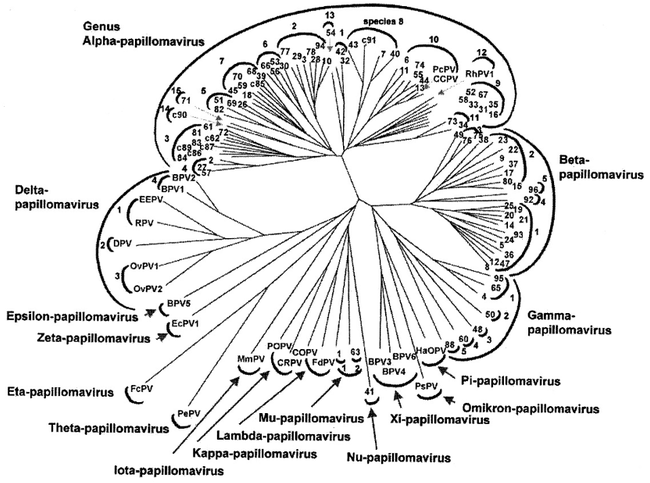


Fig. 2.5.9 *Phylogenetic tree of HPV. The different types of papilloma viruses have been grouped in genera according to similarity in DNA sequence. The most-studied types of HPV associated with cervical cancer are included in genus Alpha. From de Villiers et al. (2004), Virology 324(1):17-27. From de Villiers et al. (2004), Virology 324(1):17-27*

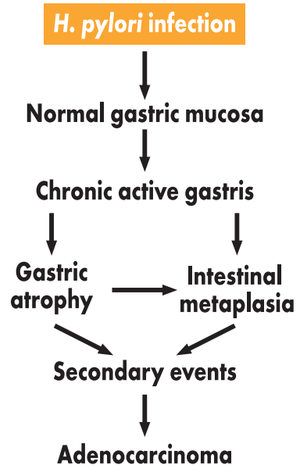


Fig. 2.5.10 *Proposed model of stomach carcinogenesis as progressive process associated with atrophy and intestinal metaplasia with reduced acidity*

HCV or HBV alone. Other cancers associated or suspected to be associated with chronic infections that may occur more frequently among PHIV include cancers of stomach (*H. pylori*), head and neck (HPV), conjunctiva (HPV) and non-melanoma skin cancer (cutaneous HPV), but results from the literature are not quite consistent. Strong evidence for a direct role for HIV-related immune suppression in the development of all these cancers is the similar pattern of excess cancer risk seen among immunosuppressed transplant recipients, who do not share the same behavioural risk factors for viral infection as PHIV [16].

Mechanisms of carcinogenesis

Direct and indirect pathogenic mechanisms have both been implicated for infectious agents involved in human carcinogenesis. HPV, EBV, HTLV1 and HHV8 encode oncoproteins that play a direct role; being able to deregulate fundamental events, e.g. cellular proliferation, DNA repair, apoptosis, chromosomal stability and the immune response. These virus-induced events are explained by the fact that the replication of their DNA is totally dependent on cellular mechanisms. These infectious agents have developed several mechanisms to keep the infected cells alive and in a high proliferative status, even in the presence of cellular stresses that normally lead to exit of cell cycle and/or apoptosis resulting in efficient multiplication of their progeny. In doing so, these viruses facilitate the accumulation of chromosomal abnormalities promoting long-term cellular transformation. A rapid elimination of infected cells by the immune system would drastically decrease the risk of generation of precursor cancer cells. Thus, the carcinogenic potential of these viruses is facilitated by their ability to stimulate cellular proliferation and their efficiency in evading the host immune surveillance.

HPV is one of the best characterised and understood examples of infectious agent with a direct role in carcinogenesis. The products of three early genes, E5, E6 and E7, result in evasion of host immuno-surveillance allowing viral persistence and cellular transformation. Since the integration of viral DNA, which occurs in the majority, if not all, tumour cells, results in a loss of E5 gene expression, it is clear that E5 is involved in early events during the multi-step process of cervical carcinogenesis, and that its function is no longer required after the establishment of the transformed phenotype. In contrast, E6 and E7 are actively expressed in all cervical cancer cells, and inhibition of their transcription leads to a rapid loss of the transformed phenotype. E6 and E7 from the high-risk mucosal HPV types promote cellular transformation targeting several cellular proteins, including the tumour suppressors, p53 and retinoblastoma (pRb), respectively [17].

HPV is a non-lytic virus that is permissive for viral replication only in epidermal keratinocytes. The ability of the virus to influence the immune system is therefore limited to the localised environment of the infected epidermis. It is now clear that several HPV proteins are able to down-regulate the innate and adaptive immunity affecting Toll Like Receptor (TLR)-regulated pathways and antigen presentation [18,19].

Similarly to HPV, EBV, HTLV1 and HHV8 are able to alter the regulation of pathways involved in cellular transformation and/or immune surveillance. The EBV oncoprotein Latent Membrane Protein 1 (LMP1) is an aggregated membrane protein responsible for most of the carcinogenic properties of EBV. LMP1 is expressed in all the EBV-associated malignancies and transform cell *in vitro*, by altering the control of cell cycle and apoptosis. Indeed, LMP1 acts as a constitutively activated tumour necrosis factor receptor (TNFR) mimicking CD40, therefore activating several cellular signalling pathways in a ligand-independent manner, during EBV-induced B-cell immortalization. Hence, LMP1 promotes cell survival and cell proliferation by constitutively activating NF-κB, JNK, p38, STAT and hTERT [22-24]. In addition, LMP1 can down regulate MHC expression, an efficient mechanism for the virus to alter immune surveillance. Other latent EBV genes including EBNA1, LMP2A and the EBV-encoded small RNA EBERs are thought to play a role in EBV-mediated oncogeneis [25].

The oncoprotein Tax from HTLV1, similarly to HPV 16 E6 and E7, targets several tumour suppressors, e.g. p53 and pRb altering the regulation of cellular proliferation and apoptosis. HTLV1 Tax promotes G1/S transition by different mechanisms. For instance, it induces pRb phosphorylation by activating several CDK complexes and directly increasing the intracellular levels of E2F. The TAX mechanism of p53 inactivation is not fully elucidated, but appears to be mediated by targeting the transcriptional co-activator p300/CBP and the NF-κB pathway. Also HHV8 encode proteins that are able to interfere with the regulation of cell cycle and apoptosis. For instance, latency-associated nuclear antigen (LANA) binds pRb and p53 and co-operates with the cellular oncogene H-ras in transformation of primary rat embryo fibroblasts. In addition, HHV8 encodes a viral cyclin (v-cyc) that can bind and activate CDK4/6, which in turn lead to the hyperphosphorylation of pRb. Interestingly the v-cyc/CDK complexes appear to be resistant to $p16^{INK4a}$, a potent inhibitor of the G1-phase CDK complexes, cycDs/CDK4 or 6. As shown for HPV, HHV8 is able to down-regulate the Interferon pathways and down-regulate MHC class I. The virus is also able to promote Th2, thus inhibiting Th1 cell associate responses that are more favourable in an antiviral response. Furthermore, HHV8 encodes a homologue of IL-6 (vIL-6). As IL-6 in the host plays a key role in haematopoiesis, inflammation and oncogenesis, vIL-6 promotes haematopoiesis and acts as an angiogenic factor through the induction of vascular endothelial growth factor.

In contrast, HBV, HCV, *H. pylori* and parasites act via an indirect mechanism inducing tissue damage and chronic inflammation that in turn promote cancer development. The data available so far show that hepatitis viruses do not display *in vitro* transforming activities, but infection may lead to cancer via induction of chronic liver injury and hepatitis. Chronic hepatitis caused by HBV is characterised by chronic liver cell necrosis that stimulates a sustained regenerative response. The inflammatory component includes activated macrophages that are a rich source of free radicals. The cooperation of these mitogenic and mutagenic stimuli has the potential to determine accumulation of chromosomal abnormalities in the infected cells, which may facilitate the multi-step process of liver carcinogenesis. Viral components of HBV (HBx, PreS2, insertion of the viral genome) and HCV (HCV core, NS5A) also play a direct role in liver carcinogenesis by altering several cellular signalling pathways which are important for regulating cell proliferation and apoptosis (Figures 2.5.4 and 2.5.5).

H. pylori infection causes gastritis and atrophy, which in turn alter gastric acid secretion, elevating gastric pH, changing the gastric flora and allowing anaerobic bacteria to colonise the stomach. In addition, *H. pylori* produces active reductase enzymes that transform food nitrate into nitrite, an active molecule capable of reacting with amines, amides and urea generating carcinogenic N-nitroso compounds. (Figure 2.5.9) The carcinogenicity of the different *H. pylori* strains appears to correlate with the presence in the bacterium genome of a region called pathogenicity island, a 40 kb segment that include the cytoxin-associated gene A (cagA). cagA is a protein of 125-145 kDa and is injected by the bacteria into epithelial cells of the gastric mucosa hijacking signal transduction pathways and increasing cellular proliferation, mobility and apotosis. However, the precise role of all these cagA-induced events in carcinogenesis is not entirely elucidated.

REFERENCES

1. Epstein MA (2001). Historical background. *Philos Trans R Soc Lond B Biol Sci* 356: 413-420.

2. zur Hausen H (1996). Roots and perspectives of contemporary papillomavirus research. *J Cancer Res Clin Oncol* 122: 3-13.

3. Ganem D and Prince AM (2004). Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med* 350: 1118-1129.

4. Ou JH (2006). Hepatitis B, Hepatitis C. and Hepatocellular Carcinoma. In: Warshawsky D, Landolph JR, eds., *Molecular carcinogenesis and the molecular biology of human cancer.* Boca Raton: CRC, Taylor and Francis 151-177.

5. Harris HE, Eldridge KP, Harbour S, et al. (2007). Does the clinical outcome of hepatitis C infection vary with the infecting hepatitis C virus type? *J Viral Hepat* 14: 213-220.

6. Schaefer S (2007). Hepatitis B virus taxonomy and hepatitis B virus genotypes. *World J Gastroenterol* 13: 14-21.

7. Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044.

8. de Villiers EM, Fauquet C, Broker TR, et al. (2004). Classification of papillomaviruses. *Virology* 324: 17-27.

9. Cogliano V, Baan R, Straif K, et al. (2005). Carcinogenicity of human papillomaviruses. *Lancet Oncol* 6: 204.

10. Munoz N, Bosch FX, de Sanjose S, et al. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 348: 518-527.

11. Pfister H (2003). Chapter 8: Human papillomavirus and skin cancer. *J Natl Cancer Inst Monogr* 31: 52-56.

12. Epstein MA, Achong BG, Barr YM (1964). Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* 1: 702-703.

13. Klein E, Kis LL, Klein G (2007). Epstein-Barr virus infection in humans: from harmless to life endangering virus-lymphocyte interactions. *Oncogene* 26: 1297-1305.

14. UNAIDS, World Health Organization (2006). *AIDS epidemic update; special report on HIV/AIDS, December 2006.* Geneva: UNAIDS.

15. Grulich AE, van Leeuwen MT, Falster MO, et al. (2007). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 370: 59-67.

16. Clifford G and Franceschi S (2007). Immunity, infection, and cancer. *Lancet* 370: 6-7.

17. Tommasino M (2001). Early genes of human papillomaviruses. In: Schwab M, ed., *Encyclopedic Reference of Cancer.* Berlin: Springer. 266-272.

18. Hasan UA, Bates E, Takeshita F, et al. (2007). TLR9 expression and function is abolished by the cervical cancer-associated human papillomavirus type 16. *J Immunol* 178: 3186-3197.

19. O'Brien PM and Campo MS (2003). Papillomaviruses: a correlation between immune evasion and oncogenicity? *Trends Microbiol* 11: 300-305.

20. Raza SA, Clifford GM, Franceschi S (2007). Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review. *Br J Cancer* 96: 1127-1134.

21. Plummer M, van Doorn LJ, Franceschi S, et al. (2007). Helicobacter pylori cytotoxin-associated genotype and gastric precancerous lesions. *J Natl Cancer Inst* 99: 1328-1334.

22. Soni V, Cahir-McFarland E, Kieff E. (2007). LMP1 TRAFficking activates growth and survival pathways. Adv Exp Med Biol.597:173-187.

23. Sylla BS, Hung SC, Davidson DM, et al. (1998). Epstein-Barr virus-transforming protein latent infection membrane protein 1 activates transcription factor NF-kappaB through a pathway that includes the NF-kappaB-inducing kinase and the IkappaB kinases IKKalpha and IKKbeta.

Proc Natl Acad Sci U S A. 95:10106-10111.

24. Terrin L, Dal Col J, Rampazzo E, et al. (2008). Latent membrane protein 1 of Epstein-Barr virus activates the hTERT promoter and enhances telomerase activity in B lymphocytes. J Virol. 82:10175-10187.

25. Young LS, Rickinson AB. (2004). Epstein-Barr virus: 40 years on. Nat Rev Cancer. 4:757-768.

2.6 Alcohol Drinking

Summary

- A causal association has been established between alcohol drinking and cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and, in women, breast
- The global burden of alcohol-associated mortality (1 804 000 deaths, or 3.2 % of all deaths) is substantial, according to the WHO Global Burden of Disease project
- In the case of breast and colorectal cancer, a causal association with alcohol drinking has been established only recently, and the public health implications of these associations have not been fully elucidated
- The mechanisms by which alcohol drinking exerts its carcinogenic effects are not fully elucidated, although possible hypotheses include a genotoxic effect of acetaldehyde, an increase in estrogen level, a role as a solvent for other carcinogens, the production of reactive oxygen and nitrogen species and the alteration of folate metabolism
- There is growing evidence that the effect of alcohol is modulated by polymorphisms in genes encoding for enzymes involved in ethanol metabolism, such as alcohol dehydrogenases, aldehyde dehydrogenases and cytochrome P450 2E1, as well as folate metabolism and DNA repair
- Priorities for a research agenda on alcohol-related carcinogenicity would include: (i) the effect of drinking patterns, (ii) investigations on the risk of cancer in suspected target organs and (iii) elucidation of the role of genetic variants

A causal association has been established between alcohol drinking and cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and, in women, breast [1]. An association is suspected for lung cancer. Some studies have shown an increased risk of pancreatic cancer with heavy drinking, but the epidemiologic evidence for this is weak.

For squamous-cell carcinomas of the upper aerodigestive tract (oral cavity, pharynx, larynx and esophagus), a causal relationship was first demonstrated in the mid-1950s [2]. In epidemiological studies of this group of tumours, an effect of heavy alcohol intake and a linear relationship with amount of drinking has been consistently shown. A synergism between alcohol drinking and tobacco smoking was demonstrated in the 1970s, and has since become a paradigm of interaction of two environmental factors in human carcinogenesis. A carcinogenic effect of alcohol drinking independent from that of smoking (i.e. an increased risk of head and neck cancers in non-smokers) was first reported in 1961 [2], and replicated in a recent large-scale pooled analysis (Figure 2.6.1) [3].

Heavy alcohol intake increases the risk of hepatocellular carcinoma, with the most likely mechanism through development of liver cirrhosis, although alternative mechanisms such as alteration in the hepatic metabolism of carcinogens may also play a role. Alcoholic liver cirrhosis is probably the most important risk factor for hepatocellular carcinoma in populations with low prevalence of HBV and HCV infection, such as North America and northern Europe. Synergistic interactions on the risk of liver cancer are also thought to occur between tobacco and alcohol, and between HBV/HCV and alcohol [2].

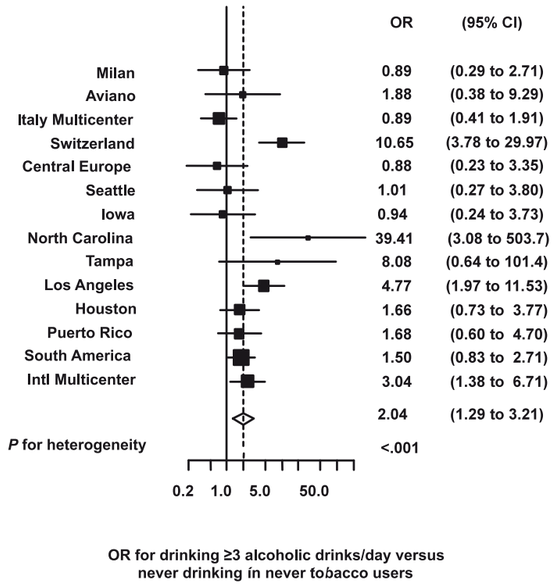


Fig. 2.6.1 *The risk of head and neck cancer, (oral cavity, pharynx and larynx) associated with alcohol drinking in never users of tobacco, overall and by study, using International Head and Neck Cancer Epidemiology consortium pooled data. Odds ratios were adjusted for age, sex, race/ethnicity, education level, and study centre*
From Hashibe et al. [3]

Though the effects may be moderate, there does appear to be a causal relation of alcohol consumption with colorectal and breast cancer risk. Studies on the association of alcohol drinking and adenocarcinoma of the esophagus, stomach cancer, pancreatic cancer and lung cancer have not been consistent. Alcohol drinking does not appear to increase the risk of endometrial, bladder or prostate cancers. In the case of ovarian and kidney cancers, the evidence from epidemiological studies is of a possible protective effect, but further investigation is necessary to clarify the relationships. A reduced risk of non-Hodgkin lymphoma among alcohol drinkers has also been reported. This effect, if real, might differ by lymphoma type, which would contribute to explaining the inconsistencies in results of earlier studies of alcohol and lymphoma.

The major non-neoplastic diseases caused by alcohol drinking include hypertension, haemorrhagic stroke, liver cirrhosis and fibrosis, as well as acute and chronic pancreatitis [1]. In addition, alcohol drinking is a major cause of several types of injuries, and alcohol consumption during pregnancy is associated with various adverse effects including fetal alcohol syndrome, spontaneous abortion, low birth weight, prematurity and intrauterine growth retardation. On the other hand, there is strong evidence that moderate consumption of alcohol reduces the risk of ischaemic heart disease, ischaemic stroke and cholelithiasis.

A global assessment of the burden of alcohol drinking on human health is complicated by several factors, including (i) the background rate of the major diseases, including ischaemic heart disease and liver cirrhosis, (ii) the age distribution of the population, since the incidence of many alcohol-related injuries decreases with age while that of cancer and ischaemic heart disease increases with age and (iii) the pattern of consumption, since the protective effect on ischaemic heart disease is not present at high levels of intake. The most comprehensive estimate of the number of deaths either caused or prevented by alcohol drinking has been conducted within the WHO Global Burden of Disease project [4]. According to this estimate, in 2000 in developed countries the drinking of alcohol was responsible for 185 000 deaths among men, while it prevented 71 000 deaths in men for the same year. For women in developed countries, 277 000 deaths were prevented compared with the 142 000 caused by alcohol. The picture is different in developing countries, because of a lower burden of cardiovascular disease and a greater role of injuries: alcohol drinking is responsible for 1 524 000 extra deaths among men and 301 000 among women. The global burden of alcohol-associated mortality therefore represents 1 804 000 deaths, or 3.2 % of all deaths.

The mechanisms by which alcohol drinking exerts its carcinogenic effects are not fully elucidated: plausible hypotheses include a genotoxic effect of acetaldehyde (the main metabolite of ethanol), an increase in estrogen levels (relevant for breast carcinogenesis), a role as a solvent for other carcinogens, the production of reactive oxygen and nitrogen species and the alteration of folate metabolism. Table 2.6.1 lists the main mechanistic hypotheses, together with our subjective assessment of the strength of the available supporting evidence. The table is restricted to mechanisms known or suspected to operate in cancers with an established association with alcohol drinking.

There is growing evidence that the effect of alcohol is modulated by polymorphisms in genes encoding for enzymes involved in ethanol metabolism, such as alcohol dehydrogenases, aldehyde dehydrogenases and cytochrome P450 2E1, as well as folate metabolism and DNA repair. Alcohol dehydrogenases (ADHs) are enzymes involved in the oxidation of ethanol to acetaldehyde (Figure 2.6.2.) [5]. Subsequent oxidation of acetaldehyde to acetate is catalyzed by the enzyme aldehyde dehydrogenase (ALDH). The efficiency in converting ethanol to acetaldehyde, and subsequent conversion to acetate, is largely determined by the ADH and ALDH gene families, with potential inter-individual

Mechanism	Potential target organs
Strong evidence*	
DNA damage by acetaldehyde	Head and neck, esophagus, liver
Increased estrogen level	Breast
Moderate evidence*	
Solvent for other carcinogens	Head and neck, esophagus
Production of reactive oxygen and nitrogen species	Liver, others?
Alteration of folate metabolism	Colon and rectum, breast, others?
Weak evidence*	
DNA damage by ethanol	Head and neck, esophagus, liver
Nutritional deficiencies (e.g., vitamin A)	Head and neck, others?
Reduced immune surveillance	Liver, others?
Carcinogenicity of constituents other than ethanol	Head and neck, esophagus, liver, others?

Table 2.6.1 *Possible mechanisms of carcinogenicity of alcoholic beverages*
** Subjective assessment of strength of supportive evidence*

differences in acetaldehyde exposure due to the presence of some well-studied common genetic variants with a functional role. Cytochrome P-450 2E1 (CYP2E1) is induced by ethanol, oxidizes ethanol into acetaldehyde, and also activates tobacco procarcinogens including nitrosamines [6]. Methylenetetrahydrofolate reductase (MTHFR) converts 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, which is important for DNA synthesis and methylation. Sequence variants in DNA repair genes such as those on the nucleotide excision pathway, and on the base excision pathway have been studied as susceptibility factors for various cancers. While the study of genetic variation in alcohol metabolizing genes and their association to cancer is a promising area of research [7], it is unclear at present whether the observed associations are true, and whether they will have clinical or public health relevance.

Alcohol drinking is one of the most important known causes of human cancer. With the exception of aflatoxin, for no single dietary factor is there such a strong and consistent evidence of carcinogenicity. In some populations, namely countries of Central and Eastern Europe, where alcoholic intake is thought to be high (Table 2.6.2), the burden of alcohol-associated cancer (and of other alcohol-associated diseases) is substantial. Alcohol consumption is rapidly increasing in large regions of the world, such as East Asia [8]. In the case of breast and colorectal cancer, two major human neoplasms, a causal association with alcohol drinking has been established only recently, and the public health implications of these associations have not been not fully elucidated. In many countries, people of lower socioeconomic status or education consume more alcohol, which contributes to social inequalities in the cancer burden [9].

Despite its importance in human carcinogenesis, research on alcohol and cancer remains limited in clinical, epidemiological and experimental settings. Priorities for a research agenda on alcohol-related carcinogenicity would include: (i) better epidemiological studies on the effect of drinking patterns (in particular binge drinking, the prevalence of which is increasing in many countries) and of specific alcoholic beverages, (ii) investigations on the risk of cancer in suspected target organs, including pancreatic and kidney cancer, and (iii) elucidation of the role of genetic variants in modifying the risk of alcohol-associated cancer, which would also shed light on possible mechanisms of action.

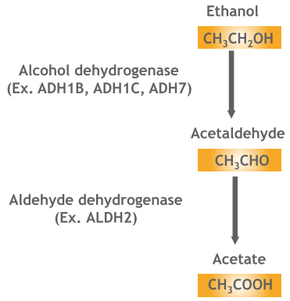


***Fig.* 2.6.2** *The major pathway of alcohol metabolism in humans*

Beer		Wine		Spirits	
Country	**APC**	**Country**	**APC**	**Country**	**APC**
Czech Republic	9.43	Luxembourg	9.43	Republic of Moldova	10.94
Ireland	9.24	France	8.38	Reunion	8.67
Swaziland	7.49	Portugal	7.16	Russian Federation	7.64
Germany	7.26	Italy	6.99	Saint Lucia	7.27
Austria	6.42	Croatia	6.42	Dominica	7.20
Luxembourg	6.16	Switzerland	6.23	Thailand	7.13
Uganda	6.14	Argentina	5.63	Bahamas	7.05
Denmark	6.02	Spain	5.07	Latvia	6.62
The United Kingdom	5.97	Bermuda	4.95	Haiti	6.46
Belgium	5.90	Greece	4.78	Belarus	6.34

***Table* 2.6.2** *Countries with the highest adult per capita (APC) consumption, in litres of pure alcohol by alcoholic beverage type*
** Adapted from the WHO Global Status Report on Alcohol, 2004 [7]*

REFERENCES

1. Boffetta P, Hashibe M (2006). Alcohol and cancer: *Lancet Oncol 7*: 149-156.

2. IARC (1988). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 44, Alcohol drinking. Lyon, France: International Agency for Research on Cancer.*

3. Hashibe M, P Brennan, S Benhamou, et al. (2007). Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst* 99: *777-789.*

4. Rehm J, Room R, Monteiro M, et al. (2004). Alcohol use. In: Ezzati M, Murray C, Lopez AD, Rodgers A (eds). *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors.* Geneva: World Health Organization; 959-1108.

5. Brennan P, Lewis S, Hashibe M, et al. (2004). Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. *Am J Epidemiol* 159: 1-16.

6. Brennan P, Boffetta P (2004). Mechanistic considerations in the molecular epidemiology of head and neck cancer. In: Buffler P, Rice J, Baan R, Bird M, Boffetta P (eds). *Mechanisms of Carcinogenesis: Contributions of Molecular Epidemiology. IARC Sci. Publ. No.157.* Lyon: International Agency for Research on Cancer; 393-414.

7. Hashibe M, McKay JD, Curado MP, et al. (2008). Multiple ADH genes are associated with upper aerodigestive cancers. Nat Genet 40(6):707-709.

8. World Health Organization (2004). *Global Status Report on Alcohol.* Geneva: World Health Organization.

9. Møller H, Tønnesen H (1997). Alcohol drinking, social class and cancer. In: Kogevinas M, Pearce N, Susser M, Boffetta P (eds). *Social Inequalities and Cancer. IARC Sci. Publ. No.138.* Lyon: International Agency for Research on Cancer; 251-63.

2.7 Reproductive Factors and Endogenous Hormones

Summary

> Reproductive factors are strongly involved in the etiology of breast, endometrial and ovarian cancers

> Age at menarche, age at first birth, number of pregnancies, age at last birth and age at menopause have all been associated with cancer risk in women

> Long-term exposure to high levels of endogenous sex steroids increases the risk of breast and endometrial cancers in post-menopausal women

Evidence is accumulating in the literature on the implication of endogenous hormones (particularly sex steroids and growth factors) in the etiology and in the development of several human cancers, especially breast cancer and those of the female reproductive organs (such as ovary and endometrium).

Breast cancer

The incidence of breast cancer is very low in females below the age of 15, and increases very steeply (in the order of about a hundred-fold) by the age of 45. After menopause, the production of estrogens and progesterone from the ovaries ceases, and the increase in breast cancer incidence rates with age slows down compared to pre-menopausal women. This suggests a significant implication of hormones in the etiology/development of breast cancer. *In vitro* experiments have shown that estrogen increases mammary cell proliferation, and *in vivo* experiments in animals have demonstrated that estrogen increases tumour development. Further elements strengthen the association between endogenous sex steroids and breast cancer: an early age at menarche, a late age at menopause and the use of hormone replacement therapy in post-menopausal women have been repeatedly associated with an increase in breast cancer risk [1].

Increases in breast cancer risk are generally explained by the longer lifetime exposure of women to high levels of endogenous sex steroids, especially estradiol, that increase the proliferation and inhibit apoptosis of mammary epithelium (Figure 2.7.1). In addition, overweight and obesity in post-menopausal women not taking exogenous hormones have also been associated with an overall 40% increase in breast cancer risk, and the most widely accepted explanation is again related to the exposure to elevated levels of sex steroids, since in post-menopausal women the ovaries stop producing estrogens, which are instead produced by the aromatisation of androgens in the adipose tissues. Obese women have higher estrogen and lower sex hormone binding globulin (SHBG) levels compared to non-obese women, and therefore increased concentrations of bioavailable estrogens to target tissues.

Early age at first pregnancy, high parity and prolonged breast feeding have been associated with decreased risk of breast cancer (Figure 2.7.2) [1], mainly explained by the differentiation of mammary tissue induced by pregnancy-related hormones. Pregnancy has, however, a double effect on breast cancer risk: a short-term increase and a long-term reduction in risk. The most likely explanation for this double effect is related to the hormone-related differentiation of the cells of the glandular tissues, which reduces the number of susceptible cells (long-term effect), but also stimulates the growth of already existing pre-clinical cancers (short-term effect).

Results from re-analyses and from large-scale prospective epidemiological studies have confirmed a strong implication of endogenous sex steroids in the onset of breast cancer in post-menopausal women (Figure 2.7.3) [2]. Results from these studies showed that women with elevated serum estrogen (estradiol, estrone and free estradiol), as well as androgen (testosterone, free testosterone, androstenedione and dehydrepiandrosterone) concentrations in the upper quintile of the hormones examined were at about two-fold increase in breast cancer risk compared to women in the lowest quintile. SHBG levels were inversely associated with cancer risk. It has also been suggested that the association of circulating sex hormone levels may be stronger with breast cancer positive for estrogen and progesterone receptors. A large prospective study also provided strong evidence of an association of serum endogenous androgens (testosterone, androstenedione, and DHEAS) with breast cancer risk in pre-menopausal women, but no increase in risk was observed for estrogens [3] (Figure 2.7.4).

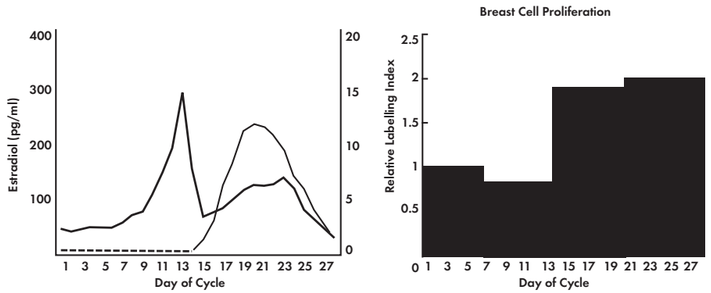


Fig. 2.7.1 *Breast mitotic rate by day of cycle [18]*

Some inconsistencies in the relationship between endogenous estrogens and breast cancer risk in pre-menopausal women across different studies may be due to the difficulty in obtaining accurate estrogen measurements in this population because of the high variability of serum concentrations throughout the menstrual period. It is also plausible that in pre-menopausal women the risk of breast cancer is related to estrogen concentrations in a non-linear manner [3]. A decrease in breast cancer risk among pre-menopausal women was observed with increasing progesterone levels.

Prolactin is a hormone that is involved in the normal development of the normal breast and in lactation. *In vitro*, it promotes cell proliferation and survival, and supports tumour vascularisation. *In vivo*, experiments in animals have shown that prolactin increases tumour growth and proliferation of metastases. A number of case–control studies nested within large cohorts have suggested a positive association between breast cancer incidence and prolactin levels, although results have been more consistent in post-menopausal women than in pre-menopausal women [4].

Insulin-like growth factor-I (IGF-I) is a polypeptide hormone that is involved in several cellular responses related to cell growth, DNA, RNA and protein synthesis. It has mitogenic and anti-apoptotic properties, and co-regulates the proliferation of many cell types, including breast epithelium [5]. Several epidemiological studies have been published on the relationship of circulating IGF-I to breast cancer risk, with different results: preliminary studies reported an overall 2-fold increase in risk with increasing circulating IGF-I levels only in women who had a diagnosis of breast cancer at a relatively young age (before 50 years of age) [6], while more recent studies reported a moderate increase in risk of about 30% in women who had a diagnosis of breast cancer when older than 50 years [7,8].

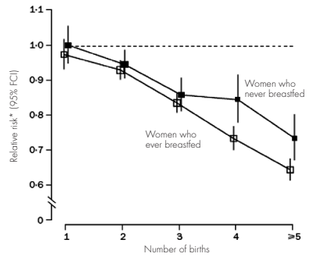


Fig. 2.7.2 *Relative risk of breast cancer in women according to breast feeding history and number of births [19]*

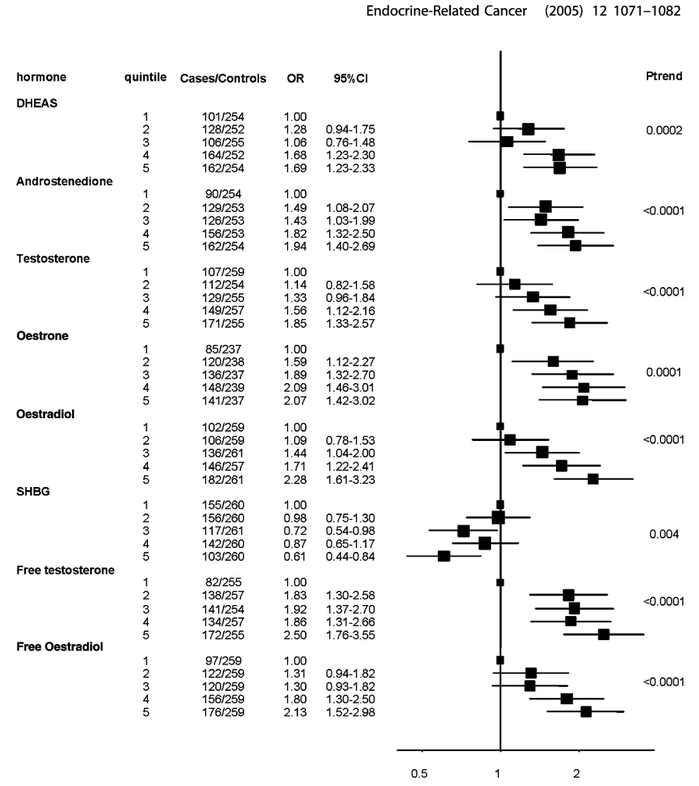


Fig. 2.7.3 *Relative risk of breast cancer among postmenopausal women by quintiles of serum steroid concentrations (the European Prospective Investigation into Cancer and nutrition -EPIC study) [2]*

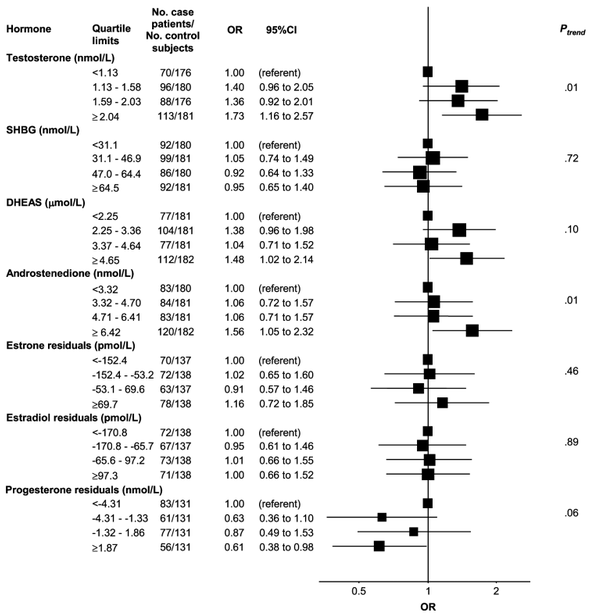


Fig. 2.7.4. *Relative risk of breast cancer among premenopausal women by quintiles of serum steroid concentrations (EPIC study) [3]*

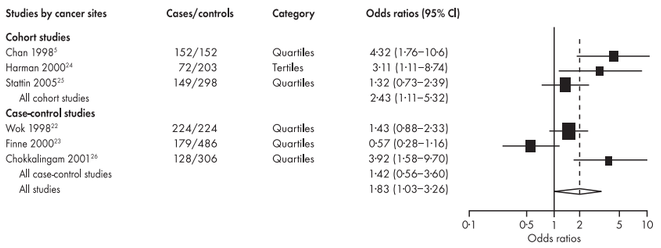


Fig. 2.7.5. *Relative risk of prostate cancer with levels of blood insulin-like growth factor-I. Reanalyses of cohort and case-control studies [17]*

Endometrial cancer

Endometrium is a tissue that is very responsive to hormone stimulation. Risk factors such as an early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity suggest a strong involvement of endogenous hormones in endometrial cancer etiology. The "unopposed estrogen" hypothesis may well explain the relationship between endometrial cancer and sex steroids [9]. This hypothesis states that endometrial cancer risk is increased in women who have relatively high circulating estrogen concentrations that are not counterbalanced by high progesterone concentrations. This theory was mainly developed from the observation that endometrial cells reach their maximum proliferation rates during the follicular phase of the menstrual cycle (a phase in which progesterone concentrations are very low), and from the fact that the use of estrogen-containing only exogenous hormones (without progestagens) increase the risk of endometrial cancer. While estrogen induces the proliferation of the epithelial endometrial cells, progesterone reduces the estrogenic action in the endometrium by stimulating the local synthesis of 17 beta-hydroxysteroid dehydrogenase and by increasing estrogen sulfatase. Progesterone also stimulates the production of insulin-like binding protein-I that lowers the concentration of bioavailable IGF-I.

The "unopposed estrogen" hypothesis can explain most of the risk factors already identified, as early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity. Strong support for the unopposed estrogen hypothesis comes from epidemiological studies, where case–control and prospective studies indicate an increase in risk with increasing circulating estradiol concentrations (Table 2.7.1) [10,11].

While androgens do not seem to have a direct proliferative effect on endometrial cells, they do seem to be involved in endometrial carcinogenesis (possibly through increasing estrogen levels): women with polycystic ovary syndrome (PCOS) (a syndrome associated with increased blood androgen levels, and with infertility, amenorrhea, hirsutism and diabetes), are at higher endometrial cancer risk compared to normal women and tend to develop premenopausal endometrial cancer [10]. Obese women are very often insulin resistant, so they constantly have very high levels of circulating insulin in their blood. Insulin induces endometrial cell proliferation, increases IGF-I activity, stimulates androgen synthesis and down-regulates SHBG concentrations [10], all factors that have been associated with increased risk of endometrial cancer .

Ovarian cancer

Most ovarian malignancies arise from the surface epithelium of the ovary. The epithelium is first trapped within the stroma to form inclusion cysts, which are then transformed into tumour cells. This second step is believed to be hormonally driven. There are already a number of established epidemiological risk factors for ovarian cancer, all suggesting the implication of hormonal factors in the disease aetiology. Infertility, low parity and family history of ovarian cancer increase the risk of ovarian cancer, while the use of oral contraceptives, breast-feeding, hysterectomy or tubal ligation have been shown to decrease the risk [12].

Several hypotheses on the etiology of this cancer have been proposed, including incessant ovulation, excessive gonadotropin stimulation or direct stimulation by steroid hormones [12]. An excessive production of gonadotropins (such as luteinising hormone) can stimulate proliferation and malignant transformations of ovarian epithelium either directly or indirectly through increased ovarian production of androgens. *In vitro* and *in vivo* experiments have shown that ovarian epithelial cell proliferation is stimulated by both androgens and estrogens. Polycystic ovary syndrome (a syndrome associated with increased ovarian androgen secretion) is associated with an increase in ovarian cancer risk, while oral contraceptive use (which suppresses pituitary lutenizing hormone secretion and androgen production) has a strong and long-lasting protective effect [12]. Only a few prospective epidemiological studies have been published so far on the association between endogenous circulating hormones and ovarian cancer risk, with inconsistent results. However, the sample size of these studies was relatively small.

Insulin-like growth factors are involved in steroidogenesis in the ovary, and in the growth and development of ovarian follicles. They have mitogenic and antiapoptotic properties on epithelial ovarian cells. The epidemiological evidence for the implication of IGF-I in ovarian cancer etiology is quite scarce. Recently two case–control studies nested within large cohorts have shown an increase in ovarian risk with increasing circulating IGF-I concentrations in blood in young women (pre- or peri-menopausal age).

Prostate cancer

Most human prostate cancers are very sensitive to androgens and respond to anti-androgen therapies. Surgical and medical castration reduces considerably the risk of metastatic prostate cancers, while some case-reports suggest a causal relationship between the use of androgenic steroids and the development of prostate cancer [13]. Within the prostate, testosterone is reduced to dihydrotestosterone through the activity of 5-alpha reductase, and dihydrotestosterone is metabolised to 3-alpha-androstanediol through the activity of 3-alpha reductase. High intra-prostatic levels of dehydrotestosterone have been associated with an increase in prostate cancer risk. Some studies

Hormone	Quartiles				p for trend
	1	2	3	4	
Estradiol	1.00	1.24 (0.59-2.62)	1.88 (0.88-4.01)	4.13 (1.76-9.72)	0.0008
Estrone	1.00	1.39 (0.66-2.93)	1.81 (0.88-3.71)	3.67 (1.71-7.88)	0.0007
Androstenedione	1.00	1.42 (0.69-2.94)	1.61 (0.75-3.45)	2.15 (1.05-4.40)	0.04
Testosterone	1.00	1.62 (0.82-3.20)	2.30 (1.16-4.55)	1.74 (0.88-3.46)	0.06
DHEAS	1.00	1.49 (0.73-3.02)	2.11 (1.05-4.24)	2.90 (1.42-5.90)	0.002
SHBG	1.00	0.73 (0.38-1.38)	0.41 (0.21-0.81)	0.46 (0.20-1.05)	0.01

Table 2.7.1 *Relative risk of endometrial cancer in postmenopausal women by quartiles of serum steroid concentrations [11]*

suggest a relationship between 5-alfa reductase activity and increased prostate cancer risk. Similarly, experiments in animals showed an increase in epithelial prostate cancer cell proliferation with exposure to androgens. All these data suggest that men exposed to elevated circulating levels of endogenous androgens may be at an increased risk of developing prostate cancer, but for the time being this hypothesis has received only very limited support from epidemiological studies. Results from the Prostate Cancer Prevention Trial showed an approximate 25% reduction in prostate cancer prevalence over the 7-year period of intervention in men taking finasteride (a 5α-reductase inhibitor). With the proportion of high-grade cancers detected in the finasteride group 25% higher than that in the placebo group [14] Updated analysis of the trial has revealed that finasteride reduces the overall risk of prostate cancer by 30% and reduces the risk of clinically significant prostate cancer, including high-grade tumours. For tumours with Gleason scores ≤6, men in the finasteride arm had a relative risk reduction (RRR) of 34% (RR0.66 95% CI 0.55, 0.80). For tumours with Gleason scores ≥7, men in the finasteride arm had an RRR of 27% (RR 0.73 95%CI 0.56, 0.96) [15].

A review of eight prospective studies showed no difference in androgen concentrations between cases and matched controls except for a small increase in androstanediol glucuronide [16]. Studies on circulating estrogens and prolactin showed very little evidence for the implication of these hormones in prostate cancer etiology [16]. IGF-I stimulates proliferation and inhibits apoptosis of prostate cancer cells. In epidemiological studies, evidence is accumulating on the association between circulating endogenous IGF-I concentrations and prostate cancer risk: a meta-analysis suggests an almost 50% increase in cancer risk with high concentrations of IGF-I (Figure 2.7.5) [17]. The increase in prostate cancer seems to be more relevant for aggressive malignancies.

REFERENCES

1. Key TJ, Verkasalo PK, Banks E (2001). Epidemiology of breast cancer. *Lancet Oncol* 2: 133-140.

2. Kaaks R, Rinaldi S, Key TJ, et al. (2005). Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. *Endocr Relat Cancer* 12: 1071-1082.

3. Kaaks R, Berrino F, Key T, et al. (2005). Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 97: 755-765.

4. Tworoger SS and Hankinson SE (2006). Prolactin and breast cancer risk. *Cancer Lett* 243: 160-169.

5. Yu H and Rohan T (2000). Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst* 92: 1472-1489.

6. Renehan AG, Harvie M, Howell A (2006). Insulin-like growth factor (IGF)-I, IGF binding protein-3, and breast cancer risk: eight years on. *Endocr Relat Cancer* 13: 273-278.

7. Rinaldi S, Peeters PH, Berrino F, et al. (2006). IGF-I, IGFBP-3 and breast cancer risk in women: The European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer* 13: 593-605.

8. Baglietto L, English DR, Hopper JL, et al. (2007). Circulating insulin-like growth factor-I and binding protein-3 and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 16: 763-768.

9. Key TJ and Pike MC (1988). The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer* 57: 205-212.

10. Kaaks R, Lukanova A, Kurzer MS (2002). Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 11: 1531-1543.

11. Lukanova A, Lundin E, Micheli A, et al. (2004). Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. *Int J Cancer* 108: 425-432.

12. Lukanova A and Kaaks R (2005). Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. *Cancer Epidemiol Biomarkers Prev* 14: 98-107.

13. Bosland MC (2000). The role of steroid hormones in prostate carcinogenesis. *J Natl Cancer Inst Monogr* 27: 39-66.

14. Thompson IM, Goodman PJ, Tangen CM, et al. (2003). The influence of finasteride on the development of prostate cancer. *N Engl J Med* 349: 215-224.

15. Sarvis JA and Thompson IM (2008). Prostate cancer chemoprevention: update of the Prostate Cancer Prevention Trial findings and implications for clinical practice. Curr Oncol Rep 10(6): 529-32

16. Eaton NE, Reeves GK, Appleby PN, et al. (1999). Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. *Br J Cancer* 80: 930-934.

17. Renehan AG, Zwahlen M, Minder C, et al. (2004). Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 363: 1346-1353.

18. Pike MC, Pearce CL, Wu AH (2004). Prevention of cancers of the breast, endometrium and ovary. *Oncogene* 23: 6379-6391.

19. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease (2002). *Lancet* 360: 187-195.

2.8 Exogenous Hormones and Cancer

Summary

- Oral contraceptive (OC) use reduces the risk of ovarian and endometrial cancer, and this protection persists for at least 20 years after stopping use
- Current OC use is associated with a modest increase in risk of breast and cervical cancer, which however disappears a few years after stopping use
- Hormone replacement therapy (HRT) in menopause is associated with an excess in breast cancer risk that levels off 5–10 years after stopping use
- Unopposed estrogen HRT increases endometrial cancer risk
- HRT may favourably influence colorectal cancer incidence, but the evidence is not conclusive

This chapter considers the cancer risks (and benefits) related to oral contraceptive (OC) and hormone replacement therapy (HRT) use. The use of OCs is associated with a protective effect against ovarian, endometrial and possibly colorectal cancer. However, OC use is associated with excess risk of breast, cervical and liver cancer [1-4]. Benefits and risks of OC use on cancer were reviewed in 1998 and in 2005 by Working Groups at the International Agency for Research on Cancer, which concluded that combined (estrogen-progestin) OCs are carcinogenic to humans based on an increased risk for hepatocellular carcinoma (HCC) [2], breast and cervical cancer [5]. HCC is related to current use of OC, but is extremely rare in young women, and the public health consequences of the association are therefore slight.

Breast cancer

Most information on the relation between breast cancer and OC use is derived from a collaborative reanalysis of individual data including 53 297 women with breast cancer and 100 239 controls from 54 epidemiological studies [6]. This provided definitive evidence that current and recent users of combined OCs have a small increase in the RR of breast cancer (RR 1.24).

However, 10 or more years after stopping use of OC, the RR levels off to approach those of never OC users. The results were similar in women with different background risks of breast cancer. Only women who had begun use before age 20 had an apparent and persistent moderate excess risk (RR 1.22) of breast cancer. Other features of OC use such as duration, dose and type of hormone formulation had little effect on breast cancer risk.

A few additional cohort [7-9] and case–control studies of OC and breast cancer [10-17] have been published after this collaborative reanalysis. In the Royal College of General Practitioners oral contraception study including 46 000 women [9,18], as well as in the Oxford FPA cohort study [19], no relevant association was found between breast cancer incidence mortality and various measures of OC use after more than three decades of follow-up. A cohort study of 426 families of breast cancer probands in Minnesota, USA [8] suggested that ever users of earlier formulations of OC with family history of breast cancer were at high risk for the disease (RR 3.3). That study was based, however, on 38 familial case users only, and contrasted with findings of the collaborative reanalysis [6] which showed no excess risk in users with a family history of breast cancer. A report from the Nurses' Health Study II cohort [20] suggested a favourable effect of physical activity on breast cancer risk in current OC users only, but the data were too limited to adequately assess the interaction between physical activity and OC use. In the Women's Contraception and Reproductive Experiences (CARE) study [21], a population-based case–control study of 1847 postmenopausal women from the USA, previous OC users were not at increased breast cancer risk, and there was a negative interaction between combined hormone replacement therapy (CHRT) use and past OC use. In fact, the excess risk for CHRT use was restricted to never OC users, but it was not observed in past OC users. A few other studies from the USA and Norway [22-24] suggested that use of more recent, low-dose OC is not materially related to breast cancer risk.

Cervical cancer

Cancer of the cervix uteri is relatively rare in developed countries, where cervical screening is widespread, but is still the third most common cancer in women worldwide, with an estimated incidence of about 470 000 cases in 2000, and the second most common in developing countries, where it accounts for about 15% of all cancers in women [25,26]. Also within Europe, the difference in mortality between Western, Central and Eastern European countries was over threefold in the late 1990s, and cervical cancer rates in Eastern Europe have been increasing since the early 1980s [27-29].

Although chronic human papillomavirus (HPV) infection is a necessary cause of cervical cancer [30], other factors are likely to have a role in cervical carcinogenesis. Among these are tobacco smoking and exogenous female hormones, including OCs [31]. Several epidemiological studies have reported an increased risk of invasive cervical carcinoma in relation to ever OC use, and a stronger risk for a longer duration of use. The evidence of an association between OC use and adenocarcinoma of the cervix is based on more limited data [2].

The RR of cervical cancer was significantly elevated among long-term OC users in a study from Morocco [32] and in three studies from the Philippines [33], Thailand [34] and the UK [35]. A study from the USA [36] found no significant association between OC use and invasive or *in situ* cervical carcinoma. In this study, however, an association emerged between long-term OC use and *in situ* adenocarcinoma. In the 35-year follow-up of the Royal College of General Practitioners (RCGP) cohort study, the RR of cervical cancer was 1.33 (95% CI 0.92–1.94, [9]).

Most studies, however, could not take into account HPV infection, and biases related to sexual behaviour or screening could not be ruled out [37]. Given the importance of HPV in cervical carcinogenesis, the relation between OCs and cervical cancer was assessed, restricting the analyses to carriers of HPV DNA. A pooled analysis coordinated by the IARC has been published on the role of OCs in women who tested positive for HPV DNA [38]. This study combined the data of eight case–control studies of invasive cervical cancer and two studies on carcinoma *in situ*, including 1676 cervical cancer cases and 255 controls. No increased risk of cervical cancer was reported for women who had used OCs for less than 5 years, but those who used OCs for 5–9 years had a RR of 2.8, as compared with never users. An even higher risk (RR 4.0) was observed for OC users for 10 or more years. OC use was not associated with HPV positivity among controls, thus suggesting that OCs do not increase the acquisition or persistence of HPV infection, but may facilitate its progression into neoplastic cervical lesions. This finding confirmed the time–risk relation from an Italian case–control study [39] that indicated that OCs have a promoting effect on the process of cervical carcinogenesis, with a fall in risk after stopping use.

In a meta-analysis of 28 cohort and case–control studies of cervical cancer including information on OCs, the overall RR was 1.1 for use of less than 5 years, 1.6 for 5–9 years, and 2.2 for 10 or more years [40]. The data suggest that the risk decreases after OC use has stopped, but the effect of stopping use, independent of duration and other time factors, could not be adequately assessed from published studies.

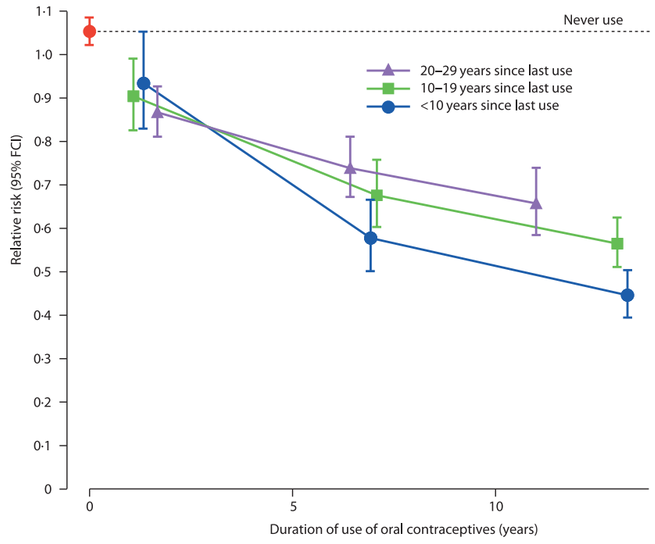


Fig. 2.8.1 *Relative risk* of ovarian cancer by duration and time since last use of oral contraceptives (46)*
**Stratified by study, age, parity, and hysterectomy*

Ovarian cancer

An indication of the favourable impact of OCs on ovarian cancer came from descriptive epidemiology. In several developed countries, young women showed declines in ovarian cancer mortality over the last few decades. Cohort analysis of trends in mortality from ovarian cancer showed that women born after 1920 (i.e. the generations who had used OCs) had reduced ovarian cancer rates, and the downward trends were greater in countries where OCs have been more widely used [2,3]. The protection was similar for newer, low-dose estrogen-progestin pills [41], as well as for various histotypes of ovarian cancer [42], while it is unclear whether the protection is similar for women with hereditary ovarian cancer [43].

The overall estimate of protection for ever use is approximately 30%, and the favourable effect of OCs on epithelial ovarian cancer persists for at least 20 years after stopping use according to the CASH study, and probably continues up to 15–20 years [2,3,5]. The RR was 0.8 up to 20 years after stopping use in a pooled analysis of European studies [44], 0.5 for 15–19 years, and 0.8 for 20 years or more since stopping OC use in a large multicentric US case–control study [45]. The RR was 0.7 for duration >10 years and 20–29 years since last use in the Collaborative Group of Epidemiological Studies of Ovarian Cancer (Figure 2.8.1).In the Oxford Family Planning Association (FPA) cohort study, the RR of death from ovarian cancer was 0.4 at the 30-year follow-up [19], and the RR of ovarian cancer incidence was 0.54 (95% confidence interval, CI 0.40-0.71) for the 35-year follow-up of the RCGP cohort study [9].

Endometrial cancer

OC use also reduces the risk of endometrial cancer by approximately 50% [2,3]. The reduced risk of endometrial cancer persists at least 20 to 30 years after cessation of intake. In the CASH study, the RR was 0.5 for 10–14 years since stopping use; in the WHO study the OR was 0.2 for high progestogen content pills 10 years or more since stopping; in a multicentric US study the OR was 0.3 for 15–19 years and 0.8 for 20 years or more after stopping OC use [2,3]. When duration and recentness of use were evaluated jointly in a case–control study from Washington State [47], longer use (>5 years) was associated with a reduced risk, irrespective of recentness of use. In a Swiss study [48], the RR was 0.4 for 10–19 years after stopping use, and 0.8 for 20 years or more. In a population-based national case–control study from Sweden [49], the RR was 0.2 for 10 or more years of use, and the subsequent use of hormone replacement therapy did not modify the long-term protective effect of OC. The RR of endometrial cancer death was 0.2 in the 30-year follow-up of the Oxford FPA study [19] and that of incidence was 0.58 after 35 years [9]. Endometrial cancer cases were less frequently OC users in a case–control study from China [50].

Colorectal cancer

A role of hormonal and reproductive factors on colorectal carcinogenesis has long been suggested, starting from the observation of an excess of colorectal cancer in nuns [51,52]. A reduction of risk for hormone replacement therapy (HRT) in menopause has also been reported [2,53,54].

Several studies have provided information on OC use and the risk of colorectal cancer. The IARC Monograph 72 [2] reviewed four cohort studies, three of which showed RR for ever OC use below unity. Among 11 case–control studies, the RR was below unity in nine, and significant in two. In a meta-analysis of epidemiological studies on colorectal cancer published up to June 2000, and including quantitative information on OC use, the pooled RR of colorectal cancer for ever OC use was 0.81 from eight case–control studies, 0.84 from four cohort studies, and 0.82 from all studies combined [55]. However, no relation with duration of use was observed. The pattern of risk was similar for colon and rectal cancer. The RR was 0.8 for ever OC use in a recent Swiss case–control study [56]. Only two studies [7,57] included information on recentness of use, and gave some indication that the apparent protection was stronger for women who had used OCs more recently. However, the RR was below unity (RR= 0.79, 95% CI 0.58–0.90) for ever OC users in the 35 years follow-up of the RCGP cohort study [9].

In these analyses, scanty information was available on the type and formulation of OC, but no consistent pattern of trends across calendar year of use (which in several countries is a good proxy of type of preparation) was observed.

Lung cancer

A population-based case–control study of 811 women with lung cancer and 922 controls from Germany [58] showed a reduced lung cancer risk (RR 0.69, 95% CI 0.51–0.92) among ever OC users, in the absence however of any trend in risk with duration of use, age at first use, or calendar year at first use. The RR was non-significantly above unity in the 30-year follow-up of the Oxford FPA cohort study [19] and 1.05 and the 35-year follow-up of the RCGP cohort study [9].

Thus, it is unlikely that any major association is present between OC and lung cancer risk.

Conclusions: OC use

OC use reduces the risk of endometrial and ovarian cancer by approximately 40%; this protection increases with longer use and is long-lasting. The data for colorectal cancer are suggestive of a protective effect of OC, but not conclusive.

With reference to breast cancer, of particular relevance on a public health level is the absence of a persistent excess breast cancer risk in the medium or long term after cessation of OC use, independent of duration of use. In terms of risk assessment for OC use and indications for prescription, these data indicate that any potential increase in risk during OC use, and in the short term after stopping, is of little relevance for younger women whose baseline breast cancer incidence of the disease is extremely low [6,19].

The same line of reasoning applies to cervical cancer. In any case, the association between OC and cervical cancer would be of major relevance in low resource countries, where cervical cancer rates are higher and cervical screening is not adequate [27,29,59,60].

HRT and cancer risk

Menopause has a profound effect on the risk of breast and other female-hormone related cancers, since the slope of incidence for most of these neoplasms levels off after menopause [61]. The most reliable estimate of the influence of menopause on breast cancer risk is given by a collaborative re-analysis of individual data from 51 epidemiological studies including over 52 000 women with breast cancer and 108 000 without breast cancer [62], which estimated an increased risk of 2.8% per year of delayed menopause.

With reference to HRT, in the same data set an elevated risk of breast cancer was reported in current and recent users. The risk increased with longer duration of use by about 2.3% per year, but dropped after cessation of use.

Unopposed estrogen use has been strongly related to endometrial cancer risk in observational studies [2], but cyclic combined estrogen–progestagen risk treatment appears to reduce such an excess risk. Indeed, combined HRT may increase cancer in lean women, but reduce it in overweight ones. However, combined HRT is associated with a higher risk of breast cancer as compared with unopposed estrogens [54,63].

Ovarian cancer risk also appears to be unfavourably influenced by HRT use [64]. Between 1979 and 1998, in the Breast Cancer Detection Demonstration Project (BCDDP) cohort study, 329 cases of ovarian cancer were observed [65]. The RR for estrogen-only HRT was 1.6 (95% confidence interval (CI) 1.2–2.0), for ever users, and rose to 1.8 for 10–19 years of use, and to 3.2 (95% CI 1.7–5.7) for 20 years of use. In the Million Women Study [18], the RR for current HRT users was 1.23 (95% CI 1.09–1.38). The RR increased with duration, and was similar for various types of preparation. There was no excess risk among past users (RR= 0.97).

In contrast, HRT has been related to decreased colorectal cancer risk, the overall RR being about 0.8 among ever users [2,53,54,66].

The most valid evidence on cancer risk in users of combined (estrogen and progestagen) HRT derives, however, from clinical trials, including the Women's Health Initiative (WHI) [67], a randomised controlled primary prevention trial including 8506 women aged 50–70 treated with combined CHRT group and 8102 untreated women. For breast cancer, no difference in risk was apparent during the first 4 years after starting treatment, but an excess risk became evident thereafter, as well as a reduced risk of colorectal cancer. Overall, at 7 years follow-up, 166 breast cancer cases were registered in the CHRT group vs. 124 in the placebo group, corresponding to a RR of 1.24 (95% CI 1.03–1.66).

Data from two other smaller randomised studies are available, one (Heart and Oestrogen/Progestin Replacement Study, HERS) with combined estrogen/progestin therapy [68], and one (Women's Estrogen for Stroke Trial, WEST) with estrogen only [69]. In

	Ever-users*	Duration of use of oral contraceptives			Percent decline in the risk for every 5 years use (95% CI), comparing ever-users
		<5 years	5–9 years	10+ years	
First use before age 20 years					
Relative risk (99% FCI)	0.71 (0.63–0.81)	0.95 (0.80–1.13)	0.65 (0.53–0.81)	0.50 (0.40–0.64)	24.6 (17.0–31.6)
Cases/controls	1009/4381	509/2159	280/1135	169/841	
Mean duration of use	5.4 years	1.9 years	7.0 years	14.2 years	
First use at age 20–24 years					
Relative risk (99% FCI)	0.69 (0.64–0.74)	0.81 (0.73–0.90)	0.68 (0.59–0.78)	0.50 (0.43–0.58)	19.6 (14.4–24.5)
Cases/controls	2051/9384	1166/5063	508/2241	328/1824	
Mean duration of use	5.3 years	1.8 years	6.9 years	13.9 years	
First use at age 25–29 years					
Relative risk (99% FCI)	0.72 (0.66–0.79)	0.84 (0.75–0.95)	0.64 (0.53–0.78)	0.50 (0.41–0.61)	20.4 (14.3–26.0)
Cases/controls	1310/6678	825/3881	249/1376	183/1260	
Mean duration of use	4.8 years	1.6 years	6.8 years	13.6 years	
First use at age 30 years or older					
Relative risk (99% FCI)	0.75 (0.69–0.82)	0.84 (0.76–0.93)	0.63 (0.53–0.74)	0.56 (0.46–0.68)	17.6 (11.6–23.2)
Cases/controls	1740/9337	1131/5583	305/1931	211/1420	
Mean duration of use	4.2 years	1.6 years	6.8 years	12.7 years	

***Table* 2.8.1** *Relative risk of ovarian cancer in ever-users of oral contraceptives compared with that in never users, by age at first use and duration of use of oral contraceptives*
***Never users include 14 703 cases and 51 908 controls with relative risk of 1·00 (99% FCI 0·96–1·04). All relative risks are stratified by study, age, parity, and hysterectomy*
Numbers do not always add to the total, because of missing values

***Fig.* 2.8.2** *Oral contraceptive use reduces the risk of ovarian and endometrial cancer*

a combined analysis of the three randomised trials [70], 205 cases of breast cancer were registered in the HRT groups vs. 154 in the placebo one, corresponding to a pooled RR of 1.27 (95% CI 1.03–1.56). There was however no excess breast cancer risk in the estrogen-only arm of the WHI (RR= 0.77, 95% CI 0.59–1.01, [71]).

Data on endometrial cancer are available from the WHI and the HERS, both based on combined estrogen–progestagen HRT. Overall, 24 cases were observed in the combined HRT groups vs. 30 in the placebo ones, corresponding to a pooled RR of 0.76 (95% CI 0.45–1.31, [70] 2002). This confirms that combined HRT is not related to a material excess risk of endometrial cancer [2,54].

With reference to colorectal cancer, in the WHI 45 cases were observed in the HRT group vs. 67 in the placebo group, corresponding to a RR of 0.63 (95% CI 0.41–0.92). As for breast cancer, the difference in risk between the HRT and the placebo groups became apparent 4 years after starting treatment. Such a time–risk relation gives support to the existence of a real association. There was however no favourable effect on colorectal cancer mortality [66,72]. The combined re-analysis with the HERS data included 56 cases in the combined HRT treatment and 83 cases in the placebo group (pooled RR=0.64, 95% CI 0.45–0.92, [70]).

Observational studies (cohort and case–control) and the limited available evidence from randomised clinical trials do not show any consistent association between HRT and lung cancer risk, as there are similar numbers of studies showing RRs around one (no association) or RRs slightly below one. The absence of any material association between HRT and lung cancer risk is plausible, as it is now apparent that women are not more susceptible to lung cancer than men for a similar level of smoking, thus indicating that female hormones probably do not play an important role in lung carcinogenesis [73]

Conclusions : HRT

Thus, with reference to HRT and cancer risk, the recent findings of the randomised trials are in broad agreement with those of observational (cohort and case–control) studies, and provide convincing evidence that:

(1) HRT, mainly combined estrogen–progestagen HRT, is associated with a moderate excess risk of breast cancer, which becomes evident after a few years of use. The excess risk levels off after 5 to 10 years of stopping use.

(2) Combined HRT is not associated with a material excess risk of endometrial cancer.

(3) HRT has a favourable effect on colorectal cancer risk, which is of interest for any global risk/benefit evaluation of menopause treatment. Its impact on colorectal cancer mortality, if any, remains unclear.

REFERENCES

1. Burkman R, Schlesselman JJ, Zieman M (2004). Safety concerns and health benefits associated with oral contraception. *Am J Obstet Gynecol* 190: S5-22.

2. IARC. (1999). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 72, Hormonal contraception and post-menopausal hormonal therapy*. Lyon, France: International Agency for Research on Cancer.

3. La Vecchia C, Altieri A, Franceschi S, et al. (2001). Oral contraceptives and cancer: an update. *Drug Saf* 24: 741-754.

4. La Vecchia C and Bosetti C (2004). Benefits and risks of oral contraceptives on cancer. *Eur J Cancer Prev* 13: 467-470.

5. Cogliano V, Grosse Y, Baan R, et al. (2005). Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. *Lancet Oncol* 6: 552-553.

6. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer (1996). *Lancet* 347: 1713-1727.

7. Beral V, Hermon C, Kay C, et al. (1999). Mortality associated with oral contraceptive use: 25 year follow-up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ* 318: 96-100.

8. Grabrick DM, Hartmann LC, Cerhan JR, et al. (2000). Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. *JAMA* 284: 1791-1798.

9. Hannaford PC, Selvaraj S, Elliott AM, et al. (2007). Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. *BMJ* 335: 651.

10. Levi F, Lucchini F, Pasche C, et al. (1996). Oral contraceptives, menopausal hormone replacement treatment and breast cancer risk. *Eur J Cancer Prev* 5: 259-266.

11. Lipworth L, Katsouyanni K, Stuver S, et al. (1995). Oral contraceptives, menopausal estrogens, and the risk of breast cancer: a case-control study in Greece. *Int J Cancer* 62: 548-551.

12. Magnusson CM, Persson IR, Baron JA, et al. (1999). The role of reproductive factors and use of oral contraceptives in the aetiology of breast cancer in women aged 50 to 74 years. *Int J Cancer* 80: 231-236.

13. Newcomb PA, Longnecker MP, Storer BE, et al. (1996). Recent oral contraceptive use and risk of breast cancer (United States). *Cancer Causes Control* 7: 525-532.

14. Shapiro S, Rosenberg L, Hoffman M, et al. (2000). Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen contraceptives. *Am J Epidemiol* 151: 396-403.

15. Tryggvadottir L, Tulinius H, Gudmundsdottir GB (1997). Oral contraceptive use at a young age and the risk of breast cancer: an Icelandic, population-based cohort study of the effect of birth year. *Br J Cancer* 75: 139-143.

16. Ursin G, Wu AH, Hoover RN, et al. (1999). Breast cancer and oral contraceptive use in Asian-American women. *Am J Epidemiol* 150: 561-567.

17. Van Hoften C, Burger H, Peeters PH, et al. (2000). Long-term oral contraceptive use increases breast cancer risk in women over 55 years of age: the DOM cohort. *Int J Cancer* 87: 591-594.

18. Beral V, Bull D, Green J, et al. (2007). Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* 369: 1703-1710.

19. Vessey M, Painter R, Yeates D (2003). Mortality in relation to oral contraceptive use and cigarette smoking. *Lancet* 362: 185-191.

20. Colditz GA, Feskanich D, Chen WY, et al. (2003). Physical activity and risk of breast cancer in premenopausal women. *Br J Cancer* 89: 847-851.

21. Norman SA, Berlin JA, Weber AL, et al. (2003). Combined effect of oral contraceptive use and hormone replacement therapy on breast cancer risk in postmenopausal women. *Cancer Causes Control* 14: 933-943.

22. Althuis MD, Brogan DR, Coates RJ, et al. (2003). Hormonal content and potency of oral contraceptives and breast cancer risk among young women. *Br J Cancer* 88: 50-57.

23. Dumeaux V, Alsaker E, Lund E (2003). Breast cancer and specific types of oral contraceptives: a large Norwegian cohort study. *Int J Cancer* 105: 844-850.

24. Marchbanks PA, McDonald JA, Wilson HG, et al. (2002). Oral contraceptives and the risk of breast cancer. *N Engl J Med* 346: 2025-2032.

25. Drain PK, Holmes KK, Hughes JP, et al. (2002). Determinants of cervical cancer rates in developing countries. *Int J Cancer* 100: 199-205.

26. Parkin DM, Bray F, Ferlay J, et al. (2001). Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 94: 153-156.

27. Levi F, Lucchini F, Negri E, et al. (2000). Cervical cancer mortality in young women in Europe: patterns and trends. *Eur J Cancer* 36: 2266-2271.

28. Levi F, Lucchini F, Franceschi S, et al. (2001). Inequalities in health in Europe. *BMJ* 322: 798.

29. Levi F, Lucchini F, Negri E, et al. (2004). Trends in cancer mortality in the European Union and accession countries, 1980-2000. *Ann Oncol* 15: 1425-1431.

30. Walboomers JM, Jacobs MV, Manos MM, et al. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 189: 12-19.

31. Schiffman MH, Brinton LA, Devesa SS, et al. (1996). Cervical cancer. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press 1090-1116.

32. Chaouki N, Bosch FX, Munoz N, et al. (1998). The viral origin of cervical cancer in Rabat, Morocco. *Int J Cancer* 75: 546-554.

33. Ngelangel C, Munoz N, Bosch FX, et al. (1998). Causes of cervical cancer in the Philippines: a case-control study. *J Natl Cancer Inst* 90: 43-49.

34. Chichareon S, Herrero R, Munoz N, et al. (1998). Risk factors for cervical cancer in Thailand: a case-control study. *J Natl Cancer Inst* 90: 50-57.

35. Deacon JM, Evans CD, Yule R, et al. (2000). Sexual behaviour and smoking as determinants of cervical HPV infection and of CIN3 among those infected: a case-control study nested within the Manchester cohort. *Br J Cancer* 83: 1565-1572.

36. Lacey JV, Brinton LA, Abbas FM, et al. (1999). Oral contraceptives as risk factors for cervical adenocarcinomas and squamous-cell carcinomas. *Cancer Epidemiol Biomarkers Prev* 8: 1079-1085.

37. Deligeoroglou E, Michailidis E, Creatsas G (2003). Oral contraceptives and reproductive system cancer. *Ann N Y Acad Sci* 997: 199-208.

38. Moreno V, Bosch FX, Munoz N, et al. (2002). Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 359: 1085-1092.

39. Parazzini F, Chatenoud L, La Vecchia C, et al. (1998). Time since last use of oral contraceptives and risk of invasive cervical cancer. *Eur J Cancer* 34: 884-888.

40. Smith JS, Green J, Berrington de Gonzalez A, et al. (2003). Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet* 361: 1159-1167.

41. Ness RB, Grisso JA, Klapper J, et al. (2000). Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. SHARE Study Group. Steroid Hormones and Reproductions. *Am J Epidemiol* 152: 233-241.

42. Tung KH, Goodman MT, Wu AH, et al. (2003). Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study. *Am J Epidemiol* 158: 629-638.

43. Modan B, Hartge P, Hirsh-Yechezkel G, et al. (2001). Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 345: 235-240.

44. Narod SA, Risch H, Moslehi R, et al. (1998). Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 339: 424-428.

45. Bosetti C, Negri E, Trichopoulos D, et al. (2002). Long-term effects of oral contraceptives on ovarian cancer risk. *Int J Cancer* 102: 262-265.

46. Rosenberg L, Palmer JR, Zauber AG, et al. (1994). A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am J Epidemiol* 139: 654-661.

47. Voigt LF, Deng Q, Weiss NS (1994). Recency, duration, and progestin content of oral contraceptives in relation to the incidence of endometrial cancer (Washington, USA). *Cancer Causes Control* 5: 227-233.

48. Levi F, La Vecchia C, Gulie C, et al. (1991). Oral contraceptives and the risk of endometrial cancer. *Cancer Causes Control* 2: 99-103.

49. Weiderpass E, Adami HO, Baron JA, et al. (1999). Use of oral contraceptives and endometrial cancer risk (Sweden). *Cancer Causes Control* 10: 277-284.

50. Xu WH, Xiang YB, Ruan ZX, et al. (2004). Menstrual and reproductive factors and endometrial cancer risk: Results from a population-based case-control study in urban Shanghai. *Int J Cancer* 108: 613-619.

51. Fernandez E, Bosetti C, La Vecchia C, et al. (2000). Sex differences in colorectal cancer mortality in Europe, 1955-1996. *Eur J Cancer Prev* 9: 99-104.

52. Fraumeni JF, Lloyd JW, Smith EM, et al. (1969). Cancer mortality among nuns: role of marital status in etiology of neoplastic disease in women. *J Natl Cancer Inst* 42: 455-468.

53. Hebert-Croteau N (1998). A meta-analysis of hormone replacement therapy and colon cancer in women. *Cancer Epidemiol Biomarkers Prev* 7: 653-659.

54. La Vecchia C, Brinton LA, McTiernan A (2001). Menopause, hormone replacement therapy and cancer. *Maturitas* 39: 97-115.

55. Fernandez E, La Vecchia C, Balducci A, et al. (2001). Oral contraceptives and colorectal cancer risk: a meta-analysis. *Br J Cancer* 84: 722-727.

56. Levi F, Pasche C, Lucchini F, et al. (2003). Oral contraceptives and colorectal cancer. *Dig Liver Dis* 35: 85-87.

57. Fernandez E, La Vecchia C, Franceschi S, et al. (1998). Oral contraceptive use and risk of colorectal cancer. *Epidemiology* 9: 295-300.

58. Kreuzer M, Gerken M, Heinrich J, et al. (2003). Hormonal factors and risk of lung cancer among women? *Int J Epidemiol* 32: 263-271.

59. Franceschi S, Herrero R, La Vecchia C (2000). Cervical cancer screening in Europe. What next? *Eur J Cancer* 36: 2272-2275.

60. Skegg DC (2002). Oral contraceptives, parity, and cervical cancer. *Lancet* 359: 1080-1081.

61. La Vecchia C and Franceschi S (2003). Hormone replacement therapy and cancer: an update. *Eur J Cancer Prev* 12: 3-4.

62. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer (1997). *Lancet* 350: 1047-1059.

63. Schairer C, Lubin J, Troisi R, et al. (2000). Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 283: 485-491.

64. Bosetti C, Negri E, Franceschi S, et al. (2001). Relationship between postmenopausal hormone replacement therapy and ovarian cancer. *JAMA* 285: 3089.

65. Lacey JV, Mink PJ, Lubin JH, et al. (2002). Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 288: 334-341.

66. La Vecchia C, Gallus S, Fernandez E (2005). Hormone replacement therapy and colorectal cancer: an update. *J Br Menopause Soc* 11: 166-172.

67. Rossouw JE, Anderson GL, Prentice RL, et al. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 288: 321-333.

68. Hulley S, Furberg C, Barrett-Connor E, et al. (2002). Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 288: 58-66.

69. Viscoli CM, Brass LM, Kernan WN, et al. (2001). A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 345: 1243-1249.

70. Beral V, Banks E, Reeves G (2002). Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet* 360: 942-944.

71. Anderson GL, Limacher M, Assaf AR, et al. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 291: 1701-1712.

72. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. (2004). Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 350: 991-1004.

73. La Vecchia C (2006). Hormone replacement therapy in menopause and lung cancer: an update. *Eur J Cancer Prev* 15: 283-284.

CANCER INSTITUTE PROFILE: Instituto Nacional de Enfermedades Neoplásicas (INEN)

The Instituto Nacional de Enfermedades Neoplásicas "Eduardo Cáceres Graziani", better known by the acronym INEN, is the most important cancer hospital in Peru and perhaps can be placed among the best in South America. The outpatient services of INEN saw more than 170 000 patients last year and 10 000 were admitted. Of these 1400 had cervical cancer, 1000 breast cancer, 300 malignant lymphoma, 200 acute leukaemia in adults and 100 in children. Stomach, prostate and lung cancer, in that order, were the most prevalent malignancies in men. Beside the important role in the management of this large number of patients, INEN plays two other roles of great relevance: education of oncologists through a residency program that started in 1952 and has already graduated close to 500 specialists, including some from neighbouring countries, and carrying out research protocols in association with important groups in the United States and Europe.

website: www.inen.sld.pe

2.9 Diet, Obesity and Physical Activity

Summary

> There were great expectations that epidemiological studies would discover the dietary habits associated with increased or decreased risk of cancer

> Results from large prospective cohort studies and randomised trials provided evidence that apart from some specific cancers (e.g., stomach cancer) diet accounted for at best a minority of cancers. In particular, intakes of fat, of fruit and vegetables and of meat were either not associated or only slightly associated with colorectal, breast and prostate cancer occurrence

> New promising research avenues investigate combinations of dietary patterns and of lifestyle (e.g. the Mediterranean pattern), and make greater use of biomarkers of exposure to specific nutrients

Epidemiological studies have found strong associations between diet and cardiovascular disease that have been largely reproduced in laboratory experiments. These findings have led to the development of efficient primary prevention of ischemic cardiovascular diseases and the discovery of pharmaceuticals that can be used for both primary prevention and treatment of these diseases. In contrast to cardiovascular diseases, diet and cancer remains at present a most difficult and complicated area of study [1].

In the 1960s, ecological observations pointed at several intriguing relationships between intake of fats and mortality from colorectal cancer or breast cancer. Figure 2.9.1 is an example of such a correlation often found between a diet component and a cancer. Additionally, studies in migrants showed that subjects moving from areas with a low incidence of several cancers, including colorectal and breast cancer, tend to acquire the cancer incidence levels of the host populations [2-5].

The incidence of and mortality from stomach cancer have declined dramatically over the past 50 years in most industrialised countries. This decline is deemed to be partly due to changes in food preservation (e.g. refrigeration instead of salting or smoking) and nutritional habits (e.g. greater availability of fresh fruits and vegetables). A decline in *Helicobacter pylori* colonisation of the stomach due to antibiotic treatment for other diseases or specific eradication of this bacterium has probably also contributed to the decrease in the stomach cancer burden [5].

All these observations led to the hypothesis that nutrition was the predominant non-genetic factor responsible for cancer. In their seminal work on cancer mortality in the USA, Doll and Peto in 1981 estimated that 35% of cancer deaths could be attributable to dietary and nutritional practices, while 30% could be attributable to tobacco smoking. However, the 35% estimate was within a wide "range of acceptable estimates" ranging between 10% and 70%. This estimate of 35% has been widely quoted and used without comment, usually without quoting the wide range of acceptable estimates. Most of the evidence available at the time of Doll and Peto's report was based on case–control studies, and selection and recall biases have been found to be particularly influential in nutrition-related case–control studies. More recently, Doll and Peto offered new estimates of which 25% of cancer deaths could be due to "diet", with a range of acceptable estimates of 15 to 35% [5,7]. As for their 1981 estimates, Doll and Peto provided little detail on how these estimates were computed.

Because ecological and case–control studies are well-known to be prone to biases and difficult to control for confounding factors, more robust study designs were needed in order to establish more firmly the possible links between dietary patterns and cancer. Prospective cohort studies were mounted in the 1980s mainly in the USA, and later in other parts of the world. Several randomised trials were also organized in the USA, e.g. on fibre intake and colorectal cancer. Contrary to all expectations, these well-conducted large-scale cohort studies and randomised trials have provided evidence against a major direct role of nutritional factors in cancer occurrence.

Diet, lifestyle and colorectal, breast and prostate cancer

Table 2.9.1 provides a brief overview of the main results of prospective cohort and randomised trials on the diet-cancer association, and on overweight/obesity and lack of physical activity on three major cancers: colorectal, breast and prostate. Randomised trials provide the strongest scientific evidence, but such trials testing the impact of modification of dietary habits on cancer risk are complex and expensive. Also, for ethical and practical reasons, many questions cannot be addressed with trials. Systematic review with meta-analysis of prospective cohort studies is the second best source of evidence. In the absence of meta-analysis, the prospective cohort studies themselves are the next best source of evidence, and several reviews (without meta-analysis) have summarised key findings from cohort studies. Case–control studies are not to be taken into account when studies with more robust designs exist. References in the table are intended to guide the reader to useful publications for more detailed literature searches.

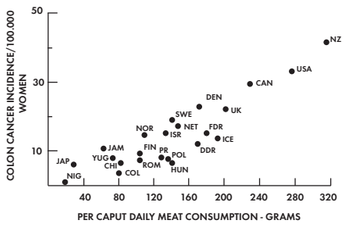


Fig. 2.9.1 *Correlation between incidence of colon cancer in women and mean individual daily meat consumption in 23 countries [6]*

Fig. 2.9.2 *Regular physical exercise appears to be correlated with decreased risk of cancer*

"Small increase" in risk in the table means a risk of cancer occurrence increased by 20 to 30% between groups of subjects with highest versus lowest intakes (groups often defined as quartiles or quintiles). In this case, about 5 to 10% of all cancers may be attributable to high intakes, and thus drastic changes in dietary habits are unlikely to substantially decrease the cancer incidence rate.

The associations between dietary factors and colorectal cancer are of particular interest since this organ may be influenced by foodstuffs in transit through the large bowel, by biological substances absorbed by the colorectal epithelium and by substances circulating in the bloodstream. Prospective cohort studies and clinical trials failed to find evidence for an association between the intake of fibre, of fat and of fruits and vegetables and colorectal cancer. Preserved meat and red meat probably increase the risk of colorectal cancer, but relative risks found so far are of the order of a 30% increase for very high versus very low intakes of red meat. Higher consumption of milk and calcium is associated with a small decreased risk of colorectal cancer, with the inverse association probably limited to cancers of the distal colon and the rectum.

For breast cancer, systematic reviews with meta-analysis have shown no evidence for a protective effect of fruits and vegetables. For fat intake, prospective cohort studies found no association between fat intake and breast cancer, but a randomised trial organized within the Women's Health Initiative trial suggested a small reduction (9%) of borderline significance in breast cancer occurrence with decreased fat intakes [5,8,9].

No association between dietary patterns and prostate cancer has been discovered. The small increase in prostate cancer risk sometimes found with intake of dairy products is probably linked to high calcium intakes rather than to fat intakes. Alcoholic beverages are part of the diet, and have been repeatedly found to be risk factors for colorectal and for breast cancer, but not for prostate cancer (see *Alcohol Drinking*, Chapter 2.6).

For the three major cancers considered in this section, results from prospective studies and randomised trials have yielded results showing no association or associations of much smaller magnitude than were anticipated by results of ecological and case–control studies. As a consequence, drastic changes in some important components of the diet (e.g. a major decrease in fat intake or a significant increase in intakes of fruits and vegetables) are not likely to result in significant change in the incidence of these three frequent cancers.

The case for fruits and vegetables

On the basis of a considerable number of laboratory findings, mechanistic biological hypotheses, and ecological and case–control studies, it was long thought that high intakes of fruits and vegetables would be one of the most efficient primary prevention methods against cancer. The evidence linking high intakes of fruit and vegetables to lower cancer risk has been reviewed by an IARC Working Group [10]: there were no cancers for which the evidence was evaluated as sufficient to conclude that higher fruit or vegetable intake had a preventive effect. Subsequently, major analyses of prospective studies have continued to demonstrate consistently a lack of association between intake of fruits and vegetables and risk of several cancers.

The World Cancer Research Fund has sponsored systematic reviews on diet and cancer. A decade after its original report [11], the current report [12] presents considerably weaker conclusions for the strength of evidence of a protective effect of high intakes of fruits and vegetables against several common epithelial

Fig. 2.9.3 *"There is sufficient evidence in humans for a cancer-preventive effect of physical activity" for cancers of the colon and breast*

Fig. 2.9.4 *"There are no cancers for which the evidence was evaluated as sufficient to conclude that higher fruit or vegetable intake has a preventive effect'*

cancers. The association was downgraded from "convincing" in the first WCRF report in 1997 to "probable" in the second WCRF report of 2007.

Overweight and obesity

The body mass index (BMI) is the weight (in kg) divided by the square of the height (in metres) of an individual. According to international standards, male and female adults with a BMI between 25 and 29.9 kg/m^2 are considered overweight, while those with a BMI equal to or greater than 30 kg/m^2 are obese. Overweight and obesity represent risk factors of considerable importance for cardiovascular diseases, diabetes mellitus and arthritis. An IARC Working Group [13] found that overweight and obesity were consistently associated with:

- in both men and women: adenocarcinoma or the esophagus, kidney cancer;
- men: colon cancer;
- women: breast and endometrial cancer in post-menopausal women.

The IARC systematic review concluded that there was not sufficient evidence for an association of overweight or obesity with prostate cancer (Table 2.9.1). More recent cohort studies [14] and a meta-analysis [15] confirmed findings from the IARC review, and added evidence for a role of obesity in gallbladder cancer in women.

In most industrialised countries, overweight and obesity are increasing, which will contribute to steadily increasing numbers of several cancers in the future. In the coming decades, if there is no reversal in the currently observed trends, obesity and overweight will significantly contribute to further increases in cancer incidence.

Physical activity

The evidence for a cancer-preventive effect of physical activity was evaluated by an IARC Working Group [13] which concluded that "there is sufficient evidence in humans for a cancer-preventive effect of physical activity" for cancers of the colon and breast, and preventive effects increase with increasing physical activity in terms of duration and intensity. This protective effect was independent of the effect of body weight. Conversely, physical inactivity is a risk factor for cancer (Table 2.9.1).

To the best of our knowledge, no study has yet tried to estimate the optimal level of physical activity for cancer prevention. However, for colon cancer, the IARC Working Group on physical activity noted that "at least 30 minutes per day of more than moderate level of physical activity might be needed to see the greatest effect in risk reduction" [13]. For breast cancer, the "risk reduction begins at levels of 30–60 minutes per day of moderate-intensity to vigorous activity in addition to the usual levels of occupational and household activity of most women" [13].

New approaches in the lifestyle-diet-cancer association

Disease occurrence among people following a strict vegetarian diet (i.e. implying no meat, very low-fat diet, and sometimes no animal products at all) has been extensively studied. The most striking observation is that the incidence of breast and prostate cancer is similar among vegetarians than in the background population, while the incidence of colorectal cancer is about half that of the background population [16]. Of interest also, was the finding that the magnitude of decrease in cancer risk (e.g. the colorectal cancer risk) was substantially more associated with a lean body mass index and regular physical exercise than with vegetarian status. These observations prompted the working hypothesis that what really matters is not a particular nutrient or class of nutrients, but rather the combination of dietary pattern and lifestyle habits that influences the likelihood of disease, and of cancer in particular.

The scientific relevance of this working hypothesis has been demonstrated by recent cohort studies that showed decreased risk in overall mortality, and in cancer and cardiovascular, and non-cancer, non-cardiovascular mortality in subjects who had a diet close to the "Mediterranean dietary pattern": rich in carbohydrates, vegetal oil, fish, fruits and vegetables, and poor in meat and animal fat [17-19]. Each single dietary item typically part of or typically at odds with the Mediterranean dietary pattern had no or little association with disease or death occurrence, but it is the combination of dietary items that contributed to lowering cancer and cardiovascular diseases. Conversely, the absence of such a combination would contribute to increasing the risk of cancer and cardiovascular diseases. Furthermore, adherence to a Mediterranean diet was also associated with less smoking, less obesity, more physical activity. Hence, a Mediterranean diet can be considered as usually associated with healthier lifestyle, which also contributes to health benefits associated with this dietary pattern.

Also in line with the working hypothesis, another prospective study showed that the combination of physical activity, absence of smoking and of obesity, low alcohol intake and higher serum vitamin C levels was associated with lower death rates [20].

Another promising research area is the use of biomarkers of exposure, which are likely to provide more reliable reflects of exposures to a variety of food items and behaviours than questionnaires. For instance, the plasma phospholipid elaidic acid level is a good biomarker of dietary intakes of manufactured foods. Results from a cohort study have suggested a strong association between plasma levels of the phospholipid elaidic acid and breast cancer occurrence [21].

	Colorectal cancer (CRC)			Breast cancer			Prostate cancer		
Increases in intakes of	Change in risk	Type of studies	References	Change in risk	Type of studies	References	Change in risk	Type of studies	References
Fruits and vegetables	No change	Review	[22]	No change	RCT	[23]	No change	Cohorts	[24]
	No change	RCT on polyps	[25]	No change	MetaA	[26]			
	No change	MetaA on CRC	[27]						
Fibres	No change	RCT on polyps	[25]	No sufficient data	Review	[12]	No sufficient data	Review	[12]
	No change	MetaA on CRC	[28]						
Fat	No change	RCT on CRC	[29]	Small increase	RCT	[9]	No sufficient data	Review	[12]
	No change	Cohorts	[30]	No change	MetaA	[31]			
Red meat, processed meat	Small increase	Review and cohorts	[22,32,33]	No sufficient data	Review	[12]	No change	Cohorts	[12]
Fish	No change	Review	[22]	No change	Review	[34,35]	No change	Review	[35]
Dairy products, including calcium	Small decrease of polyps	RCT on polyps	[36]	No change in postmenopausal women, possible small decrease in risk in pre-menopausal women	Cohorts	[37]	No change, but possible increased risk with high calcium intakes	Cohorts	[38-42]
	Small decrease of CRC incidence	Cohorts	[41]						
Alcohol	Small increase	Review, MetaA	[43]	Increased risk	MetaA	[31]	No change	Review	[43]
Lifestyle factors									
Overweight/ obesity	Increase	MetaA, Review	[13,15]	Increase after menopause	MetaA, Review	[13,15,31]	No change	MetaA, Review	[13,15]
Lack of physical activity	Increase (for colon cancer)	Review	[13,44]	Increase, mainly after menopause	Review	[13,44]	Small increase	Review	[13]

Table 2.9.1 *Summary of main findings from cohort studies and randomised trials on foodstuffs, lifestyle habits and colorectal, breast and prostate cancer*
MetaA: systematic review with meta-analysis of prospective cohort studies - RCT: randomized controlled trial - Review: exhaustive review of prospective cohort studies, but without meta-analysis
CRC: colorectal cancer

REFERENCES

1. Boyle P, Boffetta P, Autier P (2008). Diet, nutrition and cancer: public, media and scientific confusion. *Ann Oncol* 19: 1665-1667.

2. Maskarinec G and Noh JJ (2004). The effect of migration on cancer incidence among Japanese in Hawaii. *Ethn Dis* 14: 431-439.

3. McCredie M, Williams S, Coates M (1999). Cancer mortality in East and Southeast Asian migrants to New South Wales, Australia, 1975-1995. *Br J Cancer* 79: 1277-1282.

4. McCredie M, Williams S, Coates M (1999). Cancer mortality in migrants from the British Isles and continental Europe to New South Wales, Australia, 1975-1995. *Int J Cancer* 83: 179-185.

5. Tomatis L, Aitio A, Day NE, et al. (1990). *IARC Scientific Publications, Volume 100, Cancer: causes, occurrence and control.* Lyon, France: International Agency for Research on Cancer.

6. Armstrong B and Doll R (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 15: 617-631.

7. Doll R and Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66: 1191-1308.

8. Prentice RL, Caan B, Chlebowski RT, et al. (2006). Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 295: 629-642.

9. Prentice RL and Anderson GL (2008). The women's health initiative: lessons learned. *Annu Rev Public Health* 29: 131-150.

10. IARC (2003). *IARC Handbooks of Cancer Prevention, Volume 8, Fruits and vegetables*. Lyon, France: International Agency for Research on Cancer.

11. World Cancer Research Fund / American Institute for Cancer Research (1997). *Food, Nutrition and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR.

12. World Cancer Research Fund / American Institute for Cancer Research (2007). *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR.

13. IARC (2002). *IARC Handbooks of Cancer Prevention, Volume 6, Weight control and physical activity*. Lyon, France: International Agency for Research on Cancer.

14. Reeves GK, Pirie K, Beral V, et al. (2007). Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 335: 1134.

15. Renehan AG, Tyson M, Egger M, et al. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 371: 569-578.

16. Willett W (2003). Lessons from dietary studies in Adventists and questions for the future. *Am J Clin Nutr* 78: 539S-543S.

17. Mitrou PN, Kipnis V, Thiebaut AC, et al. (2007). Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. *Arch Intern Med* 167: 2461-2468.

18. Trichopoulou A, Costacou T, Bamia C, et al. (2003). Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 348: 2599-2608.

19. Trichopoulou A, Lagiou P, Kuper H, et al. (2000). Cancer and Mediterranean dietary traditions. *Cancer Epidemiol Biomarkers Prev* 9: 869-873.

20. Khaw KT, Wareham N, Bingham S, et al. (2008). Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. *PLoS Med* 5: e12 DOI:10.1371/journal.pmed.0050012.

21. Chajes V, Thiebaut AC, Rotival M, et al. (2008). Association between serum trans-monounsaturated fatty acids and breast cancer risk in the E3N-EPIC Study. *Am J Epidemiol* 167: 1312-1320.

22. Marques-Vidal P, Ravasco P, Ermelinda CM (2006). Foodstuffs and colorectal cancer risk: a review. *Clin Nutr* 25: 14-36.

23. Pierce JP, Natarajan L, Caan BJ, et al. (2007). Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA* 298: 289-298.

24. Kirsh VA, Peters U, Mayne ST, et al. (2007). Prospective study of fruit and vegetable intake and risk of prostate cancer. *J Natl Cancer Inst* 99: 1200-1209.

25. Schatzkin A, Lanza E, Corle D, et al. (2000). Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med* 342: 1149-1155.

26. Smith-Warner SA, Spiegelman D, Yaun SS, et al. (2001). Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *JAMA* 285: 769-776.

27. Koushik A, Hunter DJ, Spiegelman D, et al. (2007). Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst* 99: 1471-1483.

28. Park Y, Hunter DJ, Spiegelman D, et al. (2005). Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA* 294: 2849-2857.

29. Beresford SA, Johnson KC, Ritenbaugh C, et al. (2006). Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 295: 643-654.

30. Giovannucci E, Rimm EB, Stampfer MJ, et al. (1994). Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 54: 2390-2397.

31. Michels KB, Mohllajee AP, Roset-Bahmanyar E, et al. (2007). Diet and breast cancer: a review of the prospective observational studies. *Cancer* 109: 2712-2749.

32. Cross AJ, Leitzmann MF, Gail MH, et al. (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med* 4: e325 DOI:10.1371/journal.pmed.0040325.

33. Norat T, Bingham S, Ferrari P, et al. (2005). Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst* 97: 906-916.

34. Engeset D, Alsaker E, Lund E, et al. (2006). Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer* 119: 175-182.

35. Terry P, Rohan TE, Wolk A, et al. (2002). Fish consumption and breast cancer risk. *Nutr Cancer* 44: 1-6.

36. Baron JA, Beach M, Mandel JS, et al. (1999). Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 340: 101-107.

37. Shin MH, Holmes MD, Hankinson SE, et al. (2002). Intake of dairy products, calcium, and vitamin d and risk of breast cancer. *J Natl Cancer Inst* 94: 1301-1311.

38. Ahn J, Albanes D, Peters U, et al. (2007). Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 16: 2623-2630.

39. Giovannucci E, Liu Y, Stampfer MJ, et al. (2006). A prospective study of calcium intake and incident and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev* 15: 203-210.

40. Park SY, Murphy SP, Wilkens LR, et al. (2007). Calcium, vitamin D, and dairy product intake and prostate cancer risk: the Multiethnic Cohort Study. *Am J Epidemiol* 166: 1259-1269.

41. Park Y, Mitrou PN, Kipnis V, et al. (2007). Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol* 166: 1270-1279.

42. Rodriguez C, McCullough ML, Mondul AM, et al. (2003). Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. *Cancer Epidemiol Biomarkers Prev* 12: 597-603.

43. Boffetta P and Hashibe M (2006). Alcohol and cancer. *Lancet Oncol* 7: 149-156.

44. Kruk J (2007). Physical activity in the prevention of the most frequent chronic diseases: an analysis of the recent evidence. *Asian Pac J Cancer Prev* 8: 325-338.

CANCER INSTITUTE PROFILE: Prof. N. N. Petrov Research Institute of Oncology

The Research Institute was established on the 15th of March 1927 in Leningrad (now St. Petersburg, Russia) within the framework of the multidisciplinary hospital named after I. I. Mechnikov. Professor N. N. Petrov, the founder and initiator of oncology in Russia,, was appointed as its first Director; in 1966, his name was given to the Institute.

The Institute has the state license on performing research, clinical and experimental activities in the field of oncology as well as educational, international and editorial work. The main issues of the investigations are as follows: etiology and pathogenesis of cancer, new methods of prevention and detection of cancer, surgery, radiotherapy, chemotherapy and combined treatment of adult and paediatric cancer patients, as well as their follow-up and rehabilitation.

The Institute's hospital consists of 405 beds and is able to treat all principal malignancies. Many tumours can be cured by the endoscopic methods; conservative, organ-saving surgery is being carried out on the early stages of cancer.

Our Institute is associated with many international organisations such as the International Agency for Research on Cancer (IARC), International Union Against Cancer (UICC), World Health Organization (WHO), and the United Nations Environment Program (UNEP). Some Institute scientists are members of different international scientific and social organizations as well (ASCO, ESMO, ESO, ESSO, ESTRO, EORTC, Reach to Recovery, etc.).

Our current areas of specific research interest include:

- study of carcinogenesis mechanisms, and the roles of endo- and exogenous factors influencing cancer development and indicating means for its prevention;
- investigation of biochemical, molecular and immunological factors that allow assessment of cancer risk and greater understanding of its development;
- development of methods of biotherapy of solid tumours (dendrite cell vaccines, genotherapy, cytokines);
- elaboration and introduction of new highly-effective drugs and high-quality methods, based on the latest scientific achievements, and complex usage of new and standard techniques of cancer treatment;
- study and introduction of new drugs and methods for improving tolerance of anti-cancer therapy, reducing its toxicity and increasing the quality of cancer patients' lives;
- improvement of organ-saving surgery aimed at better quality of life for cancer patients; and improvement of methods for accurate estimation and correct planning of cancer control activities in Russia by studying different kinds of indices in cancer (mortality, morbidity, demography, etc.) as well as dynamic prognostication of these indices in the future by using Cancer Registry data.

2.10 Ionising Radiation

Summary

> Exposure to ionizing radiation from natural as well as from industrial, medical and other sources can increase the risk of a variety of neoplasms, including leukaemia, breast cancer and thyroid cancer

> Over 20 years have passed since the nuclear accident at Chernobyl, and it is now estimated that by 2065 there will be 16 000 cases of thyroid cancer and 28 000 cases of other cancers in Europe as a result of this accident

Natural and man-made sources generate radiant energy in the form of electromagnetic waves. Their interaction with biological systems is principally understood at the cellular level. Electromagnetic waves are characterised by their wavelength, frequency or energy. Effects on biological systems are determined by the intensity of the radiation, the energy in each photon and the amount of energy absorbed by the exposed tissue.

The electromagnetic spectrum extends from waves at low frequency (low energy), referred to as "electric and magnetic fields", to those at very high frequencies, which are often called "electromagnetic radiation" (Figure 2.10.1). The highest-energy electromagnetic radiation is X- and gamma-radiation, which have sufficient photon energy to produce ionization (i.e. create positive and negative electrically-charged atoms or parts of molecules) and thereby break chemical bonds. Other forms of ionizing radiation are the sub-atomic particles (neutrons, electrons (beta-particles) and alpha-particles) that make up cosmic rays and are also emitted by radioactive atoms. Non-ionizing radiation is a general term for that part of the electromagnetic spectrum which has photon energies too weak to break chemical bonds, and includes ultraviolet radiation, visible light, infrared radiation, radiofrequency and microwave fields, extremely low frequency (ELF) fields, as well as static electric and magnetic fields.

Ionizing radiation

Exposure to ionizing radiation is unavoidable [1]. Humans are exposed both to X-rays and gamma-rays from natural sources (including cosmic radiation and radioactivity present in rocks and soil) and typically, to a much lower extent, from man-made sources (Figure 2.10.2).

On average, for a member of the general public, the greatest contribution comes from medical X-rays and the use of radiopharmaceuticals, with lower doses from fallout from weapons testing, nuclear accidents (such as Chernobyl) and accidental and routine releases from nuclear installations. Medical exposures occur both in the diagnosis (e.g. radiography) of diseases and injuries and in the treatment (e.g. radiotherapy) of cancer and of some benign diseases. Occupational exposure to ionizing radiation occurs in a number of jobs, including the nuclear industry and medicine. Airline pilots and crew are exposed to cosmic radiation. The risk projections suggest that (by 2006) Chernobyl may have caused about 1000 cases of thyroid cancer and 4000 cases of other cancers in Europe, representing about 0.01% of all incident cancers since the accident. Models predict that by 2065 about 16 000 (95% CI 3400–72 000) cases of thyroid cancer and 25 000 (95% CI 11 000–59 000) cases of other cancers may be expected due to radiation from the accident, whereas several hundred million cancer cases are expected from other causes [2-4].

Although these estimates are subject to considerable uncertainty, they provide an indication of the order of magnitude of the possible impact of the Chernobyl accident. It is unlikely that the cancer burden from the largest radiological accident to date could be detected by monitoring national cancer statistics. Indeed, results of analyses of time trends in cancer incidence and mortality in Europe do not at present indicate any increase in cancer rates—other than of thyroid cancer in the most contaminated regions—that can be clearly attributed to radiation from the Chernobyl accident.

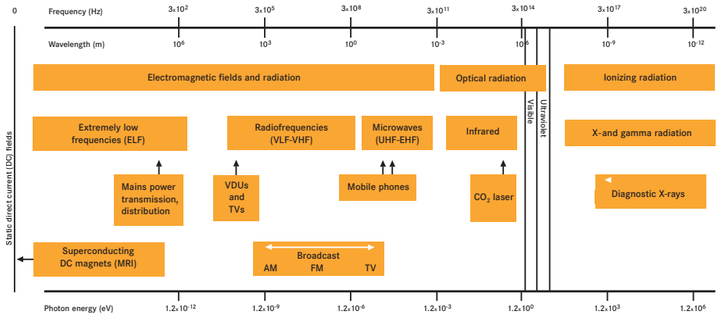


Fig. 2.10.1 *The spectrum of electromagnetic fields and their use in daily life*

Cancer causation

Ionizing radiation is one of the most intensely studied carcinogens [5-7]. Knowledge of associated health effects comes from the epidemiological study of hundreds of thousands of exposed persons, including the survivors of the atomic bombings in Hiroshima and Nagasaki, patients irradiated for therapeutic purposes, populations with occupational exposures and people exposed as a result of accidents. These data are complemented by findings from large-scale animal experiments carried out to evaluate the effects of different types of radiation, taking account of variation in dose and exposure pattern, and with reference to cellular and molecular endpoints. Such experiments are designed to characterise the mechanisms of radiation damage, repair and carcinogenesis.

Survivors of the atomic bombings in Hiroshima and Nagasaki were exposed primarily to gamma rays. Among these people, dose-related increases in the risk of leukaemia, breast cancer, thyroid cancer and a number of other malignancies have been observed. Increased frequency of these same malignancies has also been observed among cancer patients treated with X-rays or gamma rays. The level of cancer risk after exposure to X-rays or gamma rays is modified by a number of factors in addition to radiation dose, and these include the age at which exposure occurs, the length of time over which radiation is received and the sex of the exposed person. Exposure to high-dose radiation increases the risk of leukaemia by over five-fold. Even higher relative risks have been reported for thyroid cancer following irradiation during childhood.

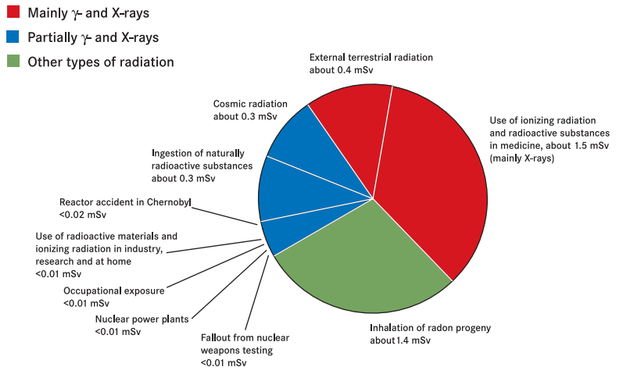


Fig. 2.10.2 *Estimated annual dose of ionizing radiation received by a member of the general public*

	Lifetime risk		Number of years of life lost per case	
	0.2 Sv	1 Sv	0.2 Sv	1 Sv
Solid cancers	2.4%	10.9%	11.2	11.6
Leukaemia	0.14%	1.1%	31	31

Table 2.10.1 *Estimated risk of cancer following acute whole-body exposure to gamma-radiation at two dose levels*

In a study of nuclear industry workers from 15 countries, 1–2% of cancer-related deaths other than leukaemia may be attributable to protracted low-dose radiation exposure while on the job [8]. Other than leukaemia, associations were the most significant for lung cancer and multiple myeloma [9].

Internalised radionuclides that emit alpha-particles and beta-particles are carcinogenic to humans. For most people, exposure to ionizing radiation from inhaled and tissue-deposited radionuclides is mainly from naturally-occurring radon-222. Exposure to thorium-232, which occurs in soil, is less common. Cancers associated with exposure to particular nuclides, usually in an occupational context, include lung cancer, bone sarcomas, liver cancer, leukaemia and thyroid cancer.

The United Nations Scientific Committee on the Effects of Atomic Radiation [10] has estimated the lifetime risk of solid cancers and of leukaemia following an acute whole-body exposure to gamma-radiation, together with the corresponding estimated numbers of years of life lost per radiation-induced case. The current recommendations of the International Commission for Radiological Protection are to limit exposures to the general public to 1 mSv per year, and doses to workers to 100 mSv over 5 years [11] (1 Sievert equals 1 joule per kilogram).

Another source of ionizing radiation to the public and workers is from accidents and releases from nuclear power plants. The largest nuclear accident in history occurred on April 26, 1986 at the Chernobyl nuclear plant in northern Ukraine. The Chernobyl accident resulted in a large release of radionuclides, which were deposited over a very wide area, particularly in Europe. In 2003, the WHO convened an Expert Group on Health (EGH) that produced a comprehensive technical report on the health effects of the Chernobyl accident. The main long-term health effect of radiation exposure as a result of the accident is expected to be cancer [12]. To date, a dramatic risk in the incidence of thyroid cancer has been observed among those who were

exposed as children and adolescents in the most heavily contaminated areas following the accident. There has been anecdotal evidence of rises in other cancers, but such increases could not be differentiated from improvement in registration, diagnosis and reporting [12].

A large increase in the incidence of childhood thyroid cancer was reported in contaminated areas. Most of the radiation exposure to the thyroid was from iodine isotopes, especially I-131. Cardis et al. [13] studied 276 case patients with thyroid cancer through 1998 and 1300 matched control subjects, all aged younger than 15 years at the time of the accident. Individual doses were estimated for each subject based on their whereabouts and dietary habits at the time of the accident and in the following days, weeks and years; their likely stable iodine status at the time of the accident was also evaluated. A strong dose-response relationship was observed between radiation dose to the thyroid received in childhood and thyroid cancer risk (P<.001). For a dose of 1 Gy, the estimated odds ratio of thyroid cancer varied from 5.5 (95% CI= 3.1–9.5) to 8.4 (95% CI= 4.1–17.3), depending on the risk model. A linear dose-response relationship was observed up to 1.5–2 Gy.

The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas (relative risk [RR]= 3.2, 95% CI = 1.9–5.5) than elsewhere. Administration of potassium iodide as a dietary supplement reduced this risk of radiation-related thyroid cancer by a factor of 3 (RR = 0.34, 95% CI = 0.1–0.9 for consumption of potassium iodide versus no consumption).

Exposure to I-131 in childhood is associated with an increased risk of thyroid cancer. Both iodine deficiency and iodine supplementation appear to modify this risk. These results have important public health implications: stable iodine supplementation in iodine-deficient populations may substantially reduce the risk of thyroid cancer related to radioactive iodines in the case of exposure to radioactive iodines in childhood that may occur after radiation accidents or during medical diagnostic and therapeutic procedures.

It has taken longer to estimate the impact of the accident on the risk of other cancers in Europe. An IARC Working Group was established to estimate the human cancer burden in Europe as a whole from radioactive fallout from the accident [14].

Fig. 2.10.3 *The Chernobyl nuclear power plant*

Agent or substance	Cancer site/cancer
IARC Group 1: Carcinogenic to humans	
X-rays and gamma-radiation	Various – all sites
Solar radiation	Skin
Radon-222 and its decay products	Lung
Radium-224, -226, -228 and their decay products	Bone
Thorium-232 and its decay products	Liver, including haemangiosarcoma; leukaemia
Radioiodines (including iodine-131)	Thyroid
Plutonium-239 and its decay products (aerosols)	Lung, liver, bone
Phosphorus-32	Leukaemia
Neutrons	Various
Alpha (a) particle-emitting radionuclides	Various
Beta (b) particle-emitting radionuclides	Various
IARC Group 2A: Probably carcinogenic to humans	
Sunlamps and sun beds, use of	Skin
Ultraviolet radiation	Skin

Table 2.10.2 *Various forms and sources of radiation that are carcinogenic to humans (IARC Group 1) or probably carcinogenic to humans (IARC Group 2A)*

REFERENCES

1. IARC (2000). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 75, Ionizing Radiation, Part 1: X- and Gamma-radiation and Neutrons*. Lyon, France: International Agency for Research on Cancer.

2. Cardis E, Howe G, Ron E, et al. (2006). Cancer consequences of the Chernobyl accident: 20 years on. *J Radiol Prot* 26: 127-140.

3. Cardis E, Kesminiene A, Ivanov V, et al. (2005). Risk of thyroid cancer after exposure to 131I in childhood. *J Natl Cancer Inst* 97: 724-732.

4. Cardis E, Krewski D, Boniol M, et al. (2006). Estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident. *Int J Cancer* 119: 1224-1235.

5. United Nations Scientific Committee on the Effects of Atomic Radiation (2000). *Sources and effects of Ionizing radiation: 2000 Report*. Vienna: UNSCEAR.

6. US National Academy of Sciences (1990). *Health effects on populations of exposure to low levels of ionizing radiation (BEIR V Report)*. Washington, DC: National Academy of Sciences.

7. US National Academy of Sciences (1998). *Health effects of radon and other internally deposited Alpha-emitters (BEIR IV Report)*. Washington, DC: National Academy of Sciences.

8. Cardis E, Vrijheid M, Blettner M, et al. (2005). Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *BMJ* 331: 77.

9. Cardis E, Vrijheid M, Blettner M, et al. (2007). The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. *Radiat Res* 167: 396-416.

10. United Nations Scientific Committee on the Effects of Atomic Radiation (1994). *Sources and Effects of Ionizing Radiation: 1994 Report*. Vienna: UNSCEAR.

11. International Commission on Radiological Protection (1991). *Recommendations of the International Commission on Radiological Protection*. Oxford: Pergamon Press.

12. Lahkola A, Auvinen A, Raitanen J, et al. (2007). Mobile phone use and risk of glioma in 5 North European countries. *Int J Cancer* 120: 1769-1775.

13. Schoemaker MJ, Swerdlow AJ, Ahlbom A, et al. (2005). Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. *Br J Cancer* 93: 842-848.

14. Lonn S, Ahlbom A, Christensen HC, et al. (2006). Mobile phone use and risk of parotid gland tumor. *Am J Epidemiol* 164: 637-643.

2.11

Sunlight and Ultraviolet Radiation

Summary

> Sunlight is by far the most significant source of ultraviolet irradiation and causes several types of skin cancer, particularly in highly-exposed populations with fair skin, e.g. Australians of Caucasian origin

> Sunlight is recognised as the cause of squamous and basal cell cancer, and of cutaneous melanoma

> Genetically determined sensitivity to sunlight is associated with high propensity to sunburn, poor tanning ability, red hair and freckles.

> Artificial sources of ultraviolet radiation have become common in many countries, mainly as sunlamps for indoor tanning purposes. Indoor tanning is associated with increased risk of cutaneous melanoma and of squamous cell cancer when exposure started before 30 years old

> Sun protection should be based on seeking shade, clothes and hat wearing. Sunscreens should be applied only on body parts that cannot be protected with clothes or hats

Exposure to sunlight has been shown to be the main cause of skin cancer, including cutaneous melanoma (CM), basal skin cancer (BCC) and squamous skin cancer (SCC), and since 1992 solar radiation has been classified as a Group I carcinogenic agent by the IARC [1]. Approximately 5% of the total solar radiation received at the surface of the earth is in ultraviolet range, and the sun is the main source of exposure to UVR for most individuals. Sufficient evidence shows that the ultraviolet radiation (UVR) is the main environmental cause of SCC and BCC. This radiation is also deemed to be the main environmental cause of CM in humans. There are currently no recommendations for "safe doses" for human skin, i.e. there is no threshold UVR dose below which there would not be increased risk of skin cancer. Sunlight and UVR are also suspected to play a role in ocular melanoma, but further evidence of a possible causal association is needed.

Sunlight consists of visible light (400–700 nm), infrared radiation (>700 nm) and UVR. UVR belongs to the non-ionizing part of the electromagnetic spectrum and ranges from 100 nm to 400 nm; 100 nm has been chosen arbitrarily as the boundary between non-ionizing and ionizing radiation. UV radiation is conventionally categorised into 3 regions: UVA (>315–400 nm), UVB (>280–315 nm) and UVC (>100–280 nm). The quality (spectrum) and quantity (intensity) of sunlight are modified during its passage through the atmosphere. The ozone contained in the stratosphere (10–50 km above the earth's surface) stops almost all UV radiation <290 nm (UVC) as well as 70 to 90% of the UVB.

On the Mediterranean coast at noon in the summer, the UVR radiation from sunlight consists of about 95% UVA and about 5% UVB. UVB has long been recognised as the carcinogenic component of UVR. Since the end of the 1990s, both UVA and UVB have been known as having carcinogenic effects, but much more UVA is needed to achieve carcinogenic effects (e.g. DNA damage) similar to those observed with UVB. Also, UVA penetrates deeper into the skin than UVB, and causes biological damage that is qualitatively different from that induced by UVB, and which might also be implicated in skin carcinogenesis.

An individual's level of exposure to UV varies with latitude, altitude, time of year, time of day, clouding of the sky and other atmospheric components such as air pollution. At the Earth's surface, compared to UVA, UVB irradiation is more related to latitude (highest around the equator and lowest around the poles), season (highest in hot seasons, lowest in colder seasons), time of day (highest around 10 AM–2 PM solar hours), altitude (higher at altitude than at sea level), and earth surface cover (e.g. UVB is reflected by snow or by water).

Ozone depletion

Ozone depletion has been caused by substances released in the atmosphere that destroy the ozone (ozone-depleting substances (ODS)), for instance the chlorofluorocarbons (CFC) that were used as spray propellants until 1992, when an international ban known as the revised Montreal Protocol was applied to use of these substances [2]. The stratospheric ozone levels have decreased annually since the 1970s, especially in the southern hemisphere. Because the atmosphere in thinner at the poles, the ozone depletion is maximal at the most Northern and most Southern areas, and lowest at the equator. Thus the Nordic countries, Australia, New Zealand, Canada, and Russia, all generally populated with light-skinned people, are at higher risk of increased SCC and cutaneous melanoma because of ozone depletion [3].

In the past few years, the ozone layer seems to have stabilised, and current prospects of recovery of the ozone layer are also linked to the evolution of global climate change [4,5].

Acute effects of exposure to sunlight and other sources of UVR

The most common acute skin reaction induced by exposure to sunlight and other sources of UVR is an inflammatory process at skin level expressed as an erythema (i.e. skin reddening in light-skinned individuals). With increasing UVR dose, skin erythema develops as sunburn that is often painful and may sometimes be complicated with blisters. The minimal erythemal dose (MED) was the first way to biologically quantify exposure to UVR in humans, and is defined as the minimal amount of energy from sunlight (or other UVR sources) required for producing a qualifying erythemal response, usually after 24h.

Acquisition of a suntan is the other acute affect. But contrary to many beliefs, an acquired tan offers little protection against DNA damage induced by UVR. An acquired tan is mainly triggered by UVR-induced DNA damage itself, and is thus more an indicator of carcinogenic skin damage than a protection against this damage. It is the constitutive pigmentation that represents a real protection against the damaging effects of UVR.

UVB is far more efficient than UVA in inducing the synthesis of melanin, and for producing a deep, persistent tan. UVB is also one thousand times more potent than UVA for inducing sunburn.

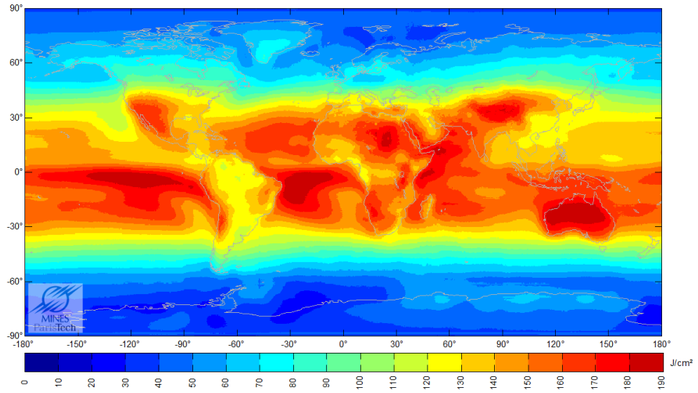


Fig. 2.11.1 *Yearly mean of daily UV (280-400 nm) irradiation in the world (Joules/cm2, 1990-2004)*

Individual susceptibility to skin carcinogenic damage due to sunlight and UVR

Susceptibility to carcinogenic effects of sunlight and UVR is highly genetically determined. The most susceptible individuals are those with very pale skin who always burn and never tan when in the sun. Red hair and numerous freckles (or solar lentigines) on the face, arms or shoulders are other host characteristics indicative of high sun sensitivity. The latter characteristics are sometimes termed the "Celtic phenotype", which has been discovered to be associated with mutations in the MC1R gene. This gene regulates the formation of eumelanin (that is brown or black and photoprotective) by melanocytes and also the capacity of the melanocyte to resist UVR-induced DNA damage. The MC1R gene is highly polymorphic, and about 80 mutations of this gene have been described [6]. These mutations may induce functional defects resulting in variable increases in the susceptibility to UVR-induced skin lesions [7]. These mutations also lead to the synthesis of pheomelanin (instead of eumelanin) that is red or yellow and is suspected to also play a role in skin cancer occurrence [8].

Individuals with light skin but low propensity to sunburn and who tan easily are much less susceptible to carcinogenic effects of sunlight and UVR. Individuals with naturally pigmented skin (i.e. constitutive pigmentation) have a very low susceptibility to carcinogenic effects of sunlight or UVR. As a result, skin cancer is rare in dark-skinned populations. The rare cutaneous melanoma occurring in individuals with naturally pigmented skin will often develop on the soles of feet or under toenails, as a result of skin insult due to barefoot walking.

Individual susceptibility may be greatly increased by inherited or acquired diseases or by treatments. For instance, subjects with rare inherited deficits in DNA repair (e.g. *xeroderma pigmentosum*) develop hundreds of times more skin cancers. African albino subjects are at high risk of developing multiple SCC. Psoriasis patients treated with PUVA (oral psoralens combined with sessions of UVA irradiation) have a higher risk of developing SCC as well as BCC. Patients under immune suppression therapy for organ transplant have a high risk of developing skin cancer.

Age and susceptibility to sunlight and UVR

A large body of data shows that in light-skinned populations, susceptibility to carcinogenic effects of sunlight and UVR relevant to cutaneous melanoma (and probably also to BCC) are greater during childhood and adolescence. Studies in migrants indicate that the younger the age at exposure, the greater the risk of cutaneous melanoma in later life [9]. Also, sun exposure during adult life is associated with cutaneous melanoma occurrence only if sun exposure took place during childhood [10]. This age-related susceptibility is most probably related to the immaturity of the skin, it being more vulnerable to UVR-induced damage in younger populations.

Gender and anatomical differences in susceptibility to sunlight and UVR

Sharp gender contrast exists for the body distribution of cutaneous melanoma: in males, most cutaneous melanoma occur on the trunk and shoulders, then on the upper arms and on the face, while in women, most cutaneous

melanoma occur on the lower limbs, and then on the upper limbs [11]. The number of acquired nevi is the strongest individual predictor of cutaneous melanoma, and the body distribution of nevi in young children parallels the body distribution of CM in adults [12]. These findings further underline the importance of childhood exposure to sunlight for the development of CM during adult life. They also illustrate that different body parts have different susceptibility to sunlight and UVR that this also varies with gender.

BCC usually occurs on the head and the neck, but recent data show increasing BCC incidence on body sites that are only intermittently sun-exposed, e.g. the trunk [13]. SCC occurs nearly always on chronically sun-exposed areas, such as the head and the neck.

Sunlight, artificial sources of UVR and human behaviours

Exposure to sunlight or to other sources of UVR encompasses a large variety of behaviours. In the 1980s, epidemiological studies evidenced that SCC was more associated with the chronic sun exposure pattern, i.e. lifetime accumulation of exposure to sunlight (e.g. outdoor workers, farmers), while cutaneous melanoma was associated with the so-called intermittent sun exposure pattern, i.e. subjects spending most of their time indoors and having brutal acute sun exposures during holidays in sunny areas, with often the pursuit of tanned skin or of a "healthy look" [1,14,15]. BCC was associated with both exposure patterns.

More recently, it has been suggested that all these behaviours can be grouped into two broad categories distinguishing between non-intentional and intentional sun exposure [16,17]. Non-intentional sun exposure (NISE) represents sun exposure during daily activities, without willingly acquiring a tan or intentionally spending a long time in the sun. During NISE, skin areas most usually sun exposed are the head and neck, the hands, the forearms, and in subjects wearing short trousers or skirts, the lower legs and the dorsum of feet. Examples of NISE are outdoor activities such as gardening or work on building sites or in farming fields, as well as sport activities like skiing.

Intentional sun exposure (ISE) is essentially motivated by the acquisition of a tan or by the possibility or going uncovered in the sun. During ISE, significant portions of the trunk, shoulders and of the upper parts of limbs are frequently uncovered.

Cutaneous melanoma occurrence is more associated with ISE situations, while SCC occurrence is more associated with NISE situations. BCC occurrence is most probably associated with both types of sun exposure.

Non-intentional exposures to sunlight and other sources of UVR (NISE)

Artificial sources of UVR are used in numerous industrial processes, and also in research laboratories. UVR is part of the treatment of many diseases, such as psoriasis and dermatitis. The type and spectrum of UVR lamps may be different from one condition to another. In some diseases, like psoriasis, the cumulative exposure to UVR can be substantial, can be accompanied by use of oral photocarcinogens (the PUVA therapy combining UVA and oral 8-methoxypsoralen) and is sometimes supplemented with sunbed use. In these patients, higher rates of SCC and BCC than in the general population are usually observed.

Lighting through use of fluorescent tubes contains a small proportion of UV radiation. These small amounts could represent a hazard, as fluorescent lighting is widely distributed. Epidemiological studies have not however produced data consistent with an effect of fluorescent lighting on melanoma occurrence.

Intentional exposure to sunlight or to artificial sources of UVR (ISE)

The most common ISE behaviour is sunbathing. The tanned skin fashion started in the 1930s in light-skinned populations after popularisation of the healthy effects of sunlight, e.g. for prevention of rickets [18].

Since the end of the 1980s, in countries populated with light-skinned people, deliberate exposure to artificial sources of UVR has become common through the use of sunbeds, mainly for the acquisition of a tanned skin. This new fashion has been largely facilitated by ungrounded beliefs such as the putative lower carcinogenic potential of sunbeds (as compared to sunlight), the psychological benefits of UVR exposure during the winter, and more recently, the maintenance of so-called "optimal vitamin D status".

In large, powerful tanning units, the UVR intensity may be 10 to 15 times higher than that of the midday sun [19], and UVA doses per unit of time received by the skin during a typical sunbed session are well above what is experienced during daily life or during sunbathing. Annual UVA doses received by frequent indoor tanners may be 1.2 to 4.7 times that received from the sun, and in addition to those received from the sun. Such powerful sources of UVA radiation probably do not exist on the Earth's surface, and repeated exposures to high doses of UVA constitute a new phenomenon in humans. Health hazards associated with repeated exposures to powerful indoor tanning devices remain largely unknown, as this fashion developed quite recently, and the full health

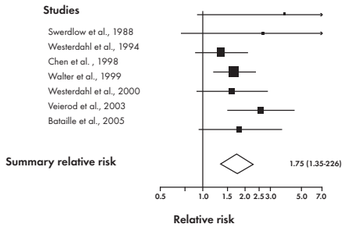


Fig. 2.11.2 *Relative risk for cutaneous melanoma associated with first use of indoor tanning equipment at age < 35 years : estimates of 7 studies and summary estimate*

impact of such exposure may not be seen for another one or two decades.

A systematic review carried out by an IARC Working Group in 2006 has shown that the risk of cutaneous melanoma is increased by 70% when sunbed use starts before about 30 years of age (Figure 2.11.2) [19,20]. This finding is in line with known susceptibility to carcinogenic effects of UVR at younger ages. Recent surveys have revealed that substantial numbers of teenagers use sunbeds; with respect to this, priority for the prevention of damage caused by sunbed use should concentrate on limiting sunbed use by adolescents and young adults [19-21].

Sun protection

The main goal of sun protection is to decrease the incidence of SCC, BCC and cutaneous melanoma through methods that have in common the reduction of exposure to sunlight and to other sources of UVR. Avoidance of sunshine or exposure to UVR sources, and seeking of shade are the most straightforward sun protection methods. When in the sun, barriers to UVR usually consist of wearing a hat and clothing, and use of sunscreens. Hats should be broad-brimmed so that the scalp, the face, the ears and the neck are protected. Common fabrics represent efficient barriers against UVR transmission to the skin. Dark colours are more protective than light colours, and wet clothes are less protective than dry clothes. Some fabrics and clothes have been specifically devised to protect the skin against sun damage, and are recommended for individuals highly susceptible to the damaging effects of UVR (e.g. red-haired people, patients under photosensitising treatment). The ability of a fabric to block UVR is called the ultraviolet protection factor (UPF), but there is no international standardisation of its measurement.

The sun protection factor (SPF) of sunscreens provides an internationally standardised estimate of the ability of a *thick* layer of sunscreen to delay the occurrence of a sun-induced skin erythemal reaction. The higher the SPF, the longer the time needed to develop an erythema. Because sunburn occurrence is associated with greater risk of skin cancer, the SPF has been thought to be an indicator of the ability of sunscreens to protect against sun-induced skin carcinogenic phenomena. However, the causal link between sunburn and melanoma is questioned, as this association may simply reflect the genetically determined propensity to sunburn [22,23]. Also, UVR can induce biological damage (such as immune suppression or oxidative damage) at doses lower than those needed to induce an erythema [19].

Observational and randomized studies have provided evidence that during NISE, reduction of amounts of UVR reaching skin surface through clothing, sunscreen use or reduction of time spent in the sun can decrease the occurrence of SCC, and also of sunburns and of skin precursor lesions of SCC (e.g. skin keratoses). [24-27].

During ISE, however, observational and randomised studies have demonstrated that sunscreen use may have the consequence of increasing the time spent in the sun, mainly because tan acquisition is longer when a sunscreen is used, and also because it takes more

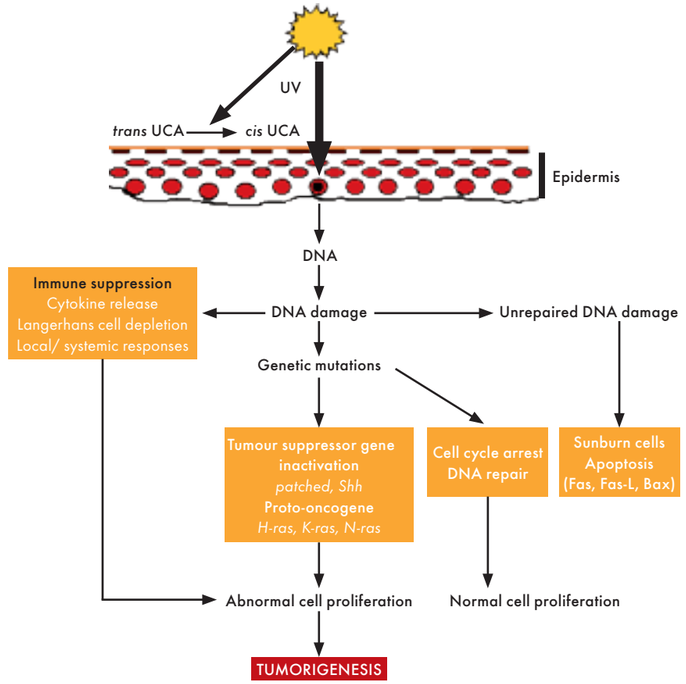


Fig. 2.11.3 *Pathways implicated in the induction of non-melanoma skin cancer by ultraviolet radiation (UCA= urocanic acid)*

time to get a sunburn [24,28,29]. So, sunscreen use during ISE may actually increase the risk of cutaneous melanoma (and probably also of BCC) [17] Sunscreen use during ISE does not decrease sunburn occurrence and allows suntan seekers to adopt more hazardous sun exposure behaviours, such as sunbathing around noon, when UVB irradiation is maximal [10,24,28,30]. In contrast, during ISE situations, clothing protects against melanoma occurrence and nevi development in children [31].

Hence, sunscreens should be rather used during NISE, and in these situations, application onto the skin should be liberal, as the usual tendency is to apply too small a quantity of sunscreen, which results in an actual SPF 3 to 5 times lower than indicated on the bottle.

In this respect, generous application of SPF 15 sunscreen is better than parsimonious application of a sunscreen of higher SPF. If one cannot refrain from intentional sun exposure (essentially for tan acquisition), it is better to avoid using a sunscreen in order to avoid staying in the sun longer than if a sunscreen was not used. It is also better not to sunbathe during the hottest hours of the day, when UVB irradiation is maximal. Suntan seeker should start with short sunbathing sessions, depending on natural sun sensitivity, and then gradually increase time spent in the sun as their tan gets deeper. Individuals who do not tan or tan only after burning should by no means engage in sunbathing and should not have recourse to a sunscreen for increasing their ability to stay in the sun.

Sun protection of children should be based on seeking shade, hat wearing and clothing. If sunscreen is used, it should only be applied on skin areas that cannot be protected with hats and clothes. So, by definition, sunscreen should never be applied on the trunk of a child, as sun protection of the trunk should be done with clothes.

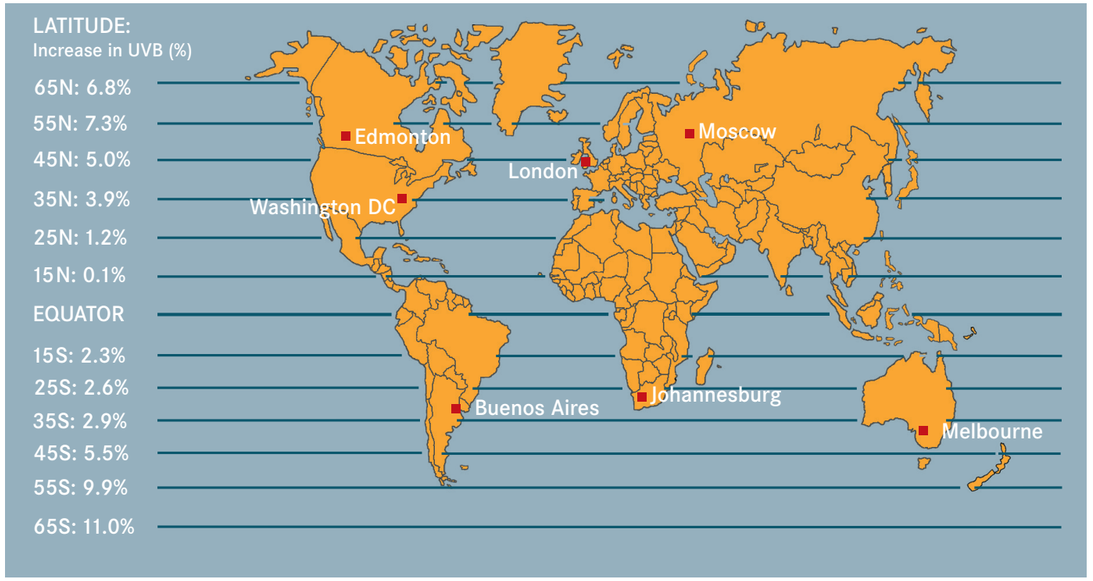


Fig. 2.11.4 *Satellite-based analyses (1996) demonstrate increases in average annual levels of ultraviolet B (UVB) radiation reaching the Earth's surface over the past ten years. These changes are strongly dependent on latitude*

REFERENCES

1. IARC. (1992). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 55, Solar and ultraviolet radiation*. Lyon, France: International Agency for Research on Cancer.

2. Rowland FS (2006). Stratospheric ozone depletion. *Philos Trans R Soc Lond B Biol Sci* 361: 769-790.

3. de Gruijl FR, Longstreth J, Norval M, et al. (2003). Health effects from stratospheric ozone depletion and interactions with climate change. *Photochem Photobiol Sci* 2: 16-28.

4. Velders GJ, Andersen SO, Daniel JS, et al. (2007). The importance of the Montreal Protocol in protecting climate. *Proc Natl Acad Sci U S A* 104: 4814-4819.

5. Weatherhead EC and Andersen SB (2006). The search for signs of recovery of the ozone layer. *Nature* 441: 39-45.

6. Gerstenblith MR, Goldstein AM, Fargnoli MC, et al. (2007). Comprehensive evaluation of allele frequency differences of MC1R variants across populations. *Hum Mutat* 28: 495-505.

7. Raimondi S, Sera F, Gandini S, et al. (2008). MC1R variants, melanoma and red hair color phenotype: a meta-analysis. *Int J Cancer* 122: 2753-2760.

8. Rouzaud F, Kadekaro AL, Abdel-Malek ZA, et al. (2005). MC1R and the response of melanocytes to ultraviolet radiation. *Mutat Res* 571: 133-152.

9. Whiteman DC, Whiteman CA, Green AC (2001). Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. *Cancer Causes Control* 12: 69-82.

10. Autier P and Dore JF (1998). Influence of sun exposures during childhood and during adulthood on melanoma risk. EPIMEL and EORTC Melanoma Cooperative Group. European Organisation for Research and Treatment of Cancer. *Int J Cancer* 77: 533-537.

11. Elwood JM and Gallagher RP (1998). Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int J Cancer* 78: 276-280.

12. Autier P, Boniol M, Severi G, et al. (2004). Sex differences in numbers of nevi on body sites of young European children: implications for the etiology of cutaneous melanoma. *Cancer Epidemiol Biomarkers Prev* 13: 2003-2005.

13. de Vries E, Louwman M, Bastiaens M, et al. (2004). Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *J Invest Dermatol* 123: 634-638.

14. Armstrong BK (1988). Epidemiology of malignant melanoma: intermittent or total accumulated exposure to the sun? *J Dermatol Surg Oncol* 14: 835-849.

15. Elwood JM, Gallagher RP, Hill GB, et al. (1985). Cutaneous melanoma in relation to intermittent and constant sun exposure--the Western Canada Melanoma Study. *Int J Cancer* 35: 427-433.

16. Vainio H, Miller AB, Bianchini F (2000). An international evaluation of the cancer-preventive potential of sunscreens. *Int J Cancer* 88: 838-842.

17. IARC (2001). *IARC Handbooks of Cancer Prevention, Volume 5, Sunscreens*. Lyon, France: International Agency for Research on Cancer.

18. Albert MR and Ostheimer KG (2003). The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 2. *J Am Acad Dermatol* 48: 909-918.

19. International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer (2007). The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. *Int J Cancer* 120: 1116-1122.

20. IARC (2006). *IARC Working Group Reports, Volume 1, Exposure to Artificial UV Radiation and Skin Cancer*. Lyon, France: International Agency for Research on Cancer.

21. Autier P and Boyle P (2008). Artificial ultraviolet sources and skin cancers: rationale for restricting access to sunbed use before 18 years of age. *Nat Clin Pract Oncol* 5: 178-179.

22. Marks R and Whiteman D (1994). Sunburn and melanoma: how strong is the evidence? *BMJ* 308: 75-76.

23. Whiteman D and Green A (1994). Melanoma and sunburn. *Cancer Causes Control* 5: 564-572.

24. Autier P, Boniol M, Dore JF (2007). Sunscreen use and increased duration of intentional sun exposure: still a burning issue. *Int J Cancer* 121: 1-5.

25. Green A, Williams G, Neale R, et al. (1999). Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 354: 723-729.

26. Naylor MF, Boyd A, Smith DW, et al. (1995). High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 131: 170-175.

27. Thompson SC, Jolley D, Marks R (1993). Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 329: 1147-1151.

28. Autier P, Dore JF, Negrier S, et al. (1999). Sunscreen use and duration of sun exposure: a double-blind, randomized trial. *J Natl Cancer Inst* 91: 1304-1309.

29. Autier P, Dore JF, Reis AC, et al. (2000). Sunscreen use and intentional exposure to ultraviolet A and B radiation: a double blind randomized trial using personal dosimeters. *Br J Cancer* 83: 1243-1248.

30. Autier P, Dore JF, Cattaruzza MS, et al. (1998). Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. *J Natl Cancer Inst* 90: 1873-1880.

31. Autier P (2005). Cutaneous malignant melanoma: facts about sunbeds and sunscreen. *Expert Rev Anticancer Ther* 5: 821-833.

2.12 Electromagnetic Radiation

Summary

> Extremely low frequency electromagnetic fields generated by electrical power transmission have been associated with an increased risk of childhood leukaemia, but the findings are not conclusive. Even if this association is real, the number of excess cases is likely to be very small

> Radiofrequency radiation emitted by mobile telephones has been investigated in a number of studies. There is some evidence that long-term and heavy use of mobile/cellular phones may be associated with moderate increased risks of gliomas, parotid gland tumours, and acoustic neuromas; however, evidence is conflicting and a role of bias in these studies cannot be ruled out

> With reference to radio frequency, available data do not show any excess risk of brain cancer and other neoplasms associated with the use of mobile phones

> With reference to ELF fields, available data allow us to exclude any excess risk of (childhood) leukaemia and other cancers at the levels of exposure likely to be encountered by most (>99%) of the population)

> To date there is no convincing biological or biophysical support for a possible association between exposure to ELF fields and the risk of leukaemia or any other cancer

Although a source of exposure to man for many decades, electromagnetic fields (EMF) have seen an unprecedented increase in the number and diversity of sources in recent years [1], principally extremely low frequency and radiofrequency fields. Such sources include all equipment using electricity, television, radio, computers, mobile telephones, microwave ovens, anti-theft gates in large shops, radars and equipment used in industry, medicine and commerce. Static fields and extremely low frequency fields occur naturally, and also arise as a consequence of the generation and transmission of electrical power and through the operation of a range of industrial devices and domestic appliances, the latter often at a greater field intensity. Exposure to extremely low frequency fields is mainly from human-made sources for the generation, transmission and use of electricity. Occupational exposure occurs, for example, in the electric and electronics industry, in welding and in the use and repair of electrical motors. Environmental exposure to extremely low frequency fields occurs in residential settings due to proximity to electricity transmission lines and use of electrical appliances. Levels of exposure from many environmental sources are typically low [2].

Exposure to radiofrequency radiation can occur in a number of ways. The primary natural source of radiofrequency fields is the sun. Manmade sources, however, are the main source of exposure. Radiofrequency fields are generated as a consequence of commercial radio and television broadcasting and from telecommunications facilities. Radiofrequency fields in the home are generated by microwave ovens and burglar alarms. However, mobile telephones are now the greatest source of radiofrequency exposure for the general public.

A major obstacle in conducting epidemiological studies of EMF is the difficulty in accurately measuring the dose and exposure pattern. This is particularly true in the case of mobile telephones, where the dose emitted by phones has been changing between models and over time, and the use pattern of left or right side also varies within individuals. Measuring exposure to total EMF is also fraught with difficulty, and estimating the exposure to individual components of the spectrum involved is extremely difficult to the point of being impossible.

The INTERPHONE study is an ambitious project aiming at assessing the risk of cancer from the use of mobile phones. A number of the individual components have been published [3].

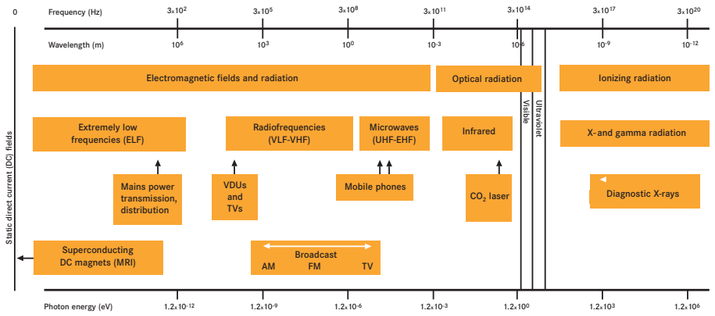


***Fig.* 2.12.1** *The spectrum of electromagnetic fields and their use in daily life*

Separate studies have been carried out for acoustic neurinoma, glioma, meningioma and tumours of the parotid gland. The studies used a common core protocol and were carried out in Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK. Details of the study protocol and procedures have been published [4]. The overall study includes approximately 2600 gliomas, 2300 meningiomas, 1100 acoustic neurinomas, 400 parotid gland tumours and their respective controls. This is by far the largest epidemiological study of these tumours to date. A number of methodological issues have been addressed including study design, participation bias, recall error and exposure assessment that are essential in the interpretation of results from the study.

Results of national analyses of the relation between mobile phone use and risk of specific tumour types in some of the participating countries have indicated that in most studies, the OR related to ever having been a regular mobile phone user was below 1, in some instances statistically significantly. This possibly reflects participation bias or other methodological limitations.

For glioma, although results by time since start of use and amount of phone use vary, the number of long-term users is small in individual countries and results are therefore compatible. Pooling of data from Nordic countries and part of the UK yielded a significantly increased risk of glioma related to use of mobile phones for a period of 10 years or more on the side of the head where the tumour developed [5]. This finding could either be causal or artifactual, related to differential recall between cases and controls.

For meningioma and acoustic neurinoma, most National studies provided little evidence of an Increased risk. The numbers of long-term heavy users in individual studies were even smaller than for glioma, however, and prevent any definitive conclusion about a possible association between mobile telephone use and the risk of these tumours. A pooled analysis of data from Nordic countries and the UK found a significantly increased risk of acoustic neurinoma related to duration of use of 10 years or more on the side of tumour [6]. Again, this finding could either be causal or artifactual, related to differential recall between cases and controls.

For parotid gland tumours, no increased risk was observed overall for any measure of exposure investigated. In a combined analysis of data from Sweden and Denmark [7], a nonsignificantly increased risk of benign tumours was observed for ipsilateral use of 10 years or more, while a decreased risk was seen for contralateral use, possibly reflecting differential recall between cases and controls. In the Israeli study, where study subjects tended to report substantially heavier use of mobile phones, results suggest a possible relation between heavy mobile phone use and risk of parotid gland tumours. Additional investigations of this association, with longer latency periods and large numbers of heavy users, are needed to confirm these findings. In respect of the work environment, employees working in close proximity to radiofrequencyemitting systems may receive high levels of exposure. This includes workers

***Fig.* 2.12.2** *Child and cellphone*

Frequency	Class	Type of device or service
30 - 300 kHz	LF (low)	LF broadcast and long-range radio
300 - 3,000 kHz	MF (medium)	AM radio, radio navigation, ship-to-shore
3 - 30 MHz	HF (high)	CB radio, amateurs, HF radio communications and broadcast
30 - 300 MHz	VHF (very high)	FM radio, VHF TV, emergency services
300 - 3,000 MHz	UHF (ultra high)	UHF TV, paging, mobile telephones, amateur radios
3 - 30 GHz	SHF (super high)	Microwaves, satellite communications, radar, point to point microwave communications
30 - 300 GHz	EHF (extremely high)	Radar, radioastronomy, short-link microwave communications

***Table* 2.12.1** *Radiofrequency range: class and type of device or service*

***Fig.* 2.12.3** *Power line*

in the broadcasting, transport and communication industries, and in antenna repair, military personnel (e.g. radar operators) and police officers (utilising traffic control radars). There are also industrial processes that use radiofrequency fields, including dielectric heaters for wood lamination and sealing of plastics, industrial induction heaters and microwave ovens, medical diathermy equipment to treat pain and inflammation of body tissues, and electrosurgical devices for cutting and welding tissues.

Cancer causation

Several expert groups have recently reviewed the scientific evidence concerning the carcinogenicity of extremely low frequency fields [8-10]. A number of epidemiological studies on childhood leukaemia indicate a possible relationship between risk and exposure to extremely low frequency fields. Studies of adult cancers following occupational or environmental exposures to extremely low frequency fields are much less clear. There is little experimental evidence that these fields can cause mutations in cells. Mechanistic studies and animal experiments do not show any consistent positive results, although sporadic findings concerning biological effects (including increased cancers in animals) have been reported. IARC has classified extremely low frequency fields as possibly causing cancer in humans (Group 2B), based on childhood leukaemia findings [11].

The evidence for the carcinogenicity of radiofrequency fields is even less clear. A few epidemiological studies in occupational settings have indicated a possible increase in the risk of leukaemia or brain tumours, while other studies indicated decreases. These studies suffer from a number of limitations. The experimental evidence is also limited, but suggests that radiofrequency fields cannot cause DNA mutations. The lack of reproducibility of findings limits the conclusions that can be drawn.

REFERENCES

1. Bernhardt JH, Matthes R, Repacholi M (1997). *Nonthermal effects of RF electromagnetic Fields: Proceedings of the International Seminar on Biological Effects of RF Electromagnetic Fields and Related Health Risks - Munich, Germany, 20-21 November 1996*. Geneva: International Commission on Non-Ionizing Radiation Protection.

2. Bernhardt JH, Matthes R, Repacholi M (1998). *Static and extremely low frequency electric and magnetic fields*. Geneva: International Commission on Non-Ionizing Radiation Protection.

3. *INTERPHONE Study - Latest results update*. Available from: http://www.iarc.fr/en/content/download/8384/61101/file/Interphone8oct08.pdf Date Accessed: October 27, 2008.

4. Cardis E, Richardson L, Deltour I, et al. (2007). The INTERPHONE study: design, epidemiological methods, and description of the study population. *Eur J Epidemiol* 22: 647-664.

5. Lahkola A, Auvinen A, Raitanen J, et al. (2007). Mobile phone use and risk of glioma in 5 North European countries. *Int J Cancer* 120: 1769-1775.

6. Schoemaker MJ, Swerdlow AJ, Ahlbom A, et al. (2005). Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. *Br J Cancer* 93: 842-848.

7. Lonn S, Ahlbom A, Christensen HC, et al. (2006). Mobile phone use and risk of parotid gland tumor. *Am J Epidemiol* 164: 637-643.

8. US National Institute of Environmental Health Sciences. *Electric & Magnetic Fields*. Available from: http://www.niehs.nih.gov/health/topics/agents/emf/ Date Accessed: October 27, 2008.

9. Royal Society of Canada (2000). *A Review of the Potential Health Risks of Radiofrequency Fields from Wireless Telecommunication Devices*. Ottawa: Royal Society of Canada.

10. Independent Expert Group on Mobile Phones (Great Britain), Stewart WD (2000). *Mobile Phones and Health*. Didcot, Oxon: National Radiological Protection Board.

11. IARC (2002). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 80, non-ionizing radiation, Part 1: static and extremely low-frequency (ELF) electric and magnetic fields*. Lyon, France: International Agency for Research on Cancer.

2.13 Occupational Exposures

Summary

> Twenty-nine occupational agents, as well as 15 exposure circumstances are carcinogenic to humans

> Exposure is still widespread for several important carcinogens such as asbestos, polycyclic aromatic hydrocarbons, heavy metals and silica

> The burden of occupational cancer among exposed subjects may be substantial

> Prevention of occupational cancer is feasible and has taken place in industrialized countries during recent decades

> Limited data on occupational cancer risk are available from low-income countries

It has been known for over 200 years that exposures encountered at the workplace are a cause of cancer. Occupational cancers were initially detected by clinicians. From the early findings of Pott of scrotal cancer among chimney sweeps in 1775 [1] to Creech and Johnson's identification of angiosarcoma of the liver among vinyl chloride workers two centuries later [2], unusual cancers among persons with unusual occupations were sufficient evidence to judge that the occupational exposure caused the cancer. The era of initial identification of occupational cancer by a clinician has extended into the last quarter of the 20th century. The period of formal epidemiological assessment of the occurrence of cancer in relation to workplace exposures started after World War II. Knowledge of the occupational and other environmental causes of cancer grew rapidly in the 1950s and 1960s. Cancer hazards in the workplace in the earlier decades of this century were substantial, causing, in extreme cases, all of the most heavily exposed to develop cancer, as occurred in some groups of manufacturers of 2-naphtylamine and benzidine, while coal-tar fumes and asbestos have been so widespread that tens of thousands of skin and lung cancers have developed. While the remaining hazards are now starting to disappear through elimination of these substances and of exposures to them, some of the consequences of the earlier exposures still exist. Estimates of the burden of occupational cancer in high-resource countries are in the order of 2–5% [3].

At present, there are 29 chemicals, groups of chemicals and mixtures for which exposures are mostly occupational, that are established human carcinogens (Table 2.13.1). While some agents such as asbestos, benzene, and heavy metals, are currently widely used in many countries, other agents have mainly a historical interest (e.g. mustard gas and 2-naphthylamine). An additional 28 occupational agents are classified as probably carcinogenic to humans (Group 2A): these are listed in Table 2.13.2, and include exposures that are currently prevalent in many countries, such as diesel engine exhaust and trichloroethylene. A large number of important occupational agents are classified as possible human carcinogens (Group 2B): e.g. acetaldehyde, carbon black, chloroform, chlorophenoxy herbicides, DDT, dichloromethane, glass wool, polychlorophenols and styrene. The complete list can be found on the IARC web site (http://monographs.iarc.fr).

The distinction between occupational and environmental carcinogens is not always straightforward. Several of the agents listed in Tables 2.13.1 and 2.13.2 are also present in the general environment, although exposure levels tend to be higher at the workplace. This is the case for the examples of 2,3,7,8-TCDD, diesel engine exhaust, radon and asbestos. On the other hand, there are agents that have been evaluated in IARC groups 1 or 2A, for which exposure is not primarily occupational, but which often encountered in the occupational environment. They include drugs such as cyclophosphamide and cyclosporin (occupational exposure can occur in pharmacies and during their administration by nursing staff); food contaminants such as aflatoxins, to which food processors can be exposed; biological agents, such as Hepatitis B virus, Hepatitis C virus and Human Immunodeficiency virus, to which medical personnel can be exposed; environmental agents, in particular solar radiation (exposure in agriculture, fishing and other outdoor occupations); and lifestyle factors, in particular secondhand tobacco smoke in bars and other public settings.

Polycyclic aromatic hydrocarbons (PAHs) represent a specific problem in the identification of occupational carcinogens. This group of chemicals includes several potent experimental carcinogens, such as benzo[*a*]pyrene, benz[*a*]anthracene and dibenz[*a,h*]anthracene. However, humans are always exposed to mixtures of PAHs (several of which are listed in Tables 2.13.1 and 2.13.2: e.g. coal-tars, soots, creosotes), and an assessment of the carcinogenicity of individual PAHs in humans is difficult.

Current understanding of the relationship between occupational exposures and cancer is far from complete; in fact, for many experimental carcinogens no definitive evidence is available from exposed workers. In some cases, there is considerable evidence of increased risks associated with particular industries and occupations, although no specific agents can be identified as etiological factors. Table 2.13.3 reports occupations and industries that entail (or are suspected to entail) a carcinogenic risk on the basis of the IARC Monographs programme. Fifteen occupations and industries are listed in IARC Group 1 and four in Group 2A.

Fig. 2.13.1 *Coal mine*

Constructing and interpreting lists of chemical or physical carcinogenic agents and associating them with specific occupations and industries is complicated by a number of factors. Information on industrial processes and exposures is frequently poor, not allowing a complete evaluation of the importance of specific carcinogenic exposures in different occupations or industries. In addition, exposures to well-known carcinogenic exposures, such as vinyl chloride and benzene, occur at different intensities in different occupational situations. Furthermore, changes in exposure occur over time in a given occupational situation, either because identified carcinogenic agents are substituted by other agents or (more frequently) because new industrial processes or materials are introduced. Finally, any list of occupational exposures can only refer to the relatively small number of chemical exposures that have been investigated with respect to the presence of a carcinogenic risk.

The same factors complicate the estimates of the burden of cancer attributable to occupation. Figures in the order of 4–5% of total cancer deaths have been proposed in the past [4], but estimates based on systematic evaluations of relative risks and data on exposure prevalence have resulted in lower estimates, in the order of 2–3% [5,6]. A single figure on the proportion of cancers due to occupations might be misleading as exposure concentrates on subgroups of the population, namely male blue-collar workers, among whom the burden can be substantial.

Exposure	Target organ	Main industry or use
4-Aminobiphenyl	Bladder	Rubber
Arsenic and arsenic compounds	Lung, skin	Glass, metals, pesticides
Asbestos	Lung, pleura	Insulation, construction
Benzene	Leukemia	Solvent, fuel
Benzidine	Bladder	Pigment
Beryllium and beryllium comp.	Lung	Aerospace, metals
Bis(chloromethyl)ether*	Lung	Chemical
1,3-Butadiene	Leukemia	Plastic, rubber
Chloromethyl methyl ether*	Lung	Chemical
Cadmium and cadmium comp.	Lung	Pigment, battery
Chromium[VI] compounds	Nasal cavity, lung	Metal plating, pigment
Coal-tar pitches	Skin, lung, bladder	Construction, electrodes
Coal-tars	Skin, lung	Fuel
Ethylene oxide	NA**	Chemical, sterilant
Formaldehyde	Nasopharynx	Plastic, textile
Gallium arsenide	NA**	Semiconductors
Mineral oils, untreated and mildly treated	Skin	Lubricant
Mustard gas (sulphur mustard)*	Pharynx, lung	War gas
2-Naththylamine*	Bladder	Pigment
Nickel compounds	Nasal cavity, lung	Metal, alloy
Radon-222 and its decay products	Lung	Mining
Shale-oils	Skin	Lubricant, fuel
Silica, crystalline	Lung	Construction, mining
Soots	Skin, lung	Pigment
Strong-inorganic-acid mists containing sulphuric acid	Larynx, lung	Chemical
Talc containing asbestiform fibers	Lung	Paper, paint
2,3,7,8-Tetrachlorodibenzo-p-dioxin	NA**	Chemical
Vinyl chloride	Liver	Plastic
Wood dust	Nasal cavity	Wood

Table 2.13.1 *Agents, groups or agents and mixtures classified as established human carcinogens [9], for which exposure is mainly occupational*
** Agent mainly of historical interest*
*** Not applicable (agent classified in Group 1 on the basis of mechanistic evidence).*

Exposure	Suspected target organ	Main industry or use
Acrylamide	-	Plastic
Benzidine-based dyes	Bladder	Pigment, leather
Captafol	-	Pesticide
α-Chlorinated toluenes (benzal chloride, benzotrichloride, benzyl chloride, benzoyl chloride)	-	Pigment, chemical
4-Chloro-o-toluidine	Bladder	Pigment, textile
Cobalt metal with tungsten carbide	Lung	Hard metal production
Creosotes	Skin	Wood
Diesel engine exhaust	Lung	Transport, mining
Diethyl sulfate	-	Chemical
Dimethylcarbamoyl chloride	-	Chemical
1,2-Dimethylhydrazine	-	Research
Dimethyl sulfate	-	Chemical
Epichlorohydrin	-	Plastic
Ethylene dibromide	-	Fumigant
Indium phosphide	-	Semiconductors
Lead compounds, inorganic	Lung, stomach	Metals, pigments
Methyl methanesulfonate	-	Chemical
4-4′-Methylene-bis-2-chloroaniline (MOCA)	Bladder	Rubber
Non-arsenical insecticides	Leukemia	Agriculture
Polychlorinated biphenyls	Liver, lymphoma	Electrical components
Styrene-7,8-oxide	-	Plastic
Tetrachloroethylene	Oesophagus, lymphoma	Solvent
o-Toluidine	Bladder	Pigment
Trichloroethylene	Liver, lymphoma	Solvent, dry cleaning
1,2,3-Trichloropropane	-	Solvent
Tris(2,3-dibromopropyl)phosphate	-	Plastic, textile
Vinyl bromide	-	Plastic, textile
Vinyl fluoride	-	Chemical

Table 2.13.2 *Agents, groups or agents and mixtures classified as probable human carcinogens [9], for which exposure is primarily occupational*

While the study of occupational cancer has concentrated on specific jobs, industries and agents, it is likely that indirect effects of occupation have become more important. For example, the increasing employment of women in jobs outside the home has probably contributed to changes in reproductive habits, which may entail an increased risk of hormone-related cancers. Recently, shiftwork that involves circadian disruption has been classified as a probable human carcinogen by the IARC Monographs Programme, on the basis of limited evidence of an increased risk of breast cancer [7].

Occupational cancer is likely to be a more important problem in medium- and low-resource countries than in high-resource countries because of the importance of the informal sector, the lack of stringent implementation of existing regulations, the low level of attention paid by management and the workforce to industrial hygiene, and the presence of child labour [8]. However, detailed information on prevalence of exposure and of cancer risk is currently lacking.

Fig. 2.13.2 *Asbestos insulation is common in buildings and presents a hazard when disturbed during demolition. Protective clothing must be worn to avoid contact with asbestos fibres.*

Industry/occupation	Target organs*
Group 1	
Aluminium production	Lung, bladder
Auramine, manufacture of	Bladder
Boot and shoe manufacture and repair	Nasal cavity, leukaemia
Chimney sweeping	Skin, lung
Coal gasification	Skin, lung, bladder
Coal-tar distillation	Skin
Coke production	Skin, lung, kidney
Furniture and cabinet making	Nasal cavity
Haematite mining (underground) with exposure to radon	Lung
Iron and steel founding	Lung
Isopropanol manufacture (strong-acid process)	Nasal cavity
Magenta, manufacture of	Bladder
Painter	Lung, bladder
Paving and roofing with coal-tar pitch	Lung
Rubber industry	Bladder, leukaemia
Group 2A	
Art glass, glass containers and pressed ware, manufacture	(Lung, stomach)
Carbon electrode manufacture	(Lung)
Hairdresser or barber	(Bladder, lung)
Petroleum refining	(Leukaemia, skin)

Table 2.13.3 *Industrial processes and occupations evaluated in IARC Monographs* Volumes 1-98 [9]
** Suspected target organs are given in parentheses*

REFERENCES

1. Pott P (1775). Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures, and the mortification of the toes and feet. London: T.J. Carnegy.

2. Creech JL and Johnson MN (1974). Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 16: 150-151.

3. Siemiatycki J, Richardson L, Boffetta P (2006). Occupation. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press. 322-354.

4. Doll R, Peto R (1981). *The causes of cancer quantitative estimates of avoidable risks of cancer in the United States today*. Oxford: Oxford University Press.

5. IARC (2007). *IARC Working Group Reports, Volume 3, Attributable Causes of Cancer in France in the Year 2000*. Lyon, France: International Agency for Research on Cancer.

6. Dreyer L, Andersen A, Pukkala E (1997). Avoidable cancers in the Nordic countries. Occupation. *APMIS* 105 Suppl: 68-79.

7. Straif K, Baan R, Grosse Y, et al. (2007). Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol* 8: 1065-1066.

8. Pearce N, Matos E, Vainio H, et al. (1994). *IARC Scientific Publications, Volume 129, Occupational cancer in developing countries*. Lyon, France: International Agency for Research on Cancer.

9. IARC (1972-2007). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volumes 1 - 98*. Lyon, France: International Agency for Research on Cancer.

Fig. 2.13.3 *Asphalt road-workers are exposed to polycyclic aromatic hydro-carbons*

2.14 Environmental Pollution

Summary

> Environmental pollution contributes to the world's cancer burden in a limited way

> Many known, probable and possible carcinogens can be found in the environment, and all people carry traces of these pollutants in their bodies

> Some environmental pollutants are widely dispersed, and others are concentrated in small geographic areas

> There are wide disparities in exposure, and pollution levels can be high in newly-industrialised countries with less stringent regulations

> Much environmental pollution can be prevented

In a broad sense, environmental factors are implicated in the causation of the majority of human cancers [1]. "Environmental factors" is generally understood to encompass everything that is not specifically genetic in origin. This includes many significant causes of cancer that are considered discretionary (although marketing and societal influences are also important): tobacco smoking, alcohol consumption and dietary habits. Evidence for the role of environmental factors comes from a variety of sources: from geographic variations in the distribution of the world cancer burden, from time trends showing increases or decreases in different forms of cancer, from studies of people migrating from one country to another, and from studies of twins raised in different environments.

There is a prominent subset of environmental factors, however, over which the individual has little control: environmental pollution, which includes the chemical contamination of the air we breathe, the water we drink, the food we eat, and the soil, sediment, surface waters and groundwater that surround the places we live. Many carcinogens can be found in the environment, and all people carry traces of environmental pollutants in their bodies.

The cancer risks from environmental pollution are difficult to study. People are exposed to hundreds, if not thousands, of chemicals and other agents through their environment, and environmental exposure assessment can be exceedingly complex. Some environmental pollutants are widely dispersed across the globe while others are concentrated in small geographic areas near specific industrial sources. This results in wide disparities in the level of exposure to environmental pollutants, and some population groups may face high risks that do not have a noticeable impact on national cancer incidence statistics. Nonetheless, there are several examples to indicate that the carcinogens that pollute our environment do contribute to the world cancer burden (Table 2.14.1).

Asbestos

Asbestos is one of the best characterised causes of human cancer in the workplace (see *Occupational exposures*, Chapter 2.13). The carcinogenic hazard associated with asbestos fibres has been recognized since the 1950s [1,2]. Non-occupational exposure to asbestos may occur domestically and as a consequence of localised pollution. People who live with asbestos workers may be exposed to asbestos dust brought home on clothes. The installation, degradation, removal and repair of asbestos-containing products in the context of household maintenance represent another mode of residential exposure. Whole neighbourhoods may be exposed to asbestos as a result of local asbestos mining or manufacturing. Some parts of the world also experience asbestos exposure as a result of the erosion of asbestos or asbestiform rocks.

In common with occupational exposure, exposure to asbestos due to residential circumstances results in an increased risk of mesothelioma, a rare tumour derived from the cells lining the peritoneum, pericardium or pleura [3]. Likewise, non-occupational exposure to asbestos may cause lung cancer, particularly among smokers [4]. A very high incidence of mesothelioma as a consequence of neighbourhood exposure is evident among inhabitants of villages in Turkey where houses and natural surroundings contain the mineral erionite.

Outdoor air pollution

Ambient air pollution has been implicated as a cause of various health problems, including cancer, and in particular as a cause of lung cancer. Air pollution entails a complex mixture of different gaseous and particulate components whose concentrations vary greatly with place and time. Human exposure to air pollution is therefore difficult to quantify. It may be possible, however, to attribute some carcinogenic risk to specific atmospheric pollutants, including benzo[a]pyrene, benzene, 1,3-butadiene, some metallic compounds, particulate matter (especially finer particles) and possibly ozone.

Emissions of traditional industrial air pollutants such as sulphur dioxide and particulate matter have decreased in developed countries, but high exposures still remain. Motor vehicle exhaust remains a continuing or even increasing problem as the number of vehicles increases. In a study based on air monitoring and population data for 100 western European urban areas, a high proportion of the population was exposed at levels above the WHO's air quality guidelines [5]. In the United States, modelled concentrations of hazardous air pollutants sometimes exceeded applicable reference concentrations [6].

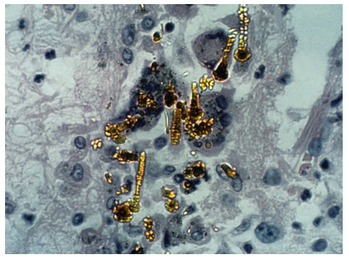


Fig. 2.14.1 *Lung tissue with infiltrate of asbestos fibres*

In developing countries, outdoor air pollution is likely to represent a greater public health problem than in more developed countries. In addition to vehicle emissions and industrialization, there may be poorly regulated use of coal, wood and other biomass (e.g. animal dung, crop residues) for electricity production, cooking, and heating. Although the proportion of global energy derived from biomass fuels has decreased from 50% in 1900 to about 13% in 2000, use of such fuels is increasing in some impoverished regions [7].

Numerous studies have compared residence in urban areas, where air is considered to be more polluted, to residence in rural areas as a risk factor for lung cancer [8]. In general, lung cancer rates were higher in urban areas, and in some studies were correlated with levels of specific pollutants such as benzo[a]pyrene, metallic compounds and particulate matter, or with mutagenicity in bacterial assay systems of particulate extracts. Other studies have attempted to address exposure to specific components of outdoor air, providing risk estimates in relation to quantitative or semi-quantitative exposure to pollutants. In general, these studies have provided evidence for an increased risk of lung cancer among residents in areas with higher levels of air pollution.

Localised air pollution may be a hazard in relation to residence near to specific sources of pollution, such as coal-fired power plants, petroleum refineries, metal manufacturing plants, iron foundries, incinerators and smelters. In general, an increased risk of lung cancer in the proximity of pollution sources has been demonstrated. In three Scottish towns, for example, increased lung cancer mortality occurred in the vicinity of foundries from the mid-1960s to the mid-1970s and later subsided in parallel with emission

Agent	Cancer site/Cancer
IARC Group I	
Aflatoxins	Liver
Arsenic and arsenic compounds*	Lung, skin
Asbestos	Lung, pleura, peritoneum
Benzene	Leukaemia
1,3-Butadiene	Leukaemia, lymphoma
Chromium[VI] compounds	Lung, nasal cavity
Erionite	Lung, pleura
Environmental tobacco smoke	Lung
Ethylene oxide	Leukaemia
Formaldehyde	Nasopharynx
Radon and its decay products	Lung
Solar radiation	Skin
Silica, crystalline	Lung
2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD)	Several organs
IARC Group 2A	
Diesel engine exhaust	Lung, bladder
Ultraviolet radiation A	Skin
Ultraviolet radiation B	Skin
Ultraviolet radiation C	Skin
Polychlorinated biphenyls	Liver, bile ducts, leukaemia, lymphoma
Tetrachloroethylene	Esophagus, lymphoma
Trichloroethylene	Kidney, liver, lymphoma

Table 2.14.1 *Some carcinogens that are found in the environment*

reductions [9]. Similar results were obtained in studies focusing on industrial emissions of arsenic from coal burning and non-ferrous metal smelting. The evidence for an increased risk of cancers other than lung cancer from outdoor air pollution is inconclusive at present.

Air pollution by chlorofluorocarbons (CFCs) is believed to be indirectly responsible for increases in skin cancers around the globe. These chemicals, including halons, carbon tetrachloride and methyl chloroform, are emitted from home air conditioners, foam cushions and many other products. CFCs are carried by winds into the stratosphere, where the action of strong solar radiation releases chlorine and bromine atoms that react with, and thereby eliminate, molecules of ozone. Depletion of the ozone layer is believed to be responsible for global increases in UVB radiation (see Chapter 2.11).

Indoor air pollution

About half of the world's population, mostly in low-resource and medium-resource countries, uses solid fuels for cooking or heating, often in poorly ventilated spaces. The WHO identified indoor smoke from combustion of solid fuels as one of the top ten risks for the global burden of disease. Very high lung cancer rates occur among non-smoking women who use solid fuels in some parts of China and other Asian countries. Young children who are home for most of the day are also highly exposed. The components of this indoor smoke include coarse, fine, and ultrafine particles and many organic compounds, including carcinogens such as benzo[a]pyrene, formaldehyde and benzene. There is also strong epidemiologic and experimental evidence that cooking-oil emissions from high-temperature frying may pose a cancer hazard [10].

Tobacco smoke is an important source of indoor air pollution (see *Passive smoking*, Chapter 2.3). Environmental exposure to tobacco smoke has been linked to lung cancer and heart disease in adults and respiratory disease, middle ear disease, asthma and sudden infant death syndrome in children [11,12].

Among the most prominent pollutants of indoor air are radon and formaldehyde. Outdoor air pollutants can also accumulate indoors when buildings are not well ventilated. This problem can be exacerbated by efforts to weatherproof buildings to make them more energy-efficient.

Water and soil pollution

Access to clean water is one of the basic requirements of human health. Water quality is influenced by seasons, geology of the soil and discharges from agriculture and industry. The greatest concern relates to infectious disease. Microbiological contamination of water is controlled by disinfection methods based on chlorine, hypochlorite, chloramine or ozone. As a result of the interaction of chlorine with organic chemicals already present, drinking water may contain chlorination by-products, some of which are potentially carcinogenic [13]. Chloroform and other trihalomethanes are among those most commonly found. Studies of bladder cancer have suggested an increased risk associated with consumption of chlorinated drinking water [14], although doubts remain as to whether such associations are causal because of the way in which the studies measured exposure [15]. Given the large number of people exposed to chlorination by-products, however, even a small increase in risk, if real, would result in a substantial number of cases attributable to this factor. It is desirable to reduce such by-products without reducing the effectiveness of disinfection procedures.

Arsenic causes cancer in the skin, lung, bladder and other organs [13,16]. The main source of environmental exposure to arsenic for the general population is through ingestion of contaminated drinking water. High exposure to arsenic from drinking water is found in several areas of Argentina, Bangladesh, Chile, India, Mexico, Mongolia, Taiwan and the USA. There is strong evidence of an increased risk of bladder, skin, and lung cancers following consumption of water with high arsenic contamination [13,15]. The data on other cancers, such as those of the liver and kidney, are less clear but suggestive of a systemic effect. The studies have been conducted in areas of high arsenic content (typically above 200 ug/L). The risks at lower arsenic concentrations (e.g., above 5 ug/L) are not established, but an increased risk of bladder cancer in the order of 50% is plausible.

Several other groups of pollutants of drinking water have been investigated as possible sources of cancer risk in humans [15]. These include organic compounds (such as chlorinated solvents and pesticides) derived from industrial, commercial, and agricultural activities, and in particular from waste sites. Organic pollutants that persist in the environment and accumulate in fish (such as polychlorinated dibenzo-p-dioxins, polychlorinated biphenyls (PCBs), and organochlorine pesticides) are of particular concern, as well as nitrates and nitrites, radionuclides, hormonally-active compounds, and asbestos. For most pollutants, the epidemiological studies are inconclusive; however, an increased risk of stomach cancer has been repeatedly reported in areas with high nitrite levels in drinking water and an increased risk of leukaemia has been observed among residents in areas with elevated levels of radium in drinking water.

Estimating cancer risks from environmental pollution

Many of the carcinogens in our environment were first recognized as such through studies in experimental animals or through studies of highly-exposed workers (see *Identifying human carcinogens*, Chapter 2.1). Accordingly, the total cancer burden from environmental exposure in the general population can only be estimated by mathematical models. Several analyses have attributed only a small percentage of cancers to environmental pollution [2,17]. These reviews generally considered only known human carcinogens, most of which were identified through occupational studies several decades ago and are less present in today's environment thanks to government regulation. Environmental pollution levels may be higher in newly-industrialised countries with less stringent regulations or enforcement, and there is not as much information about cancer risks in less-studied groups such as women, children, and the elderly.

Also important is the potential cancer burden from exposure to hundreds of probable and possible human carcinogens that have been identified and from thousands of new chemicals that have not been tested for their cancer potential. Little is known about risks from combinations of exposures at levels found in the environment or from exposures during critical time windows of development or in susceptible populations. Cancers may have multiple causes, so that environmental factors may contribute to cancers that are attributed to occupational or lifestyle factors. The known interactions between radon and smoking or between asbestos and smoking support the idea that individual cancers may have multiple causes.

Finally, it is important to remember that environmental pollution is not only a cancer problem. Much environmental pollution can be prevented, and reducing environmental pollution can contribute to reductions in diseases other than cancer and to increases in aesthetics and in the overall quality of life.

REFERENCES

1. Tomatis L, Aitio A, Day NE, et al. (1990). *IARC Scientific Publications, Volume 100, Cancer: causes, occurrence and control*. Lyon, France: International Agency for Research on Cancer.

2. Doll R and Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66: 1191-1308.

3. Boffetta P (2006). Human cancer from environmental pollutants: the epidemiological evidence. *Mutat Res* 608: 157-162.

4. Health Effects Institute, Asbestos Literature Review Panel (1991). *Asbestos in public and commercial buildings : a literature review and synthesis of current knowledge*. Cambridge, MA: Health Effects Institute-Asbestos Research.

5. WHO European Center for Environment and Health (1995). Air Pollution. In: *Concern for Europe's tomorrow: health and the environment in the WHO European region* Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft. 139-175.

6. Woodruff TJ, Caldwell J, Cogliano VJ, et al. (2000). Estimating cancer risk from outdoor concentrations of hazardous air pollutants in 1990. *Environ Res* 82: 194-206.

7. Bruce N, Perez-Padilla R, Albalak R (2000). Indoor air pollution in developing countries: a major environmental and public health challenge. *Bull World Health Organ* 78: 1078-1092.

8. Katsouyanni K and Pershagen G (1997). Ambient air pollution exposure and cancer. *Cancer Causes Control* 8: 284-291.

9. Williams FL and Lloyd OL (1988). The epidemic of respiratory cancer in the town of Armadale: the use of long-term epidemiological surveillance to test a causal hypothesis. *Public Health* 102: 531-538.

10. Straif K, Baan R, Grosse Y, et al. (2006). Carcinogenicity of household solid fuel combustion and of high-temperature frying. *Lancet Oncol* 7: 977-978.

11. United States Environmental Protection Agency (1992). *Respiratory health effects of passive smoking: lung cancer and other disorders*. Washington, DC: Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Report No. EPA/600/6-90/006F.

12. IARC. (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking*. Lyon, France: International Agency for Research on Cancer.

13. IARC. (2004). IIARC Monographs on the Evaluation of Carcinogenic Risks to Humans, *Volume 82, Some drinking-water disinfectants and contaminants, including arsenic*. Lyon, France: International Agency for Research on Cancer.

14. Morris RD, Audet AM, Angelillo IF, et al. (1992). Chlorination, chlorination by-products, and cancer: a meta-analysis. *Am J Public Health* 82: 955-963.

15. Cantor KP (1997). Drinking water and cancer. *Cancer Causes Control* 8: 292-308.

16. IARC. (1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7, Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42*. Lyon, France: International Agency for Research on Cancer.

17. Boffetta P, Tubiana M, Hill C, et al. *The causes of cancer in France*. Available from: http://annonc.oxfordjournals.org/cgi/content/full/mdn597 Date Accessed: September 2, 2008.

WEBSITES

United States Environmental Protection Agency: http://www.epa.gov/

Health Effects Institute (jointly funded by the U.S. Environmental Protection Agency and the motor vehicle manufacturing industry): http://www.healtheffects.org/

***Fig.* 2.14.2** *Industrial atmospheric emissions may include carcinogens*

2.15 Genetic Susceptibility

Summary

> Cancer genetic susceptibility is due to inheritance of specific sequence variants in cancer susceptibility genes that confer increased risk of cancer

> Cancer susceptibility genes may be oncogenes, tumour suppressor genes or risk modifier genes

> Genetic risk is a continuous variable. Susceptibility genes, and pathogenic sequence variants in them, fall into a spectrum from high-risk through intermediate-risk to modest-risk

> The field of high-risk susceptibility genes, especially for common cancers such as breast cancer and colon cancer, is fairly well explored; many and perhaps most such genes (i.e. BRCA1, BRCA2, APC, MLH1 and MSH2) are already known

> Intermediate-risk and modest-risk susceptibility genes are known to exist, but their identities and genetics are much less thoroughly understood. This is an extremely active research area

Cancer genetics comprices of two main subfields: genetic susceptibility and somatic cell genetics. Genetic susceptibility focuses on inherited (constitutional or germline) genetic variation in cancer susceptibility genes, and the effects of that inherited variation on an individual's lifetime cancer risk. In contrast, somatic cell genetics focuses on mutations that arise in an individual's cells during their lifetime and the role that those mutations play during tumour initiation and progression.

What kinds of genes can be cancer susceptibility genes? In a grand biochemical sense, cancer genes are largely organised into three groups: oncogenes, tumour suppressor genes and risk modifiers. The unifying characteristic of oncogenes is that their normal function tends to drive a process required for tumour initiation, progression, invasion, or metastasis forward. From a genetics point of view, this means that oncogenes are genes where either over-expression or gain of function mutations contribute to tumorigenesis. Classic examples include the RAS and MYC families of oncogenes. Tumour suppressor genes are the opposite; their normal function tends to inhibit a process required for tumorigenesis. Thus, from a genetics point of view, tumour suppressors are genes where either under-expression or loss of function mutations contribute to tumorigenesis. Classic examples include the retinoblastoma predisposition gene RB and the melanoma predisposition gene CDKN2A (p16). Within the tumour suppressors, there is a special subclass termed caretaker genes. Caretakers are involved in detection or repair of DNA damage, and loss of function of caretaker genes results in problems such as loss of cell cycle arrest that should be triggered by DNA damage, loss of apoptosis that should be triggered by DNA damage, and/or reduced DNA repair efficiency. Classic examples of caretakers include the Li-Fraumeni susceptibility gene TP53 and the breast/ovarian cancer susceptibility gene BRCA1. Finally, risk modifier genes are not main-effect oncogenes or tumour suppressors but rather genes whose normal function can modify the risk due to a carcinogenic exposure (either environmental or genetic). Examples include the alcohol dehydrogenases and acetaldehyde dehydrogenases (ADHs and ALDHs) that modify risk of head and neck cancer attributable to heavy alcohol consumption but have little effect on cancer risk in non-drinkers [1] and RAD51, which can modify the risk of breast cancer in BRCA2 carriers but has little effect on risk in non-carriers [2].

Evidence for a genetic component of risk for common cancers dates back at least to breast cancer pedigree studies carried out in the 1860s by Paul Broca [3]. Since that time, pedigree analyses have been complemented with linked genealogy/cancer registry studies, twin studies, segregation analyses, and a panoply of molecular genetic approaches. In a descriptive sense, these classes of studies have delivered three important pieces of information about genetic susceptibility: (i) For most of the common cancers, about 25% of the difference in risk between individuals is attributable to genetic susceptibility [4]. This measurement places a lower limit on the genetic population attributable fraction (gPAF)—the proportion of disease burden among the individuals in a population that is caused by that genetic variant—of these cancers, but the upper limit of gPAF could approach 100% [5]. (ii) The ratio of familial relative risk (FRR) experienced by first-degree relatives of breast cancer cases, colon cancer cases and prostate cancer cases versus unselected cases is ~2.0–2.5, and considerable evidence is consistent with the idea that the majority of this FRR is due to inherited susceptibility rather than, for example, shared environment [6-8]. (iii) Excess familial risk is most evident among the relatives of early onset cases for these cancers [7].

At this time, genetic susceptibility to breast cancer and colon cancer are better understood than genetic susceptibility for any of the other common cancers. For breast cancer, molecular studies have revealed that the FRR attributable to the ensemble of known susceptibility genes BRCA1, BRCA2, ATM, CHEK2, TP53, and PTEN is about 1.25, and their combined gPAF is about 5% [9,10]. For colon cancer, risks attributable to the ensemble of known susceptibility genes APC, MLH1, MSH2, MSH6, and MYH appear to be comparable to the known breast cancer susceptibility genes [11-13]. Thus we generally conclude that these genes are responsible for 5% of the attributable fraction and 20–25% of the familial relative risk of breast cancer and colon cancer. What categories of genes, and what classes of sequence variants in those genes, are responsible for the yet unexplained risk?

To assist this discussion of cancer susceptibility genes and deleterious sequence variants, we have prepared two graphs of genotype relative risk by carrier frequency. The first, Figure 2.15.1, is annotated with contour lines of gPAF, providing a frame of reference familiar to molecular epidemiologists. The second, Figure 2.15.2, is annotated with contour lines of FRR, a reference frame more familiar to genetic epidemiologists. On these graphs, risk and frequency are both divided into three strata. On the risk axes, high-risk refers to sequence variants with odds ratios ≥5.0, intermediate-risk refers to odds ratios in the range of 2.0<OR<5.0, and modest-risk refers to OR≤2.0, as annotated. On the frequency axes, common refers to sequence variant carrier frequencies ≥10%; uncommon refers to variants with frequencies in the range of 1% to 10%, and rare refers to variants with frequencies of <1%. Used this way, the 3x3 stratifications define 9 sectors. A question that we would eventually like to answer is what fraction of the risk of the common cancers is attributable to each of these categories of genes/sequence variants?

High risk genes/variants. For the common cancers, any high-risk variants with carrier frequencies above 1% in the general population (sectors 2 and 3) would have been found long ago by linkage analysis; it appears that none exist. While linkage analyses followed by positional cloning led to the discovery of susceptibility genes, such as APC, MSH2, BRCA1, and BRCA2, that harbour many rare, high-risk variants (sector 1) [14-22], lack of clear positional cloning successes since 1996 and failure to find strong evidence of new linkages in the very large breast cancer and prostate cancer genome scans recently reported by Smith et al. and Xu et al., respectively [23,24], has led some to argue that few genes harbouring high-risk breast, colon, or prostate cancer susceptibility alleles remain to be identified. While it remains possible that homogenous family selection through close attention to tumour phenotype will lead to identification of more genes harbouring true high-risk sequence variants, it seems at least as likely that the deleterious variants in remaining susceptibility genes will confer lower risk than those in the already established high-risk breast cancer susceptibility genes and therefore lie at or below the conceptual border with the intermediate risk stratum.

Intermediate risk genes/variants. Linkage analysis provides a systematic route to localising high-risk susceptibility genes, and genomewide SNP association studies provide a systematic route to localizing common, modest-risk genetic variants. However, current technology does not provide an economical genomewide approach to that which logically lies in-between: intermediate-risk susceptibility genes harbouring pathogenic sequence variants that are individually uncommon or rare. Nonetheless, studies of individual genes have demonstrated that these exist. Perhaps the three best-understood intermediate-risk susceptibility genes are ATM, CHEK2 and MC1R. Inheritance of a heterozygous truncating variant in ATM or CHEK2 confers an approximately 2-fold risk of breast cancer plus increased risks of a number of other cancers [28,29]. Similarly, inheritance of a heterozygous reduced function missense substitution in the melanocortin receptor MC1R can confer twofold to fourfold increased risks of melanoma; interestingly, these MC1R genotypes are also associated with easily visible melanoma prone phenotypes such as very fair skin, freckling and red hair [30].

Modest risk genes/variants. The disequilibrium structure of the human genome and gene pool is such that there tend to be few common SNP patterns (or haplotypes or SNP groups) at any given locus. This feature dramatically reduces the number of markers required to carry out genomewide SNP association studies as well as the degree of multiple testing inherent in such studies [31]. The result is that recently conducted genomewide SNP association studies had >80% power to detect associations at carrier frequencies of 10% for ORs of 1.5, and studies that use early-onset or familial cases should achieve sufficient power at ORs of 1.25. Although we do not currently know how much risk is attributable to variants in this frequency range (sectors 4&5), large-scale association studies are beginning to find and replicate evidence of risk association for some SNPs [32,33], and the optimistic view is that most common main effect genotype associations with risk of breast cancer, colon cancer, prostate cancer and some of the less common cancers should be found in the next few years.

The contour lines of gPAF and FRR plotted in Figures 2.15.1 and 2.15.2 provide another view of both potential importance and likelihood of the nine risk x frequency sectors. Individual deleterious sequence variants can be repre-

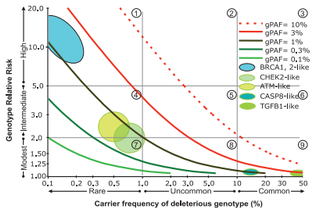


Fig. 2.15.1 *Genetic population attributable fraction contour lines. Calculations from [25-27]*

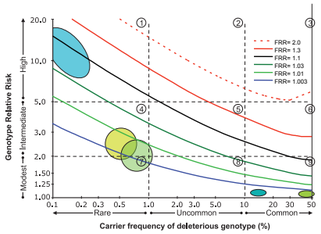


Fig. 2.15.2 *Familial relative risk contour lines. Calculations from [25-27]*

sented as a point on the graph. Alternatively, the pooled characteristic of a class of mutations in a susceptibility gene, for instance all of the high-risk mutations in BRCA1, can also be represented as a point on the graph. At some future time when most of the genetic basis of the common cancers is understood, the risk conferring genes could all be plotted on the graph, resulting in some kind of cloud of points. But what will the shape and density distribution of that cloud of points be? Under the common disease/common variant (CD/CV) hypothesis, we would expect the density distribution to be skewed towards the high-frequency end of the graph, at or above a carrier frequency of 10%, unless most of the risk is in minor allele homozygotes. In contrast, the common disease/rare variant (CD/ RV) hypothesis predicts a density distribution that peaks at lower carrier frequencies.

One relationship revealed by examination of these two graphs is that high-risk genes (e.g. BRCA 1 & 2) contribute to FRR relatively more efficiently than they contribute to gPAF; conversely, modest-risk SNPs (e.g. Caspase-8, TGFB1, FGFR2 [32,33]) contribute to gPAF more efficiently than they contribute to FRR [25,26]. We can deduce an interesting consequence from this relationship. On the one hand, the missing genetic component of breast cancer risk cannot be explained entirely by high-risk susceptibility genes. For example, an ensemble of high-risk genes, each with OR=10 and a pooled deleterious variant carrier frequency of 0.1%, could account for all of the unexplained familial relative risk and yet not account for the unexplained gPAF. Not to mention that linkage studies exclude the possibility of enough unidentified high-risk genes to account for the missing FRR. On the other hand, the missing genetic component of breast cancer risk cannot be explained entirely by modest-risk susceptibility genes either. For example, an ensemble of common modest-risk SNP with OR=1.25 and carrier frequency of 20% could have a gPAF far in excess of 100% without accounting for the missing FRR. Therefore, while we cannot yet specify the shape and density distribution of the aforementioned cloud of points in risk-frequency space, we can exclude the possibility that most of the risk (as measured by FRR) is accounted for by either rare, high-risk genes or common modest-risk SNPs.

Since the first major susceptibility genes for the common cancers were found in the early 1990s, we have learned a considerable amount about genetic cancer susceptibility, underlying susceptibility genes, and the biochemical pathways in which they function. For the known high-risk susceptibility genes, our growing understanding has led to genetic tests and to medical and surgical interventions that can add years to the lives of gene mutation carriers (see *Genetic testing*, Chapter 4.14). Whether improved understanding of intermediate-risk and modest-risk susceptibility genes will lead to similar medical utility remains a question for the future.

REFERENCES

1. Hashibe M, Boffetta P, Zaridze D, et al. (2006). Evidence for an important role of alcohol- and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev* 15: 696-703.

2. Antoniou AC, Sinilnikova OM, Simard J, et al. (2007). RAD51 135G->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. *Am J Hum Genet* 81: 1186-1200.

3. Broca PP (1866). *Traité des tumeurs*. Paris: Asselin.

4. Lichtenstein P, Holm NV, Verkasalo PK, et al. (2000). Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 343: 78-85.

5. Rothman KJ, Greenland S (1998). *Modern epidemiology*. Philadelphia, PA: Lippincott-Raven.

6. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. (2004). Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med* 1: e65.

7. Goldgar DE, Easton DF, Cannon-Albright LA, et al. (1994). Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 86: 1600-1608.

8. Kerber RA and O'Brien E (2005). A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. *Cancer* 103: 1906-1915.

9. Pharoah PD, Dunning AM, Ponder BA, et al. (2004). Association studies for finding cancer-susceptibility genetic variants. *Nat Rev Cancer* 4: 850-860.

10. Thompson D and Easton D (2004). The genetic epidemiology of breast cancer genes. *J Mammary Gland Biol Neoplasia* 9: 221-236.

11. Dunlop MG, Farrington SM, Nicholl I, et al. (2000). Population carrier frequency of hMSH2 and hMLH1 mutations. *Br J Cancer* 83: 1643-1645.

12. Ilyas M, Straub J, Tomlinson IP, et al. (1999). Genetic pathways in colorectal and other cancers. *Eur J Cancer* 35: 1986-2002.

13. Southey MC, Jenkins MA, Mead L, et al. (2005). Use of molecular tumor characteristics to prioritize mismatch repair gene testing in early-onset colorectal cancer. *J Clin Oncol* 23: 6524-6532.

14. Aaltonen LA, Peltomaki P, Leach FS, et al. (1993). Clues to the pathogenesis of familial colorectal cancer. *Science* 260: 812-816.

15. Bodmer WF, Bailey CJ, Bodmer J, et al. (1987). Localization of the gene for familial adenomatous polyposis on chromosome 5. *Nature* 328: 614-616.

16. Hall JM, Lee MK, Newman B, et al. (1990). Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 250: 1684-1689.

17. Leppert M, Dobbs M, Scambler P, et al. (1987). The gene for familial polyposis coli maps to the long arm of chromosome 5. *Science* 238: 1411-1413.

18. Miki Y, Swensen J, Shattuck-Eidens D, et al. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 266: 66-71.

19. Peltomaki P, Aaltonen LA, Sistonen P, et al. (1993). Genetic mapping of a locus predisposing to human colorectal cancer. *Science* 260: 810-812.

20. Tavtigian SV, Simard J, Rommens J, et al. (1996). The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. *Nat Genet* 12: 333-337.

21. Wooster R, Neuhausen SL, Mangion J, et al. (1994). Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 265: 2088-2090.

22. Wooster R, Bignell G, Lancaster J, et al. (1995). Identification of the breast cancer susceptibility gene BRCA2. *Nature* 378: 789-792.

23. Smith P, McGuffog L, Easton DF, et al. (2006). A genome wide linkage search for breast cancer susceptibility genes. *Genes Chromosomes Cancer* 45: 646-655.

24. Xu J, Dimitrov L, Chang BL, et al. (2005). A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. *Am J Hum Genet* 77: 219-229.

25. Goldgar DE (2002). Population aspects of cancer genetics. *Biochimie* 84: 19-25.

26. Hemminki K and Bermejo JL (2007). Constraints for genetic association studies imposed by attributable fraction and familial risk. *Carcinogenesis* 28: 648-656.

27. Lilienfeld AM, Lilienfeld DE (1980). *Foundations of epidemiology*. New York: Oxford University Press.

28. CHEK2*1100delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies (2004). *Am J Hum Genet* 74: 1175-1182.

29. Renwick A, Thompson D, Seal S, et al. (2006). ATM mutations that cause ataxia telangiectasia are breast cancer susceptibility alleles. *Nat Genet* 38: 873-875.

30. Hayward NK (2003). Genetics of melanoma predisposition. *Oncogene* 22: 3053-3062.

31. A haplotype map of the human genome (2005). *Nature* 437: 1299-1320.

32. Cox A, Dunning AM, Garcia-Closas M, et al. (2007). A common coding variant in CASP8 is associated with breast cancer risk. *Nat Genet* 39: 352-358.

33. Easton DF, Pooley KA, Dunning AM, et al. (2007). Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* 447: 1087-1093.

2.16 Medical and Iatrogenic Causes

Summary

> Chronic inflammation has been associated with excess risk of lung cancer, mesothelioma, oesophageal, colorectal, bladder and several other cancers

> Chronic pancreatitis has been related to a gross excess risk of pancreatic cancer

> Subjects with cirrhosis have an over tenfold excess risk of primary liver cancer

> Diabetes is associated with excess risk of endometrial, colorectal, liver and possibly pancreatic cancer

> Excess cancer risk has been reported in subjects treated with chemotherapy, radiotherapy, HRT, phenacetin and selective other drugs

Inflammation

The association between chronic inflammation and several malignancies has been recognised for many years. As early as 1863, the German pathologist Rudolf Virchow noted leucocytes in neoplastic tissues and made a connection between inflammation and cancer. Most of the early data were derived from descriptions of chronic cutaneous lesions, such as ulcers, burn scars or draining sinus tract [1,2]. Since then, the association between chronic inflammation and subsequent cancer has been recognised in many conditions (bladder cancer after schistosomiasis, ovarian cancer after pelvic inflammatory disease, esophageal cancer after Barrett's metaplasia, colorectal cancer after inflammatory bowel disease, ulcerative colitis and Crohn's disease, lung cancer and mesothelioma after silicosis, asbestosis or COPD and pancreas cancer after chronic pancreatitis). Inflammatory process is also an important cofactor in viral carcinogenesis (gastric cancer and MALT hlymphoma after *H. pylori*, cervical cancer after human papillomavirus, liver cancer after hepatitis B and C virus and Kaposi sarcoma after human herpes virus type 8 infection) [3].

Chronic pancreatitis and pancreatic cancer

Chronic pancreatitis has several causes, but the most common in western countries is heavy alcohol consumption. The frequency of chronic pancreatitis is low in light and moderate drinkers (i.e. less than about 20 units of alcohol per week); most patients with chronic alcoholic pancreatitis have consumed six or more drinks per day for a period of 20 years. Several studies have now linked chronic pancreatitis with an increased risk of pancreatic cancer [4]. The evidence comes from different types of studies, with case–control studies being the most frequent. Most of these studies have shown that compared to control subjects without chronic pancreatitis, patients with chronic pancreatitis have an increased risk of pancreatic cancer.

Cohort studies provide the most reliable evidence to substantiate a link between chronic pancreatitis and pancreatic cancer. Several such studies have been performed, and all show an elevated risk of pancreatic cancer even after excluding patients where there has been a short interval between the onset of pancreatitis and cancer [5-7]. Record linkage studies based on electronically stored data have also confirmed a link between pancreatitis and pancreatic cancer.

Besides alcohol there are other causes of chronic pancreatitis where the risk is also increased. Hereditary pancreatitis is a rare inherited disease with symptoms and findings that mimic other types of chronic pancreatitis. It is inherited as an autosomal disease with an onset in childhood or early adulthood. The cumulative lifetime risk of pancreatic cancer in these patients is about 40% [5,6]. Smoking appears to advance the age of onset of cancer, suggesting a gene–environment interaction [7].

Tropical pancreatitis has many of the characteristics of other forms of pancreatitis, except that the disease is found primarily in southern India and in parts of sub-Saharan Africa. Diabetes and abdominal pain are prominent features; pancreatic cancer is an ominous late development.

Although the link between chronic pancreatitis and pancreatic cancer is established, the molecular pathway for this association has not been fully investigated. In chronic pancreatitis, as in other benign diseases with an increased cancer risk, increased cell turnover and defective DNA repair could lead to pancreatic cancer. Loss of p16 expression, a common precursor of cancer, has been noted in patients with chronic pancreatitis [8]. K-ras mutations, found in nearly all pancreatic cancers, have also been detected in patients with chronic pancreatitis [9].

Other medical causes

Cirrhosis is a chronic degenerative lesion of the liver that is caused by infections (hepatitis B and C) and also by toxic substances, mainly alcohol. Subjects with cirrhosis have a gross excess (over 10-fold) of subsequent primary liver cancer risk (see chapter 5.4). Indeed, cirrhosis is considered a pathogenic step in liver carcinogenesis [10]. History of cirrhosis has also been related to increased risk of oral, pharyngeal and esophageal cancers [11], but incomplete allowance for alcohol drinking remains an open issue for causal inference.

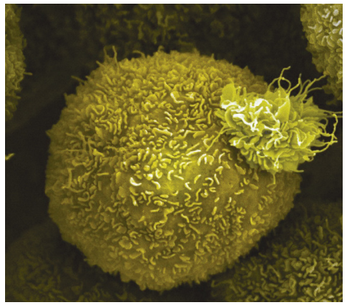


Fig. 2.15.1 *A pancreatic cancer cell*

Diabetes (and particularly type II diabetes) is related to hyperinsulinemia, and to changes in the insulin growth factor (IGF) system, which has been implicated in tumour promotion. Diabetes has been consistently related with excess risk of endometrial cancer, even after allowance for measures of body weight [12], and to colorectal, liver and perhaps pancreatic cancer risk [13].

There is no consistent evidence, in contrast, that stress (defined using several heterogeneous indicators) is related to excess cancer risk or cancer mortality [14].

Drugs and other therapies

The drugs that may cause or prevent cancer fall into several groups. Many cancer chemotherapy drugs interact with DNA, which might also result in damage to normal cells. The main neoplasm associated with chemotherapy treatment is leukaemia, although the risk of selected solid tumours—and specifically those related to viruses, such as liver, cervix or skin cancers—might also be increased. A second group of carcinogenic drugs includes immunosuppressive agents, notably used in transplanted patients. Lymphoma is the main neoplasm caused by these drugs. As discussed in chapter 2.8, hormone replacement therapy in menopause (HRT) increases the risk of breast, endometrial and ovarian cancers, and oral contraceptives increase the risk of breast, cervical and liver cancer, although they also reduce the risk of ovarian and endometrial cancer. Phenacetin-containing analgesics increase the risk of cancer of the renal pelvis.

Radiation for diagnostic purposes is likely to carry a small risk of cancer, which has been demonstrated only for childhood leukaemia following intrauterine exposure. Radiotherapy increases the risk of cancer in and near the irradiated organs. There is no evidence of an increased cancer risk following other medical procedures, including mammography and surgical implants [14].

In any case, the benefits of drugs and other therapies are usually much greater than the potential cancer risk.

REFERENCES

1. Bereston ES and Ney C (1941). Squamous-cell carcinoma arising in a chronic osteomyelitic sinus tract with metastasis. *Arch Surg* 43: 257.

2. Treves N and Pack GT (1930). The development of cancer in burn scars: an analysis and report of thirty-four cases. *Surg Gynecol Obst* 51: 749-782.

3. Balkwill F and Mantovani A (2001). Inflammation and cancer: back to Virchow? *Lancet* 357: 539-545.

4. Lowenfels AB and Maisonneuve P (2006). Epidemiology and risk factors for pancreatic cancer. *Best Pract Res Clin Gastroenterol* 20: 197-209.

5. Howes N, Lerch MM, Greenhalf W, et al. (2004). Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol* 2: 252-261.

6. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. (1997). Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst* 89: 442-446.

7. Lowenfels AB, Maisonneuve P, Whitcomb DC, et al. (2001). Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. *JAMA* 286: 169-170.

8. Rosty C, Geradts J, Sato N, et al. (2003). p16 Inactivation in pancreatic intraepithelial neoplasias (PanINs) arising in patients with chronic pancreatitis. *Am J Surg Pathol* 27: 1495-1501.

9. Lohr M, Kloppel G, Maisonneuve P, et al. (2005). Frequency of K-ras mutations in pancreatic intraductal neoplasias associated with pancreatic ductal adenocarcinoma and chronic pancreatitis: a meta-analysis. *Neoplasia* 7: 17-23.

10. La Vecchia C, Negri E, Cavalieri d'Oro L, et al. (1998). Liver cirrhosis and the risk of primary liver cancer. *Eur J Cancer Prev* 7: 315-320.

11. Randi G, Altieri A, Gallus S, et al. (2005). History of cirrhosis and risk of digestive tract neoplasms. *Ann Oncol* 16: 1551-1555.

12. Lucenteforte E, Bosetti C, Talamini R, et al. (2007). Diabetes and endometrial cancer: effect modification by body weight, physical activity and hypertension. *Br J Cancer* 97: 995-998.

13. La Vecchia C, Negri E, Franceschi S, et al. (1994). A case-control study of diabetes mellitus and cancer risk. *Br J Cancer* 70: 950-953.

14. Doll R, Peto R (2005). Epidemiology of cancer. In: Warrell DA, Cox TM, Firth JD, eds., *Oxford textbook of medicine* 193-218.

CANCER EFFORTS IN THE WHO WESTERN PACIFIC REGION

Cancer is now is the second-leading cause of death, after cardiovascular disease, in the Western Pacific Region. It claimed some 2.5 million lives in the Region in 2005, with the number expected to increase by more than 60% to over 4 million deaths in 2030. Cancer also is the leading cause of death in all developed countries in the Region—Australia, Brunei Darussalam, Hong Kong (China), Japan, Macao (China), New Zealand, the Republic of Korea and Singapore. At present, the cancer registry information available for 17 countries in the Region shows that the leading cancers in terms of mortality are lung, liver and stomach cancers. Since 2006, WHO has provided support to Brunei Darussalam, Fiji, Malaysia, Mongolia and Viet Nam for further development of cancer registries and for the development of national cancer control programmes. Support for middle- and low-income countries in the Region has focused on the prevention of lung, liver and cervical cancers, particularly through the development of national cancer control programmes.

Tobacco control initiatives have been developed as the primary focus to reduce lung cancer rates across the Region. By 2006 all Member States in the Region had ratified the WHO Framework Convention on Tobacco Control, making the Western Pacific Region the first in the world to do so. Many countries in the Region have developed effective tobacco control measures and are now implementing specific programmes.

Hepatitis B immunizations have been advocated as the principal measure in liver cancer prevention. In 1991, 29 of the 37 countries and areas in the Region had a hepatitis B virus (HBV) carrier rate greater than 8%. The Regional Office for the Western Pacific has strongly promoted the introduction of HBV vaccine into the national immunization programs of all the Member States. In 2005 a regional goal was set to reduce chronic hepatitis B infection rates to less than 2% among children 5 years of age by 2012. Since then, the Regional Office has been working with countries with high proportions of home births on strategies to deliver timely HBV birth doses. At present, 26 countries and areas in the Region, including China, are estimated to have achieved less than 2% hepatitis B chronic infection rates among children 5 years old, down from an average of 8–14% in the pre-vaccination era. Figure 1 shows the decline in chronic hepatitis B infection rates, especially in children and adolescents, in China.

Figure 2 shows that rates of cervical cancer are highest among the less-developed countries of the Western Pacific Region. Cytology (Pap smear) is carried out in developed countries in the Region and visual inspection (with acetic acid) is promoted as a cost-effective method for developing countries. The Regional Office for the Western Pacific supported Member States in the introduction of two human papillomavirus (HPV) vaccines. Australia was the first country in the world to introduce HPV vaccine, targeting all women age 12–26 years.

website: www.wpro.who.int

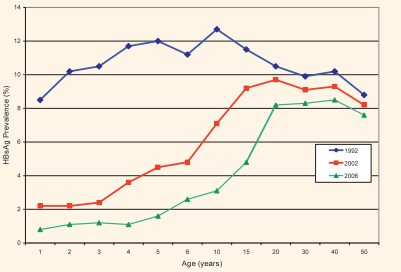


Fig. 1: *HBV population prevalence from National Surveys in China (Preliminary data)*

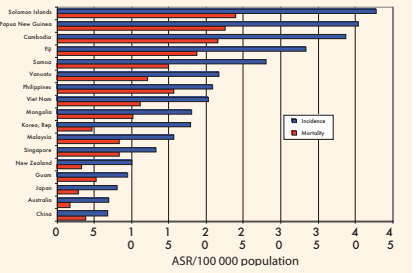


Fig. 2: *CERVICAL CANCER: Age-Standardised Death & Incidence Rates (ASR) for the Western Pacific Region: 2002*