Etiology of Cancer
Carcinogen identification is the first step in exposure to cancer-causing agents. It involves the scientific evaluation of epidemiological studies, animal bioassays, and mechanistic studies to identify human carcinogens. The first step in cancer prevention is to identify and assess risks to determine the extent of human exposure to the carcinogen, and risk characterization 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 the cancer hazard. Risk depends on both the existence of a hazard and exposure to that hazard. A cancer hazard exists even when current exposure suggests 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.

Some carcinogen identification programmes


U.S. National Toxicology Program (NTP): http://ntp.niehs.nih.gov/

U.S. Environmental Protection Agency (EPA): http://www.epa.gov/ncea/

German Research Foundation (Deutsche Forschungsgemeinschaft, DFG): Mammalian Reliable Concentrations (Mammalian Arbeitsstättenzweckverordnung, MAK) and Biological Tolerance Values (Biologische Arbeitsstättenwerte, BAT). http://www.dfg.de/

California Environmental Protection Agency (California): 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 offer an agent to experimental animals 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 experimental 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 using 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 molecular processes involved in tumour development. This has the potential to improve the analysis of studies in both humans and experimental animals. Each giving insight into the biology of cancer and helping to identify susceptible individuals and development stages.

Evaluating a body of mechanistic and other relevant data, the key scientific questions are whether the mechanistic data are strong and whether the evidence indicates causality. If mechanistic studies in experimental animals could also operate in humans. Strong support can be obtained from studies that challenge a hypothesis. If mechanistic studies are developed during cancer in humans, cancer in experimental animals, and mechanistic and other relevant data may also be used further to develop a consensus draft subgroup. 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 clinical, bias, and confounding could be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available evidence permits 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.

Some carcinogen identification programmes

Inadequate evidence of carcinogenicity: The available evidence permits 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.

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.

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. In the meeting, experts present their critical reviews, focusing on the questions of cancer in humans, cancer in experimental animals, and mechanistic and other relevant data. Critical reviews are used to develop a consensus draft subgroup.

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 clinical, bias, and confounding could be ruled out with reasonable confidence.

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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.
At the same time, another subgroup of experimental scientists reviews the mechanistic and other relevant data, the Working Group classifies in experimental animals, and the mechanistic and evaluation of the weight of evidence. Based subgroups and to discuss and develop an overall mental scientists reviews the mechanistic and At the same time, another subgroup of experimental scientists reviews the mechanistic and other relevant data, the Working Group classifies in experimental animals, and the mechanistic and evaluation of the weight of evidence. Based subgroups and to discuss and develop an overall mental scientists reviews the mechanistic and

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. Although developing more than 20 years to the IARC, the last 12 years as director, Lorenzo Tomatis retired in December 1993. Throughout those 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 28. He arrived to create and establish the Unit of Chemical Cancerisation, and spent his career 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 both human epidemiology and experimental results are both seen as essential to the identification of human risks. The overall objective of IARC is to present human cancer and identifying environmental agents as the primes of the cancer 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 IARC’s internationally recognized 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 Tomatis was most highly regarded, and for which he will be long remembered by the scientific community.

Table 2.1.1 Examples of carcinogenic agents

<table>
<thead>
<tr>
<th>Some examples of carcinogenic agents</th>
<th>Some examples of carcinogenic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemicals</td>
<td>Complex mixtures</td>
</tr>
<tr>
<td>Benzene, 1,3-butadiene, formaldehyde, vinyl chloride</td>
<td>Styrene, crotonic acid, isocyanate</td>
</tr>
<tr>
<td>Alcohol, tar, soot</td>
<td>PCBs, creosote, emissions from high-temperature frying</td>
</tr>
<tr>
<td>Occupations</td>
<td>Metals</td>
</tr>
<tr>
<td>Painting, chimney sweeping, coal gasification, coke production</td>
<td>Arsenic and compounds, beryllium and compounds, cadmium and compounds, chromium[VI]</td>
</tr>
<tr>
<td>Particles and fibres</td>
<td>Pharmaceutical agents</td>
</tr>
<tr>
<td>asbestos, crystalline silica, wood dust</td>
<td>DES, estrogen progesterone monophasic therapy, tamoxifen, phenaquine</td>
</tr>
<tr>
<td>Radiation</td>
<td>Biological agents</td>
</tr>
<tr>
<td>ionizing radiation, X- and R- and gamma ray radiation</td>
<td>Hepatitis B and C, human papillomaviruses</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td>Tobacco smoke (including passive smoking), oracul, retinol, vitamin-D and household composition of coal</td>
</tr>
</tbody>
</table>

REFERENCES


Tobacco Smoking

Summary

- Tobacco smoking causes 13 different cancers in males and females: oral cavity, nasopharynx, larynx, oesophagus, stomach, liver, pancreas, urinary bladder, kidney, uterine cervix, and myeloid leukaemia. In high-resource countries, tobacco smoking accounts for approximately 20% of all human cancers.
- Lung cancer has the highest smoking attributable fraction among all cancers induced by tobacco use and is the strongest determinant of excess lung cancer risk in smokers, with risk increasing proportionately 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 humans, 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 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-related disease vary markedly from one country to country and these differences are determined, to a large extent, by country-to-country differences in prevalence of current smoking for a 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 at times differ greatly from similar differences in the same countries a few years prior to the year of death. As a result, differences in the prevalence of current smoking for a given year in different countries may at times differ greatly from similar differences in the same countries a few years prior to the year of death. As a result, differences in the prevalence of current smoking for a given year in different countries may at times differ greatly from similar differences in the same countries a few years prior to the year of death.
- 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. 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 and where consumption levels.

WHO Region* Estimated cancer mortality attributable to smoking by WHO Region in 2000

<table>
<thead>
<tr>
<th>Region</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe C</td>
<td>133 000</td>
<td>49</td>
<td>144 000</td>
</tr>
<tr>
<td>Europe B</td>
<td>72 000</td>
<td>9 000</td>
<td>81 000</td>
</tr>
<tr>
<td>Southeast Asia (India and others)</td>
<td>174 000</td>
<td>43</td>
<td>100 000</td>
</tr>
<tr>
<td>Southeast Asia (Indonesia and others)</td>
<td>65 000</td>
<td>43</td>
<td>47 000</td>
</tr>
<tr>
<td>North America</td>
<td>131 000</td>
<td>42</td>
<td>211 000</td>
</tr>
<tr>
<td>Western Europe</td>
<td>225 000</td>
<td>40</td>
<td>272 000</td>
</tr>
<tr>
<td>Western Pacific A</td>
<td>69 000</td>
<td>36</td>
<td>87 000</td>
</tr>
<tr>
<td>Eastern Mediterranean B</td>
<td>12 000</td>
<td>30</td>
<td>16 000</td>
</tr>
<tr>
<td>Eastern Mediterranean B</td>
<td>26 000</td>
<td>28</td>
<td>30 000</td>
</tr>
<tr>
<td>Americas B</td>
<td>68 000</td>
<td>27</td>
<td>60 000</td>
</tr>
<tr>
<td>Western Pacific (China and others)</td>
<td>209 000</td>
<td>20</td>
<td>264 000</td>
</tr>
<tr>
<td>Africa E</td>
<td>23 000</td>
<td>5 000</td>
<td>28 000</td>
</tr>
<tr>
<td>Africa D</td>
<td>5 000</td>
<td>4 000</td>
<td>9 000</td>
</tr>
<tr>
<td>Americas D</td>
<td>2 000</td>
<td>6</td>
<td>2 000</td>
</tr>
</tbody>
</table>

Table 2.2.1: Projected cancer mortality attributable to smoking by WHO Region in 2050

* 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.

Fig. 2.2.1: Stages of the tobacco epidemic. Deaths from tobacco-related diseases occur very early in the life course, with both the cumulative number of deaths and the underlying dimension of the tobacco epidemic in those areas of the world. Table 2.2.3 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 (24.9 and 47.6 respectively) than less-developed regions (25.9 and 22.9 respectively) reflecting post uptake and cessation of smoking in those populations.

The majority of those daily smokers reside 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, particularly in the USA, the UK, and many countries in Southeast Asia.

Fig. 2.2.2: Tobacco consumption levels. Tobacco consumption levels are estimated from 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 reside 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, such as in the USA, the UK, and many countries in Southeast Asia.
### Table 2.2.3

<table>
<thead>
<tr>
<th>Continent</th>
<th>Country</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>ASR (W)</strong></td>
<td><strong>Std. Error</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Country</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>Tunisia, Centre</td>
<td>371.1</td>
<td>2.05</td>
</tr>
<tr>
<td></td>
<td>Zimbabwe, Harare</td>
<td>6.8</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Algeria, Sefif</td>
<td>19.9</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>Uganda, Kyandondo</td>
<td>58</td>
<td>0.69</td>
</tr>
<tr>
<td>America</td>
<td>USA, New Orleans Black</td>
<td>96.6</td>
<td>3.30</td>
</tr>
<tr>
<td></td>
<td>Kentucky, USA</td>
<td>50.3</td>
<td>0.59</td>
</tr>
<tr>
<td>North</td>
<td>USA, Kentucky</td>
<td>90.1</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Pennsylvania Black</td>
<td>46.8</td>
<td>1.09</td>
</tr>
<tr>
<td>America</td>
<td>Argentina, Bahia Blanca</td>
<td>45.5</td>
<td>2.42</td>
</tr>
<tr>
<td></td>
<td>Brazil, Brazilia</td>
<td>12.5</td>
<td>0.75</td>
</tr>
<tr>
<td>Central &amp; South</td>
<td>Brazil, Sao Paulo</td>
<td>33.5</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Brazil, Sao Paulo</td>
<td>11.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Asia</td>
<td>Turkey, Izmir</td>
<td>76.5</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>China, Guangzhou City</td>
<td>71.9</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>China, Shanghai</td>
<td>27.0</td>
<td>1.09</td>
</tr>
<tr>
<td>Europe</td>
<td>Poland, Kielce</td>
<td>76.9</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>UK, Scotland</td>
<td>34.9</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Croatia</td>
<td>22.1</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>UK, England Merseyside</td>
<td>31.9</td>
<td>0.54</td>
</tr>
<tr>
<td>Oceania</td>
<td>French Polynesia</td>
<td>62.3</td>
<td>4.06</td>
</tr>
<tr>
<td></td>
<td>French Polynesia</td>
<td>23.6</td>
<td>2.43</td>
</tr>
<tr>
<td></td>
<td>Australia, Northern Territory</td>
<td>51.4</td>
<td>4.07</td>
</tr>
<tr>
<td></td>
<td>Australia, Northern Territory</td>
<td>22.7</td>
<td>2.87</td>
</tr>
<tr>
<td>Lowest rates</td>
<td>Tunisia, Centre</td>
<td>9.5</td>
<td>0.90</td>
</tr>
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<td></td>
<td>Tunisia, Centre</td>
<td>1.7</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Uganda, Kyandondo</td>
<td>4.8</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Algeria, Sefif</td>
<td>1.7</td>
<td>0.29</td>
</tr>
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<td>America</td>
<td>USA, California, L.A.: Hispanic</td>
<td>23.2</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>USA, California, L.A.: Hispanic</td>
<td>12.3</td>
<td>0.41</td>
</tr>
<tr>
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<td>USA, New Mexico: Amer: Indian</td>
<td>12.2</td>
<td>1.91</td>
</tr>
<tr>
<td></td>
<td>USA, New Mexico: Amer: Indian</td>
<td>3.9</td>
<td>0.96</td>
</tr>
<tr>
<td>America</td>
<td>Ecuador, Quito</td>
<td>7.9</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Costa Rica</td>
<td>4.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Central &amp; South</td>
<td>Peru, Trujillo</td>
<td>5.9</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Ecuador, Trujillo</td>
<td>4.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Asia</td>
<td>India, Mumbai</td>
<td>9.7</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>India, Karachi</td>
<td>2.3</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>India, Nigpur</td>
<td>7.3</td>
<td>0.45</td>
</tr>
<tr>
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<td>India, Trivandrum</td>
<td>1.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Europe</td>
<td>Portugal, Porto</td>
<td>30.5</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Spain, Alzcoite</td>
<td>3.3</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>Spain, Granada</td>
<td>3.3</td>
<td>0.33</td>
</tr>
<tr>
<td>Oceania</td>
<td>Australia, Capital Territory</td>
<td>35.6</td>
<td>1.77</td>
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<td>Australia, Capital Territory</td>
<td>16.7</td>
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</tr>
<tr>
<td></td>
<td>New Zealand</td>
<td>35.3</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>New Zealand</td>
<td>13.7</td>
<td>1.24</td>
</tr>
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</table>

### Table 2.2.4

<table>
<thead>
<tr>
<th>Location</th>
<th>Production (tonnes / annum)</th>
<th>Import** tonnes</th>
<th>Export** tonnes</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>2,688,500</td>
<td>69,404</td>
<td>161,850</td>
</tr>
<tr>
<td>Brazil</td>
<td>889,426</td>
<td>7,900</td>
<td>614,448</td>
</tr>
<tr>
<td>India</td>
<td>550,000</td>
<td>1,152</td>
<td>201,570</td>
</tr>
<tr>
<td>Europe</td>
<td>496,916</td>
<td>126,578</td>
<td>233,177</td>
</tr>
<tr>
<td>USA</td>
<td>290,170</td>
<td>281,067</td>
<td>132,978</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>80</td>
<td>291,807</td>
<td>1,739</td>
</tr>
<tr>
<td>World</td>
<td>6,580,828</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2.4: Concentration of carcinogenic agents in mainstream tobacco smoke of non-filtered cigarettes and in smokeless tobacco

<table>
<thead>
<tr>
<th>Substances</th>
<th>Tobacco smoke</th>
<th>Smokeless tobacco</th>
<th>ng/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volatile aldehydes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>70 - 200 μg</td>
<td>1600 - 1700</td>
<td></td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>500 - 1400 μg</td>
<td>1400 - 27400</td>
<td></td>
</tr>
<tr>
<td>Crotonaldehyde</td>
<td></td>
<td>200 - 2400</td>
<td></td>
</tr>
<tr>
<td>N-Nitrosamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Nitrosodimethylaniline</td>
<td>2 - 1000 ng</td>
<td>nd - 270</td>
<td></td>
</tr>
<tr>
<td>N-Nitrosodiethylaniline</td>
<td>3 - 8 ng</td>
<td>nd - 860</td>
<td></td>
</tr>
<tr>
<td>N-Nitrosopiperidazine</td>
<td>3 - 110 ng</td>
<td>nd - 270</td>
<td></td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BaP</td>
<td>45 - 58 000 ng</td>
<td>400 - 3 085 000</td>
<td></td>
</tr>
<tr>
<td>Chrysen</td>
<td>0.03 - 1 0 000 ng/cigarette</td>
<td>0.07 - 22 900</td>
<td></td>
</tr>
<tr>
<td>Benz[a]pyrene</td>
<td>40 - 120 μg</td>
<td>nd - 270</td>
<td></td>
</tr>
<tr>
<td>Benz[a]anthracene</td>
<td>20 - 40 ng</td>
<td>nd - 0.1 90 ng/g</td>
<td></td>
</tr>
<tr>
<td>Benz[b]fluoranthene</td>
<td>20 - 70 ng</td>
<td>nd - 0.1 90 ng/g</td>
<td></td>
</tr>
<tr>
<td>Benz[a]aminothiazole</td>
<td>4 - 92 ng</td>
<td>nd - 270</td>
<td></td>
</tr>
<tr>
<td>Dibenz[a,j]pyrene</td>
<td>1.7 - 3.2 ng</td>
<td>nd - 270</td>
<td></td>
</tr>
<tr>
<td>Dibenz[a]anthracene</td>
<td>4 ng</td>
<td>nd - 270</td>
<td></td>
</tr>
</tbody>
</table>

Mechanisms of carcinogenesis

Tobacco smoke is the most common source of carcinogens to humans. It includes about 105 different chemicals and products, of which 60 are carcinogens [12]. Of these, polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most important.

Substances that are carcinogenic to humans. It includes about 105 different chemicals and products, of which 60 are carcinogens [12]. Of these, polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most important.

Tobacco-specific nitrosamines

Specific nitrosamines are the most important. In addition to nitrogen dioxide, they are also found in nitrous oxide, nitric oxide, nitric oxide, nitric oxide, and nitric oxide.

Substances that are carcinogenic to humans. It includes about 105 different chemicals and products, of which 60 are carcinogens [12]. Of these, polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most important.

Polycyclic aromatic hydrocarbons

Substances that are carcinogenic to humans. It includes about 105 different chemicals and products, of which 60 are carcinogens [12]. Of these, polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most important.

Dibenz[a,j]pyrene

Substances that are carcinogenic to humans. It includes about 105 different chemicals and products, of which 60 are carcinogens [12]. Of these, polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most important.

Dibenz[a]anthracene

Substances that are carcinogenic to humans. It includes about 105 different chemicals and products, of which 60 are carcinogens [12]. Of these, polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most important.

N-Nitrosamines

Substances that are carcinogenic to humans. It includes about 105 different chemicals and products, of which 60 are carcinogens [12]. Of these, polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most important.

Other individual carcinogenic agents

Most carcinogens are oxygenated derived from IARC monographs volumes 3 and 4, numbers in red from Hoffmann, Hoffman and El-Bayoumy, 2001. In addition, inducers of reactive oxygen species like NO, NO2, 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). Many carcinogens are generated by cells using cytochrome P450 enzymes to be transformed into excretory forms. Electrophilic oxygenated carcinogens can form covalently bound DNA adducts. Six carcinogens present in tobacco smoke are known to form other individual carcinogenic agents.

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 several 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 individual cases, without cause of the lung. These results confirmed cigarette smoking as a cause of lung cancer: the frequency of smoking and amount smoked were significantly higher in patients with lung cancer 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 study by Wynder and Graham, 43-50% of lung cancer cases had smoked cigarettes. 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 nicotine content of tobacco used in manufactured cigarettes. Lower nicotine 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 nicotine content in US blends of tobacco used to make cigarettes may have increased the formation of nitrosamines during tobacco storage, processing and smoking. Nitrosamines, such as NNN, are carcinogens that induce the formation of adenocarcinomas [17,18].

Cigar 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 lesser extent, and smokers who have switched from cigarettes to cigars/pipes have reported a higher risk of lung cancer than exclusive cigar/pipe smokers. Cigar or pipe smoking has also been associated with oral cancer, esophagyngeal, hypopharyngeneal, laryngeal and oesophageal cancers [1]. Similarly, bidi smoking is associated with lung, oral, laryngeal, esophageal and stomach cancer with the risk increasing with amount smoked and duration [1].
DNA adducts in human tissue: benz(a)pyrene ([B(a)P], NIKK, NDMA [N-nitrosodimethylamine], NNN [N-nitrosodiethylnitrosamine], aflatoxin B1 and 4-amino-1-butanol. [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 capacity, overwhelming cellular defenses and leading to 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 = 8.90 (95% CI 6.73-12.11) for lung cancer, RR = 6.08 (95% CI 3.14-11.52) for laryngeal cancer, RR = 0.79 (95% CI 0.86-15.98) for pharyngeal cancer, 3.57 (95% CI 2.63-4.84) for the upper-digestive tract and RR = 3.43 (95% CI 2.75-4.04) 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 association 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]. This result emphasizes the need to devote 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, has occurred primarily by increase in quitting at middle age [Figure 2.2.4]. The great challenge in eliminating all tobacco-related cancers, 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 [23]. Despite growing efforts from medical and public health institutions and the growing involvement of non-governmental organizations, 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.

REFERENCES


Table 2.3.5: Major cancer sites associated with smoking

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Sex</th>
<th>Pooled Relative Risk (RR)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>M</td>
<td>9.67</td>
<td>6.85-12.44</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>5.78</td>
<td>3.56-10.73</td>
</tr>
<tr>
<td>(C10-15)</td>
<td>M</td>
<td>3.62</td>
<td>2.96-8.77</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>4.67</td>
<td>1.97-7.33</td>
</tr>
<tr>
<td>Esophagus</td>
<td>M</td>
<td>3.20</td>
<td>1.81-5.25</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>3.31</td>
<td>1.82-5.20</td>
</tr>
<tr>
<td>Stomach</td>
<td>M</td>
<td>1.17</td>
<td>0.92-1.51</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.45</td>
<td>0.95-2.19</td>
</tr>
<tr>
<td>Pancreas</td>
<td>M</td>
<td>1.63</td>
<td>1.32-2.03</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.73</td>
<td>1.32-2.40</td>
</tr>
<tr>
<td>Liver</td>
<td>M</td>
<td>1.85</td>
<td>1.21-2.83</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.49</td>
<td>1.12-1.98</td>
</tr>
<tr>
<td>Bladder</td>
<td>M</td>
<td>2.80</td>
<td>2.01-3.92</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>2.73</td>
<td>1.82-4.10</td>
</tr>
</tbody>
</table>

exhaled mainstream smoke and sidestream smoke.

Secondhand tobacco smoke contains nicotine and other toxic components.

**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 epidemiologic 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, and bans and restrictions can be particularly polluted. About 10-15% of all 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.

**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 (R, 0.10). A pooled analysis of the two largest case-control studies estimated a 2.4 (95% CI 1.3-4.3) increase in lung cancer risk attributable to passive smoking for women and a 1.5 (95% CI 1.0-2.3) increase in men.**

**Mechanisms of tobacco-related carcinogenesis**

- Metabolites of the tobacco-specific nitrosamine N-Nitrosonornicotine (NNN) and N-nitroso deoxymethyl nicot ine (NDNM) have been shown in exhaled mainstream smoke and sidestream smoke (see Chapter 2.3). The most widely studied components of sidestream smoke are nicotine, carbon monoxide, suspended particles and polynuclear aro mata. The second most complete study of sidestream smoke in the air has been the quantitative analysis of compounds formed from exposure to secondhand tobacco smoke, including the assessment of exposure in homes. Based on recent studies of sidestream smoke, the inhaled nicotine in air was shown to be 1-2 times higher when smoking at home compared to 0.1-0.2 mg/m3 at 0.5 mg/m3. A review of exposure to secondhand smoke in bars, bowling alleys, billiard halls, etc. is now possible in 21 countries and the mean concentrations ranged from 24 to 112 µg/m3. Cotinine is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke. Cotinine is the only source of nicotine in children, infants, and non-smokers. It is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke. Cotinine is the only source of nicotine in children, infants, and non-smokers. It is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke.

- The exposure to passive smoking in the home can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke. Cotinine is the only source of nicotine in children, infants, and non-smokers. It is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke. Cotinine is the only source of nicotine in children, infants, and non-smokers. It is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke. Cotinine is the only source of nicotine in children, infants, and non-smokers. It is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke. Cotinine is the only source of nicotine in children, infants, and non-smokers. It is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke. Cotinine is the only source of nicotine in children, infants, and non-smokers. It is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke. Cotinine is the only source of nicotine in children, infants, and non-smokers. It is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke.

**Burden of passive smoking-related lung cancer**

- In the US, 34293 annual lung cancer deaths in never-smokers are attributed to passive smoking (16). For Europe, Yen et al (17) estimated the proportion of lung cancer deaths among never-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 12.5% in men and 13% in women (18). Work-related exposure to secondhand smoke was calculated to account for 5.7% of lung cancers in never-smokers in the US (19).

**Cancer control**

- Primary prevention is the only effective tool to decrease the burden of cancer related to passive smoking. General tobacco control interventions can be used to decrease exposure to secondhand smoke. With the Framework Convention on Tobacco Control (FCTC) the WHO has initiated a process to ban smoking in public places. Since the ratification of this first global public health treaty on tobacco control, there have been new introduced strict smoke-free bans (including Ireland, Norway, Italy, Sweden, Scotland, England, Wales and Northern Ireland) and other jurisdictions introduced in 2009 (e.g. France, and Bavaria with coverage including the Oktoberfest). The report of the U.S. Surgeon General (20) 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 periods of exposure to secondhand smoke, several jurisdictions have shown substantial decreases in respiratory suspended particles, nicotine, PAH, benzene and 1,3-butanone in indoor air and biomarkers of exposure (tobacco smoke, exhaled carbon monoxide) (e.g. [21]; Figure 2.3.1). One of these studies further demonstrated significant improvements in mean pulmonary function tests and significant reductions in well-reasoned symptoms in smokers after the ban (22). Recently, studies reported a significant reduction in acute coronary events after implementation 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.

Table 2.3.1 Yields of IARC carcinogens in sidestream smoke of regular-sized Canadian cigarettes, International Organization for Standardization (ISO) machine-smoking parameters

<table>
<thead>
<tr>
<th>Compound</th>
<th>Regular</th>
<th>Light</th>
<th>Extra light</th>
<th>Ultra light</th>
<th>Regular/ light</th>
<th>Regular/ extra light</th>
<th>Regular/ ultra light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene (μg/cig.)</td>
<td>222.0</td>
<td>250.0</td>
<td>260.0</td>
<td>296.0*</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8*</td>
</tr>
<tr>
<td>Cadmium (μg/cig.)</td>
<td>438.0</td>
<td>484.0</td>
<td>502.0*</td>
<td>627.0*</td>
<td>0.9</td>
<td>0.9*</td>
<td>0.7*</td>
</tr>
<tr>
<td>2-Hydroxypropionaldehyde (μg/cig.)</td>
<td>157.0</td>
<td>147.0</td>
<td>175.0</td>
<td>186.0</td>
<td>1.1</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Nickel (μg/cig.)</td>
<td>34.3</td>
<td>45.1</td>
<td>74.4*</td>
<td>73.0*</td>
<td>0.8</td>
<td>0.5*</td>
<td>0.5*</td>
</tr>
<tr>
<td>Chlorine (μg/cig.)</td>
<td>61.0</td>
<td>62.0</td>
<td>121*</td>
<td>82.9*</td>
<td>1.0</td>
<td>0.5*</td>
<td>0.7*</td>
</tr>
<tr>
<td>Aromatic (μg/cig.)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4-Anisidinophenol (μg/cig.)</td>
<td>23.3</td>
<td>19.5</td>
<td>21.0</td>
<td>21.2</td>
<td>1.1</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Formaldehyde (μg/cig.)</td>
<td>378.0</td>
<td>326.0</td>
<td>414.0</td>
<td>431.0</td>
<td>1.2</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>1,3-Butanedione (μg/cig.)</td>
<td>196.0</td>
<td>185.0</td>
<td>264.0</td>
<td>299.0</td>
<td>1.1</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Benzo(a)pyrene (μg/cig.)</td>
<td>48.8</td>
<td>98.3</td>
<td>92.2</td>
<td>113.0</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>NNK (ng/cig.)</td>
<td>95.2</td>
<td>153.4</td>
<td>38.3</td>
<td>34.7</td>
<td>0.6</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>NNQ (ng/cig.)</td>
<td>2.5</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>LARC Group 1 carcinogens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead (μg/cig.)</td>
<td>34.8</td>
<td>39.4</td>
<td>22.3</td>
<td>18.5</td>
<td>1.4</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>LARC Group 2B carcinogens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaldehyde (μg/cig.)</td>
<td>1416.0</td>
<td>1634.0</td>
<td>1449.0</td>
<td>1492.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Isoprene (μg/cig.)</td>
<td>1043.0</td>
<td>1164.0</td>
<td>1040.0</td>
<td>1172.0</td>
<td>0.9</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Cotinine (μg/cig.)</td>
<td>130.0</td>
<td>117.0</td>
<td>149.0</td>
<td>148.0</td>
<td>1.1</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Acrylonitrile (μg/cig.)</td>
<td>78.6</td>
<td>83.6</td>
<td>74.1</td>
<td>81.8</td>
<td>0.9</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Styrene (μg/cig.)</td>
<td>74.0</td>
<td>84.7</td>
<td>87.5</td>
<td>108.0*</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7*</td>
</tr>
</tbody>
</table>

Table 2.3.3 Yields of IARC carcinogens in sidestream smoke of regular-sized Canadian cigarettes, International Organization for Standardization (ISO) machine-smoking parameters


Table 2.3.2 Indicators of exposure to secondhand tobacco smoke

<table>
<thead>
<tr>
<th>Region</th>
<th>All students who never smoked, % (95% CI)</th>
<th>Exposed to SHS at home, % (95% CI)</th>
<th>Exposed to SHS in places other than home, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>79.3 (75.3-82.7)</td>
<td>23.6 (19.8-26.1)</td>
<td>38.2 (34.2-42.4)</td>
</tr>
<tr>
<td>Americas</td>
<td>54.7 (50.8-59.0)</td>
<td>39.1 (35.1-43.2)</td>
<td>41.7 (38.3-44.6)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>84.4 (80.2-87.0)</td>
<td>41.5 (37.7-46.4)</td>
<td>42.5 (39.0-46.5)</td>
</tr>
<tr>
<td>Europe</td>
<td>69.0 (65.0-73.0)</td>
<td>71.5 (64.6-77.0)</td>
<td>79.0 (73.9-83.7)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>86.4 (82.9-90.0)</td>
<td>42.8 (35.2-49.7)</td>
<td>38.2 (35.9-41.7)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>49.8 (46.3-53.3)</td>
<td>57.3 (50.0-64.4)</td>
<td>52.6 (49.2-56.1)</td>
</tr>
<tr>
<td>Total</td>
<td>80.3 (76.8-83.4)</td>
<td>46.8 (39.9-53.2)</td>
<td>47.8 (44.3-51.3)</td>
</tr>
</tbody>
</table>

Table 2.3.4 Prevalence of smoking in men and women

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggestory measures</td>
<td>Prevalence of smoking in men and women</td>
</tr>
<tr>
<td>Indirect measures</td>
<td>Report of secondhand tobacco smoke exposure in the home and in the workplace</td>
</tr>
<tr>
<td>Smoking in the household</td>
<td>Number of smokers</td>
</tr>
<tr>
<td>Smoking by partner(s)</td>
<td>Number of cigarettes smoked</td>
</tr>
<tr>
<td>Smoking in the workplace</td>
<td>Presence of secondhand tobacco smoke</td>
</tr>
<tr>
<td>Number of smokers</td>
<td></td>
</tr>
<tr>
<td>Direct measures</td>
<td>Concentration of secondhand tobacco smoke components</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Other markers</td>
</tr>
<tr>
<td>Respirable particles</td>
<td>Biomarker concentrations</td>
</tr>
<tr>
<td>Cotinine</td>
<td>Carboxyhaemoglobin</td>
</tr>
</tbody>
</table>

Fig. 2.3.1 Log-log scatter plot comparing particulate matter (PM) concentrations at pre- and post-ban, PM2.5 (≤2.5 mm in diameter PM2.5) concentrations at pre- and post-ban.
### Table 2.3.5 Relative risk (RR) and 95% confidence intervals (95% CI) results for highest cumulative or intensity of exposure groups

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Exposure Measure</th>
<th>RR (95% CI)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobbitt et al.</td>
<td>both</td>
<td>249 level a house/day years</td>
<td>2.07 (1.33-3.31)</td>
<td>Fitted results not adjusted for any risk factors.</td>
</tr>
<tr>
<td>Johnson et al.</td>
<td>women</td>
<td>2.64 smokers × years</td>
<td>1.58 (0.61-4.0)</td>
<td>Fitted results not adjusted for any risk factors.</td>
</tr>
<tr>
<td>Kabir et al.</td>
<td>women</td>
<td>smokers × house/64 × years</td>
<td>1.21 (0.47-3.19)</td>
<td>Fitted results not adjusted for any risk factors.</td>
</tr>
<tr>
<td>Kabir et al.</td>
<td>women</td>
<td>smokers × house/6 × years</td>
<td>1.35 (0.62-2.84)</td>
<td>Fitted results not adjusted for any risk factors.</td>
</tr>
<tr>
<td>Kralj et al.</td>
<td>women</td>
<td>duration × number of co-workers</td>
<td>1.08 (0.24-4.87)</td>
<td>Fitted results not adjusted for any risk factors.</td>
</tr>
<tr>
<td>Kreuser et al.</td>
<td>both</td>
<td>&gt;100.6 level a house/day years</td>
<td>2.64 (1.07-6.44)</td>
<td>Fitted results not adjusted for any risk factors.</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>men</td>
<td>Average</td>
<td>0.44 (0.05-4.01)</td>
<td>Fitted results not adjusted for any risk factors.</td>
</tr>
<tr>
<td>Zheng et al.</td>
<td>women</td>
<td>≥24 co-workers smoked</td>
<td>3.01 (1.8-4.9)</td>
<td>Fitted results not adjusted for any risk factors.</td>
</tr>
</tbody>
</table>

### References

During most of the 20th century, use of oral and nasal smokeless tobacco products was widespread in India and some Northern European countries, in particular among young people.

Smoking 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 tobacco products. These may be used in the product, and can be used orally or nasally.

In India, a large variety of commercial or home-made smokeless tobacco products exist. The form of chewing tobacco that is often chewed with betel quid or other preparations including areca nuts is more prevalent than the use of snuff; applying smokeless tobacco products as a dentifrice is also common. According to a 1999–99 survey, 28.1% of adult men and 12.0% of women reported chewing tobacco products. 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, qatda in Western Asia, mania in Turkey, tobak in Sudan, chinit in Vietnam and qilim 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 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 nuts, the common ingredient of betel quid, have been classified as human carcinogens; they cause cancers of the oral cavity, the pharynx and the esophagus [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 areca nut) products, with relative risks as high as 10 [6]. Additional evidence comes from ecological studies showing positive correlations between use of all smokeless tobacco products and 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 long cancer among switchers was increased 5–6 fold.

There are over 30 carcinogens in smokeless tobacco, including volatile and tobacco-specific nitrosamines, nitrosamine acids, polycyclic aromatic hydrocarbons, aldehydes, metals [6]. Smokeless tobacco use entails the highest known non-occupational human exposure to the carcinogenic nitrosamines, NNK and NNN (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 (25–150 mg, or about 1.5 mg/kg body weight) similar to that which has caused tumors in rats (1.8 mg/kg body weight), or in addition to considerable exposure to NNN [6].

There is also consistent 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 was able 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 NNK was 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 toxicological properties of the product, the complex 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 these arguments 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 tobacco 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 in 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.

<table>
<thead>
<tr>
<th>Country</th>
<th>Smokeless Tobacco Product</th>
<th>US</th>
<th>Nordic countries, India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokeless tobacco products are widely used in Asia and Africa. These products cause cancers of the oral cavity, the pharynx and the oesophagus.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of smokeless tobacco is also common in Nordic European Countries. These products increase the risk of cancers of the oesophagus and pancreas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of smokeless tobacco in Northern America has been associated with oral cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinogenicity is likely to be caused by a high concentration of nitrosamines.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokeyless 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).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The prevalence of use of smokeless tobacco varies substantially not only across countries, but also within countries, by gender, age, ethnic-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**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.

---

**Chewing (spit) tobacco (US)**

- Tobacco, sugar, flavoring agents (licorice)

**Moist snuff (snus)**

- Tobacco, sugar, flavoring agents (licorice)

**Dry snuff**

- Tobacco - US, UK, India

**Tobacco, flavoring agents (licorice)**

**Tobacco, US, UK, India**
REFERENCES

**Figure 2.4.3** Smokeless tobacco chemistry

**Figure 2.4.4** Risk model for oral cancer

**Figure 2.4.5** Geographical overview of the Programme of Action for Cancer Therapy (PACT) countries

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 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 address 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
### Summary
- Approximately 15–20% of cancers worldwide are caused by infectious agents.
- 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).
- Chronic infections such as hepatitis B virus (HBV), gastroduodenal cancer with Helicobacter pylori (H. pylori) and cervical cancer with the virus of the papilloma (HPV) family.
- Other infectious agents include hepatitis B virus (HBV), hepatitis C virus (HCV) and Epstein-Barr virus (EBV), which are among the main causes of cancer worldwide.

### Chronic Infections

**Hepatitis B virus (HBV)**

The hepatitis B virus (HBV) is a small partially double-stranded DNA virus that belongs to the Hepadnaviridae family. 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 [1]. However, the geographical distribution of chronic cancer site is variable, and the majority of chronic carriers live in Southeast Asia and sub-Saharan Africa. HBV infections occur in all age groups, and most of the chronic infection (70–80%) occurs during the perinatal period, 23–35% in infancy or early childhood, and less than 10% in adults [2]. Human HBV infection can cause liver disease such as chronic liver disease, liver cirrhosis, and liver cancer. athletes andAPOC3 are at risk of developing HBV infection. The control of HBV and HCV disease burden requires prevention strategies by reducing the risk of infection, safe injection practices, etc.

**Hepatitis C virus (HCV)**

The molecular mechanisms by which HBV and HCV induce tumours are not yet fully understood, although differences in the regulation of cell cycle, telomere/telomerase system, apoptosis and other cellular pathways may be involved in carcinogenesis.

**Human papillomavirus (HPV)**

The human papillomavirus (HPV) comprises approximately 100 different types that have been sub-grouped in different genotypes according to their genomic DNA sequence [8]. In addition, the different HPV types 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 predominantly detected in the female reproductive tract and are sexually transmitted. An IARC monograph has recently reported that the mucosal HPV types 16, 18, 31, 33, 39, 45, 51, 52, 58, 59 and 66 are clearly associated with cervical cancer. In addition, HPV16 and HPV18, at much lower extent, have a causative role for a subset of oral cancers (80%) and vulva, vagina, penis and anogenital cancers (approximately 20% in all latter cases) [9]. Another group of mucosal alpha HPV types is termed “low risk,” and is normally associated with benign genital lesions. HPV16 is the most frequently hybrik 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 carcinogenesis”). 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 carcinomas [11]. They were first isolated from 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 NSM development in EV patients, their direct role in skin carcinogenesis in normal population remains to be proved. It is possible that the carcinogenic HPV types may promote the formation of malignant lesions acting as co-carcinogens together with UV.

**Epstein-Barr virus (EBV)**

The Epstein-Barr virus (EBV) is a ubiquitous human herpes virus that infects most of human populations early in life and usually has a mild course. EBV was isolated for the first time from a B-cell lymphoma (Burkitt’s lymphoma) 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 EBV-transformed B-cell referred as lymphoblastoid cell lines (LCL). Chapter 2.5: Chronic Infections - 129
lines (LCs). 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 reactivation, EBV remains in infected individuals for the lifetime, making it one of the most persistent viruses that infect humans. In individuals with severe inherited or acquired deficiencies in T-lymphocyte function, EBV can cause oropharyngeal cancer, which may be associated with Kaposi sarcoma, T-cell leukemia, and B-cell lymphoma.

Electron microscopy of hepatitis B virus particles

In contrast, HTV-1 is rarely detected in North American and European populations. All ATL cases contain integrated HTV-1 provirus, highlighting its key role in leukemogenesis. Nevertheless, only a small minority of HTV-1-infected individuals progress to ATL. Indeed, the cumulative risks of developing ATL among virus carriers are estimated to be approximately 6.0% for males and 2.1% for females. As many as 20 million people worldwide may be infected with HTV-1. Spread of the virus may occur from the mother to the child mostly through breast-feeding beyond six months, via sexual transmission and during blood transfusion.

KSHV/HHV8

Kaposi’s sarcoma-associated herpesvirus (KSHV), also termed human herpesvirus 8 (HHV8), is a gammaherpesvirus, related genetically to simian herpesvirus saimiri, the prototype virus of the subfamily 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 Castleman’s disease (MCD). HHV8 infection is normally associated with immunocompromised states 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 populations of endemic regions as well as in high-risk populations. In bisexual men, sexual, and blood and body fluid-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 programs. The lytic program provides a stable and immunologically silent mode of persistence, while the latent program maintains the release of virus and its propagation to other hosts. Sewall virgin viral proteins are able to interfere with the immune-system-related pathways facilitating the establishment of persistent infection.

Helicobacter pylori

Helicobacter pylori (H. pylori) is a non-spore forming and spiral-shaped 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 disease, gastric cancer and microsomal-associated lymphatic tissue (MAIT). In 1994, it was classified as a group 1 carcino- gen 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 geographic alteration during the infection, due to an elevated mutation rate and frequent intraspecific recombination. Recent findings proposed the scenario that this genetic variability, which affects both host-avoidance and virulence genes, may contribute to host adaptation and persistence of the infection.

Parasites

Two liver flukes, Opisthorchis viverrini and Clonorchis sinensis, 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 intrapitoneal ducts. The evidence for cancer causation by O. viverrini, a parasite mainly prevalent in Thailand, is stronger than for C. sinensis. The incidence of Table 2.5.2: Relative Risk of Cancer by Relative Risk

Human T-cell lymphotropic virus

Human T-cell lymphotropic virus type 1 (HTLV-I) is part of the Delta retrovirus family and is responsible for the development of adult-T- cell leukemia (ATL). Based on the divergence in the nucleotide sequence, HTLV is classified into eight 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 most at risk. This may occur from the mother to the child mostly through breast-feeding beyond six months, via sexual transmission and during blood transfusion.

HHV8 is the etiological agent of all forms of Kaposi’s sarcoma and primary effusion lymphoma (PEL) and most forms of multicentric Castleman’s disease (MCD). HHV8 infection is normally associated with immunocompromised states 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 populations of endemic regions as well as in high-risk populations. In bisexual men, sexual, and blood and body fluid-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 programs. The lytic program provides a stable and immunologically silent mode of persistence, while the lytic program maintains the release of virus and its propagation to other hosts. Sewall virgin viral proteins are able to interfere with the immune-system-related pathways facilitating the establishment of persistent infection.

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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 underestimated for certain infections. For example, HCV seroprevalence surveys tend to oversample 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].

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Fig. 2.5.9 Phylogenic 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.

Fig. 2.5.10 Proposed model of stomach carcinogenesis as a progressive process associated with atrophy and intestinal metaplasia with induced acidity.
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 oncogenes 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 expected by the fact that the replication of their DNA is totally dependent on cellular mechanisms. These infectious agents have developed mechanisms to keep the infected cells alive and in a proliferative state, even in the presence of cellular stresses which normally lead to exit of cell cycle and/or apoptosis resulting in efficient multistep transformation of the infected cell to cancer. In doing so, these viruses facilitate the accumulation of chromosomal abnormalities promoting long-term cellular transformation. In addition, virus-induced alterations to 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 deregulate the regulation of cellular proliferation and/or immune surveillance. The EBV oncoprotein LMP1 (protein 1) is an aggregated membrane protein responsible for most of the carcinogenic properties of EBV (LMP1). In EBV-associated malignancies and transform cell in vitro, by altering of the control of cell cycle and abnormal, EBV-induced, abnormal cellular properties can be achieved, activating normal cellular mitogenic factor receptor (TNFR family member 1) triggering, 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-B, JNK, p38, STAT and KERT [22,24]. In addition, LMP1 can downregulate the expression of several immune genes that alter the virus to immune surveillance. Other latent EBV genes including EBNA1, LMP2A and the EBV-encoded small RNA RNAs are thought to play a role in EBV-mediated oncogenes [25].

The oncoprotein Tax from HTLV1, similarly to HPV E6 and E7, targets several tumour suppressors, such as p53 and retinoblastoma (pRb), altering their function is no longer required after the establishment of the transformed phenotype. In contrast, E6 and E7 from the high-risk HPV types promote cellular transformation targeting several cellular proteins, including the tumour suppressors, p53 and retinoblastoma (pRb), respectively [17].

HIV is a non-lytic virus that is permissive for viral replication only in epithelial keratinocytes. The ability of the virus to influence the immune system is therefore limited to the localized environment of the infected epithelium. It is now clear that several HIV-1 proteins are able to down-regulate the innate and adaptive immunity affecting Toll-like receptor (TLR)-regulated pathways and antigen presentation [18,19].

In contrast, HPV, HCV and HBV alone. Other cancers associated with infectious agents in the year 2002.

REFERENCES


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 (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 epidemiologic studies of this group of tumours, an effect of heavy alcohol intake and alcohol dependence 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 tobacco (to a limited extent of alcohol 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 a direct role of unmetabolized alcohol or 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).

### Potential target organs

- Liver, others?
- Colon and rectum, breast, others?
- Head and neck, esophagus
- Head and neck, esophagus, liver
- Head and neck, esophagus, liver, others?

### Alcohol drinking - 137

### Mechanism

#### DNA damage by acetaldehyde

- **Strong evidence**
  - DNA damage by acetaldehyde
- **Moderate evidence**
  - Reduced immune surveillance
- **Wild evidence**
  - Altered metabolism of folate, vitamin B1, vitamin B6, and pyridoxine

#### Alcohol drinking and reactive oxygen and nitrogen species

- **Strong evidence**
  - Production of reactive oxygen and nitrogen species
- **Moderate evidence**
  - Altered metabolism of folate, vitamin B1, vitamin B6, and pyridoxine
- **Wild evidence**
  - Reduced immune surveillance

### DNA repair

- **Strong evidence**
  - DNA repair by DNA-dependent DNA polymerases
- **Moderate evidence**
  - DNA repair by DNA ligases
- **Wild evidence**
  - Altered metabolism of folate, vitamin B1, vitamin B6, and pyridoxine

### Alcohol drinking - 137

### Cancer risk factors

- 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.

### Mechanism

- **Aldehyde dehydrogenases, aldehyde dehydrogenases**
  - As alteration in the hepatic metabolism of carcinogens, the production of reactive oxygen and nitrogen species and the alteration of folate metabolism

### Potential target organs

- Liver, others?
- Colon and rectum, breast, others?
- Head and neck, esophagus
- Head and neck, esophagus, liver
- Head and neck, esophagus, liver, others?

### Alcohol drinking - 137

### Strong evidence

- DNA damage by acetaldehyde
- Increased estrogen level

### Moderate evidence

- Reduces the toxicity of acetaldehyde (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 evidence. The table is restricted to mechanisms known or suspected to operate in cancers with an established association with alcohol drinking.

### Weak evidence

- DNA damage by alcohol
- Nutritional deficiencies (e.g., vitamin A, folate, vitamin B12, pyridoxine)

### Table 2.6.1 Possible mechanisms of carcinogenicity of alcoholic beverages

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Potential target organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA damage by acetaldehyde</td>
<td>Head and neck, esophagus, liver</td>
</tr>
<tr>
<td>Increased estrogen level</td>
<td>Breast</td>
</tr>
<tr>
<td>Reduced immune surveillance</td>
<td>Liver, others</td>
</tr>
<tr>
<td>Altered metabolism of folate</td>
<td>Liver, others</td>
</tr>
<tr>
<td>DNA damage by alcohol</td>
<td>Head and neck, esophagus, liver</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>Liver, others</td>
</tr>
<tr>
<td>Carcinogenicity of otheralcohol</td>
<td>Head and neck, esophagus, liver, others</td>
</tr>
</tbody>
</table>

### Figure 2.6.1

- OR for drinking 33 alcoholic drinks/day versus drinking 12 alcoholic drinks/day
- **OR (95% C.I.)**
  - Italy Munich Switzerland
  - Central Europe
  - North Carolina
  - Atlanta
  - Puerto Rico
  - South America
  - Int'l Munich
  - P for heterogeneity

- **OR for drinking 23 alcoholic drinks/day versus drinking 12 alcoholic drinks/day**

### From Nashdale et al. [2]
differences in acetaldehyde exposure due to the presence of some well-studied common genetic variants with a functional role. Cytochrome P450 2E1 (CYP2E1) is induced by ethanol, oxidizes ethanol into acetaldehyde, and also 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 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 alcoholic and cancer remains limited. In clinical, epidemiological and experimental set- Fig. 2.6.2 The major pathways of alcohol metabolism in humans.

REFERENCES

Reproductive Factors and Endogenous Hormones

Summary

- Reproductive factors are strongly involved in the initiation 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 pre-menopausal women.

Evidence is accumulating in the literature on the reproductive factors and endogenous hormones in the etiology/development of breast cancer. Suggests a significant implication of hormones compared to pre-menopausal women. This comes as the ovaries cease, and the increase in breast cell proliferation by the age of 45. After menopause, 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.

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 50. After menopause, the production of estrogens and progesterone from the ovaries ceases, and the increase in breast cancer incidence rates with age slow 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 tumor 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 life span 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 estrogens 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 breastfeeding have been associated with increased 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. Results from these studies showed that women with the highest serum estrogen (estradiol, estrogen and free estradiol), as well as androgen (testosterone, free testosterone, androstenedione and dehydroepiandrosterone) 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 hormones 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).

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 [1]. 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 tissue in lactation. It is also believed that prolactin contributes to the development of breast cancer. Figure 2.7.5. In addition, experiments in animals have shown that prolactin increases tumor 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 it 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 2-4 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].

Evidence of an association of serum endogenous sex steroids increases the risk of breast and endometrial cancers in post-menopausal women.
Endometrial cancer

Endometrial cancer 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 long-term estrogen exposure 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 observations of women with polycystic ovary syndrome associated with increased circulating SHBG concentrations [10,11], 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 (PCOS) (a syndrome associated with increased ovarian androgen production) have a strong and long-lasting proliferative potential. Insulin-like growth factors are involved in steroid hormone action on target organs. Many studies have shown evidence for the implication of IGF-I in ovarian cancer etiology, and circulating IGF-I concentrations have been shown to be associated with increased risk of ovarian cancer with increasing circulating IGF-I concentrations in blood in young women [pre- or peri-menopausal aged].

Prostate cancer

Most human prostate cancers are very sensitive to hormone stimulation and responsive to androgens. Surgical and medical castration reduces considerably the risk of metastatic prostate cancer, while some case-reports suggest a causal relationship between the use of androgens 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 metabolized to 3-alpha-androstanediol through the activity of 3-alpha-hydroxysteroid dehydrogenase. High prostatic levels of dihydrotestosterone have been associated with an increased prostate cancer risk. Studies on breast-feeding, hysterectomy or tubal ligation have been shown to decrease the risk [12].

*Table 2.7.1: Relative risk of endometrial cancer among postmenopausal women by quartiles of serum steroid concentrations [11] p for trend

<table>
<thead>
<tr>
<th>Hormone</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>1.00</td>
<td>1.34</td>
<td>1.88</td>
<td>4.13</td>
<td>0.0008</td>
</tr>
<tr>
<td>Estrogen</td>
<td>1.00</td>
<td>1.39</td>
<td>1.81</td>
<td>3.67</td>
<td>0.0007</td>
</tr>
<tr>
<td>Testosterone</td>
<td>1.00</td>
<td>1.62</td>
<td>2.30</td>
<td>2.15</td>
<td>0.04</td>
</tr>
<tr>
<td>DHEAS</td>
<td>1.00</td>
<td>1.89</td>
<td>2.15</td>
<td>2.42</td>
<td>0.002</td>
</tr>
<tr>
<td>SHBG</td>
<td>1.00</td>
<td>0.73</td>
<td>0.41</td>
<td>0.46</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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 levels [Table 2.7.1].

Endometriosis 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 long-term estrogen exposure may well explain the relationship between endometrial cancer and sex steroids. 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 observations of women with polycystic ovary syndrome associated with increased circulating SHBG concentrations, all factors that have been associated with increased risk of endometrial cancer.

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suggest a relationship between 5-alpha reductase activity and increased prostate cancer risk. Similarly, experiments in animals showed an increase in epithelial prostate cancer cell proliferation in response to androgens. All these data suggest that men exposed to elevated circulating levels of 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 approximately 30% reduction in prostate cancer prevalence over the 7-year period of intervention in men taking finasteride (5α-reductase inhibi- tor). The proportion of high-grade cancers detected in the finasteride group 20% 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 35% 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 27% (RR 0.73, 95% CI 0.58, 0.94) [15]. For tumours with Gleason scores 7, men in the finasteride arm had an RRR of 34% (RR 0.66, 95% CI 0.55, 0.80).

A review of eight prospective studies showed no difference in androgen concentrations between cases and matched controls except for a small increase in androstenedione glucuronide [16]. Studies on circulating estrogens and prolactin showed very little evidence for the implication of these hormones in prostate cancer etiology [16].

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) is monophasic 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.

Breast cancer

Most information on the relation between breast cancer and OC use is derived from a collaboration of nested-case-control studies of individual data including 53,297 women with breast cancer and 294,088 controls from 54 epidemiological studies [6]. This provided definitive evidence that current and recent users of combined OC 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 of OC before age 20 had an appreciable and 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 [79] 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 contraceptive study including 46,000 women (918), as well as in the Oxford FPA cohort study [90], no relevant association was found between breast cancer incidence and various measures of OC use after more than three decades of followup. A cohort study of 426 families of breast cancer probands in Minnesota, USA [91] suggested that ever users of earlier formulations of OC with family history of breast cancer were at high risk for breast cancer (RR 3.3). That study was biased, however, as 38 family case users only, and contrasted with findings of the collaborative reanalysis [6] which showed no excess risk in women with a family history of breast cancer. A report from the Nurses’ Health Study II cohort [25] 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 recently from France [97] 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 programmes are in place and most cases present in early, localized stages of the disease 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 incidence between Western, Central and Eastern European countries was over threshold 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 cancers and other human cancers likely to have a role in cervical carcinogenesis. Among these, tobacco smoking and exogenous female hormones, including OCs [31]. Several epidemiological studies have reported an increased risk of invasive cervical cancers in relation to never 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 it 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, [96]).

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 OC 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 and evaluated risks among women who tested positive for HPV DNA. Although OC use has little effect on breast cancer risk, the RR levels off to approach those of never OC users, but it was not observed in past OC users. A few other studies from the USA and recently from France [97] suggested that use of more recent, low-dose OC is not materially related to breast cancer risk.

Fig. 2.8 Relative risk* of invasive cancer by duration and time since last use of oral contraceptives (OC) standardized for study, age, parity and hysterectomy.

Ovarian cancer

An indication of the favourable impact of OCs on ovarian cancer came from prospective epidemiological studies. 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 in England and Wales from 1950 to 1990 [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 other ovarian cancers persists for at least 20 years after stopping use according to the CASH study, and probably continues up to 30 years after stopping use, Ovarian cancer risk in women 0.8 up to 20 years after stopping use in a pooled analysis of European studies [44]. 0.5 for 10–19 years and 0.8 for 20 or more years after stopping use in a large multicenter US case-control study [45]. The RR was 0.7 for duration >10 years and 0.29 years since last use in the Collaborative Group of Epidemiological Studies of Ovarian Cancer (Figure 2.8). 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, 0.10–2.31) for the 30-year follow-up of the ICGP 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 use. In the CAHPS study, the OR was 0.2 for 10–19 years since stopping use, in the WHI 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 recurrence 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 recurrence of use. In a Swedish study [48], the OR 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 OR 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 twins [51,52]. A reduction in 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 every OC use below unity: Among 11 case-control studies, the RR was non-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 every OC use in a recent Swiss case–control study [56]. Only two studies [57,58] included information on recency 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 0.58–0.99) 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 trend could be observed 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 [59] 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, 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 [9] 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%: its protection increases with longer use and is lifelong. 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 is extremely low [0.19].

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 [270,950].

HRT and cancer risk

Menopause has a profound effect on the risk of breast and other hormone-related cancers, since the slope of incidence for most of these neoplasms levels off after menopause [60]. The most reliable estimate of the influence of HRT on breast cancer is given by a collaborative re-analysis of individual data from epidemiological studies [61]. In 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 2.5% 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 treatment appears to reduce such an excess risk. Indeed, combined HRT may increase breast cancer risk in long term users, but reduce it in overweight areas. 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 unaffected by HRT use [64]. Between 1970 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 [95% CI] 1.2–2.5) 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 progestagens) 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 8502 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 1.03–1.51).

Data from two other smaller randomised studies were available, one (Heart and Estrogen/Progestin Replacement Study, HERS) with combined estrogen/progestagen 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 (95% CI)

0.95 (0.89–1.01)

0.95 (0.90–1.00)

0.95 (0.89–1.00)

Cases/controls

509/2519

280/1335

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 (95% CI)

0.99 (0.96–1.02)

0.97 (0.94–1.00)

0.95 (0.92–0.99)

Cases/controls

2051/9384

1166/5663

508/2241

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 (95% CI)

0.72 (0.64–0.79)

0.75 (0.69–0.82)

0.80 (0.73–0.87)

Cases/controls

1310/6667

825/3881

269/1376

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 (95% CI)

0.75 (0.69–0.82)

0.76 (0.70–0.83)

0.83 (0.76–0.91)

Cases/controls

1782/9337

1135/5883

305/1931

Mean duration of use

4.2 years

1.6 years

6.8 years

12.7 years

Table 2.6.1 Relative risk of ovarian cancer in ever-users of oral contraceptives compared with first-users only, age at first use and duration of use of oral contraceptives.

**Mean duration: 4.7 (3.0–8.7) years, and 5.0 (1.4–9.5) years with relative risk of 1.00 (95% CI 0.99–1.01); All relative risks are studied by age, parity, and hypertension. Numbers do not always add to the total, because of missing values.

Fig. 2.8.2 Oral contraceptive use reduces the risk of colorectal cancer.

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

The Instituto Nacional de Enfermedades Neoplásicas “Eduardo Cárdenas Contreras,” 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. Since 1952 and has already graduated close to 500 specialists, including some from neighboring countries, and carrying out research protocols in association with important groups in the United States and Europe.

website: www.inen.sld.pe
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 areas with a low incidence of several cancers, in migrants showed that subjects moving from a high to a low risk area increase their risk of colorectal, breast and prostate cancer occurrence.
- New promising research avenues investigated associations between dietary patterns and life style (e.g. the Mediterranean diet), 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 effective primary prevention programs for ischaemic cardiovascular diseases and the discovery of pharmaceuticals that can be used to modify the risk for other diseases or specific eradication of this bacterium has probably also contributed to the decrease in the stomach cancer burden.

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 revisited new data and estimates of which 25% of cancer deaths could be due to “diet”, with a range of acceptable estimates of 15 to 35%. As 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 difficulties control for confounding factors, most robust studies 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 an overall weight/obesity and lack of physical activity association 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 any 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.

"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 fecal transit in 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 all 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 reduced 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 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 [5,9].

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 cancer, but not for prostate cancer [see Alcohol Drinking, Chapter 2.6].

For the three major cancers considered in this section, several randomised trials have yielded results showing no association or associations of much smaller magnitudes 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 intake of fruits and vegetables) are not likely to result in significant change in the incidence of these three 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 has a protective 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...
The body mass index (BMI) is the weight (in kg) divided by the square of the height (in meters) of an individual. According to international standards, males and female adults with a BMI between 25 and 29.9 kg/m² are considered overweight, while those with a BMI equal to or greater than 30 kg/m² 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 of the esophagus, kidney cancer;
- men: colon cancer;
- women: breast and endometrial cancer in postmenopausal women.

The IARC systematic review concluded that there was no 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 overweight in bladder cancer in women.

In most industrialised countries, overweight and obesity are increasing, which will contribute to sharply rising 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 vegans than in the background population, while the incidence of colorectal cancer is about half of that in 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 than in regular physical exercise than with vegetari- an 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 influence 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 mor- tality in subjects who had a diet close to the “Mediterranean dietary pattern” rich in carbohydrates, vegetables, fish, fruits, and vegetables, and poor in meat and animal fat [17,18]. 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 Mediterraneandom diet can be considered as usually associated with healthier lifestyle, which also contributes to health ben- efits 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 reflections 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 consumption of manufactured foods. Results from a cohort study have suggested a strong associa- tion between plasma levels of the phospholipid elaidic acid and breast cancer occurrence [21].

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<table>
<thead>
<tr>
<th>Lifestyle factors</th>
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</thead>
<tbody>
<tr>
<td><strong>Overweight/ obe-</strong></td>
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<tr>
<td><strong>Obesity</strong></td>
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<tr>
<td>Increase</td>
</tr>
<tr>
<td>MatoA, Review</td>
</tr>
<tr>
<td>[13,15]</td>
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<tr>
<td>Increase after</td>
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<tr>
<td>metastasis</td>
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<tr>
<td>MatoA, Review</td>
</tr>
<tr>
<td>[13,15,31]</td>
</tr>
<tr>
<td>No change</td>
</tr>
<tr>
<td>MatoA, Review</td>
</tr>
<tr>
<td>[13,15]</td>
</tr>
<tr>
<td><strong>Lack of physi-</strong></td>
</tr>
<tr>
<td><strong>cal activity</strong></td>
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<tr>
<td>Increase (for colorectal cancer)</td>
</tr>
<tr>
<td>Review</td>
</tr>
<tr>
<td>[14,44]</td>
</tr>
<tr>
<td>Increase, mainly after metastasis</td>
</tr>
<tr>
<td>Review</td>
</tr>
<tr>
<td>[14,44]</td>
</tr>
<tr>
<td>Small increase</td>
</tr>
<tr>
<td>Review</td>
</tr>
<tr>
<td>[13]</td>
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</tbody>
</table>

Table 2.9.1 Summary of main findings from cohort studies and randomised trials on foodstuffs, lifestyle habits and colorectal, breast and prostate cancer

- **Colorectal cancer (CRC)**
- **Breast cancer**
- **Prostate cancer**

<table>
<thead>
<tr>
<th>Increases in intakes of</th>
<th>Change in risk</th>
<th>Type of studies</th>
<th>References</th>
<th>Change in risk</th>
<th>Type of studies</th>
<th>References</th>
<th>Change in risk</th>
<th>Type of studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fruits and vegetables</strong></td>
<td>No change</td>
<td>Review</td>
<td>[22]</td>
<td>No change</td>
<td>RCT</td>
<td>[23]</td>
<td>No change</td>
<td>Cohorts</td>
<td>[24]</td>
</tr>
<tr>
<td>No change</td>
<td>RCT on polyps</td>
<td>[25]</td>
<td>No change</td>
<td>MatoA</td>
<td>[26]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>MatoA on CRC</td>
<td>[27]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibres</strong></td>
<td>No change</td>
<td>RCT on CRC</td>
<td>[28]</td>
<td>No sufficient data</td>
<td>Review</td>
<td>[31]</td>
<td>No sufficient data</td>
<td>Review</td>
<td>[31]</td>
</tr>
<tr>
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<td>Cohorts</td>
<td>[30]</td>
<td>No change</td>
<td>MatoA</td>
<td>[31]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Red meat, processed meat</strong></td>
<td>Small increase</td>
<td>Review and cohorts</td>
<td>[22,32,33]</td>
<td>No sufficient data</td>
<td>Review</td>
<td>[12]</td>
<td>No change</td>
<td>Cohorts</td>
<td>[12]</td>
</tr>
<tr>
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<td>Review</td>
<td>[22]</td>
<td>No change</td>
<td>Review</td>
<td>[34,35]</td>
<td>No change</td>
<td>Review</td>
<td>[35]</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>RCT on polyps</td>
<td>[31]</td>
<td>No change in post-menopausal women, possible decrease in risk in pre-menopausal women</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohorts</td>
<td>[37]</td>
<td>No change, but possible increased risk with high calcium intakes</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Fish</strong></td>
<td>Small decrease of polyps</td>
<td>RCT on polyps</td>
<td>[32]</td>
<td>No change in post-menopausal women, possible decrease in risk in pre-menopausal women</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cohorts</td>
<td>[37]</td>
<td>No change, but possible increased risk with high calcium intakes</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dairy products, including calcium</strong></td>
<td>Small decrease of CRC incidence</td>
<td>Cohorts</td>
<td>[41]</td>
<td>No change, but possible increased risk with high calcium intakes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change, mainly after metastasis</td>
<td>Review</td>
<td>[33]</td>
<td>Small increase</td>
<td>Review</td>
<td>[43]</td>
<td></td>
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</tbody>
</table>

**References**

- Chapter 2.9: Diet, Obesity and Physical Activity - 157
- Table 2.9.1 Summary of main findings from cohort studies and randomised trials on foodstuffs, lifestyle habits and colorectal, breast and prostate cancer
- Review, meta-analysis of prospective cohort studies: RCT, randomized controlled trial; Review, exhaustive review of prospective cohort studies, but not meta-analysis; CRC, colorectal cancer
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 multi-disciplinary hospital named after I. M. Sechenov. Professor N. N. Petrov, the founder and rector of oncology in Russia, was appointed 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 new cancer methods of prevention and treatment; highly-effective drugs and high-quality methods for improving tolerance of anti-tumour methods; study and introduction of new drugs and – study and introduction of new drugs and methods for improving tolerance of anti-tumour treatment; reducing its toxicity and increasing the quality of cancer patients’ lives; improvement of organizing 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, demographics); as well as dynamic prognostication of these indices in the future by using Cancer Registry data.

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 biological, molecular and immunological factors that allow assessment of cancer risk and greater understanding of its development;
– development of methods of oncobiology of solid tumours (scleroderm cells, vaccines, genetherapy, cytokines);
– elaboration and introduction of new highly-effective drugs and high-quality methods, based on the latest scientific achievements, and complete usage of new and standard techniques of cancer treatment;

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-conserving surgery is being carried out on the early stages of cancer.

The Institute is associated with many international organizations 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 (ASC0, ESMO, ESO, ESTRO, EORTC, Rearc Cancer, etc.)
Ionising Radiation

Ionising radiation is one of the most intensely studied carcinogenic effects. Knowledge of associated health effects comes from observations of 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 malformations have been observed. Increased frequency of these same malformations 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 it occurs, and the sex of the exposed person. Exposure to high-dose radiation increases the risk of leukaemia by over fivefold. Even higher relative risks have been reported for thyroid cancer following irradiation during childhood.

In a study of nuclear industry workers from 15 countries, 12% of cancer-related deaths other than leukaemia may be attributed to occupational exposure to low-dose radiation exposure while on the job. (8) Other than leukaemia, associations were the most significant for lung cancer and multiple myelomas (9).

Ionising radiations that emit alpha-par- ticles and beta-particles are carcinogenic to humans. For most people, exposure to ionizing radiation is 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 thyroid cancer in the most contaminated regions—that can be clearly attributed to radiation from the Chernobyl accident.

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 the Health Consequences of the Chernobyl Accident to evaluate the effects of the accident on populations in the exposed regions. The Chernobyl accident 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 the Health Consequences of the Chernobyl Accident to evaluate the effects of the accident on populations in the exposed regions.

Another source of ionizing radiation to the public and workers is from accidents and releases from nuclear power plants. The largest nuclear acci- dent 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 WHOD convened an Expert Group on the Health Consequences of the Chernobyl Accident to evaluate the effects of the accident on populations in the exposed regions.
Various forms and sources of radiation that are carcinogenic to humans (IARC Group 1) or probably carcinogenic to humans (IARC Group 2A)

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)

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].

REFERENCES
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, past 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 carcinoma when exposure started before 30 years old.
- Sun protection should be based on seeking shade, clothes and hat wearing. Sunscreens should be applied 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 (CMM), 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 in ultraviolet range, and the sun is the main source of exposure to UVR for most individuals. Sun exposure appears to be related to 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 an increase in risk of skin cancer. Sunlight and UVR are also suspected to play a role in cutaneous melanoma, but further evidence of a possible causal association is needed.

Sunlight consists of visible light (>400–700 nm), infrared radiation (>700 nm), UVR, and UVR and sunlight belong to the non-ionising part of the electromagnetic spectrum and ranges from 100 nm to 400 nm; 100 nm has been chosen arbitrarily as the boundary between UVR and sunlight. UVR 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 UVR radiation >290 nm [UVG] and as well as 70% to 90% of the UVC.

On the Mediterranean coast at noon in the summer, the UVR radiation from sunlight consists of about 95% of UVA and about 5% of UVB. UVB has long been recognised as the carcinogenic component of UVR. Since the 1970s (when 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 results have been 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 UVR varies with latitude, altitude, time of year, day and night, 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 at the poles), season (highest in hot seasons, lowest in cold seasons), time of day (highest around 10 AM–2 PM solar time), altitude (higher at altitude than at sea level), and earth surface (if UVR is reflected by snow or by water).

Ozone depletion

Ozone depletion has been caused by substances released into the atmosphere that destroy the ozone (ozone-depleting substances (ODS)). For instance, the chlorofluorocarbons (CFC) that were used as spray propellants until 1992. Also, when an international ban known as the revised Montreal Protocol was applied, about 10% of ODS use was halted. The stratospheric ozone levels have decreased annually since the 1970s, especially in the southern hemisphere. Because the atmosphere in the northern poles, the ozone hole is maximal at the most Northern and most Southern areas, and lowest at the equator. Thus the Northern countries, Australia, New Zealand, Canada, and Russia, are generally populated with light-skinned people, or are at greater 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. The other acute affect is producing a suntan. An acquired tan is mainly protective against the damaging effects of UVR. 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.

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 who have pale skin who always burn and never tan when exposed to UVR, have 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 associated with mutations in the MC1R gene. This gene regulates the formation of melanin (that is bright brown or black and photoprotective) by melanocytes and also the capacity of the melanocyte to resist UV-induced DNA damage. The MC1R gene is highly polymorphic, and about 80 mutations of this gene have been described [6]. These mutations may reduce functional defects resulting in variable increases in the susceptibility to UV-induced skin lesions [7]. These mutations also lead to the synthesis of phenylalanine (instead of tyramine) that is red or yellow and is suspected to also play a role in skin cancer occurrence [6].

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 on 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 defects 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. Pсорiasis patients treated with PUVA (psoralen plus 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 [8]. Also, sun exposure during adult life is associated with cutaneous melanoma occurring only if sun exposure took place during childhood [9]. 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 melanomas: 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 head and neck. These differences have been attributed to the more frequent use of sunscreens by women.
melanomas on the lower limbs, and then on the upper limbs [11]. The number of acquired nevi is the single most specific indicator of cutaneous melanoma, and the body distribution of new in young children parallel the body dis-tribution 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 sun-light and UVR that this also varies with gender.

BCC usually occurs on the head and 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 encompases 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. sun exposure of short duration but frequent during holidays in sunny areas, with 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 asso-ociated with ISE situations, while SCC occur-rence 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 labo-ratories. UVR is part of the treatment of many diseases, such as psoriasis and dermatitis. The type and spectrum of UVR lamps may be differ-ent from one condition to another. In some dis-eases, like psoriasis, the cumulative exposure to UVR can be substantial, can be accompanied by oral photoreactive agents (the PUVA therapy combining UVA and oral 8-methoxy-psoralen) 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 con-tains a small proportion of UVR-radiation. These small amounts could represent a hazard, as fluorescent lighting is widely distributed. Epidemiological studies have not however pro-duced data consistent with an effect of fluores-cence lighting on melanoma occurrence.

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

The most common ISE behavior is sunbathing. The tanned skin fashion started in the 1930s in light-skinned populations as 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, deliber-ate exposure to artificial sources of UVR has become common through the use of sunbeds, mainly for the acquisition of a tanned skin. This fashion has been partly facilitated by ungrounded beliefs such as the putative lower carcinogenic potential of sunbeds (as com-pared 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 inten-sity may be 10 to 15 times higher than that of the midday sun [19], and 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 UVR radiation probably do not exist on the Earth’s surface, and repeated exposures to high doses of UVA/UVB radiation probably do not exist on the Earth’s surface, and repeated exposures to high doses of UVA/UVB radiation 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 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 indoor tanners use bed should con-centrate 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 cutane-ous 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, barrier-ers to UVR usually consist of wearing a hat and clothing, and use of sunscreens. Sunscreens should be broad-spectrum, i.e. that the scalp, the face, the ears and the neck are protected. Common fabrics represent efficient barriers against UVR transmission to the skin. Dark clothes are more protective than light colored clothes, and wet clothes are less protective than dry clothes. Some fabrics and clothes have been specifically devised to protect the skin against sunlight exposure and are recommended for individuals highly susceptible to the damaging effects of UVR [e.g. red-haired people, patients under photoactivating treatment (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 pro-vides an internationally standardised estimate of the ability of a thin layer of suncream to delay the occurrence of a minimal erythematous 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 disease 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, reduc-tion of average UVR reaching skin surface through clothing, sunscreen use or reduction of time spent in the sun can decrease the occur-rence of SCC, and clinical and subclinical and of skin precursor lesions of SCC [e.g. skin keratoses] [24-27].

During ISE, however, observational and ran-domised 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 sun-screen is used, and also because it takes more
time to get a sunburn [24, 28, 29]. So, sunscreen use during UVE may actually increase the risk of cutaneous melanoma [18] and probably also of BCC [17]. Sunscreen use during UVE does not decrease sunburn occurrence and allows individuals to engage in sunbathing during the hottest hours of the day, when UVE is maximal. Sunburn 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 only tan after burning should by no means engage in sunbathing and should not recover to a sunscreen for increasing their ability to stay in the sun.

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 (essen-
tially 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 UVE is maximal. Sunburn 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 only tan after burning should by no means engage in sunbathing and should not recover 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. So, by definition, sunscreen should never be applied on the trunk of a child, as sun protection of the trunk should be done on seeking shade, hat wearing and clothing.

REFERENCES


2.12 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 at 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 homes 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 hand side also varies within individuals. Measuring exposure to total EMF is also fraught with difficulty, as exposure often varies within homes. Measuring exposure to 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 individual components have been published [3]. Separate studies have been carried out for acoustic neuroma, 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, 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 neuromas, 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 natural 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 CRR 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 neither be causal or artificial, related to differential recall between cases and controls. For meningioma and acoustic neuroma, 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. The results of a pooled analysis of data from Nordic countries and the UK found a significantly increased risk of acoustic neuroma related to duration of use of 10 years or more on the side of the tumour [6]. Again, this finding could neither be causal or artificial, 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 non-significantly increased risk of benign tumours was observed for parotid use of 10 years or more, while a decreased risk was seen for control 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 radiofrequency emitting systems may receive high levels of exposure. This includes workers...
in the broadcasting, transport and communication industries, and in antenna repair, military personnel (e.g., radar operators) and police officers (using traffic control radars). These are also industrial processes that use radiofrequency fields, including dielectric heaters for wood lamination and scaling 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


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 squamous cancer among chimney sweeps in 1775 [1] to Goette 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 exposures 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; in extreme cases, all of the most heavily exposed to develop cancer as occurred in some groups of manufacturers of 2-naphthylamine and benzidine, while coal-tar fumes and asbestos were also 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, 4].

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) [5]. 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), as are arsenic, radon, carbon black, chloroform, chlorophenyl herbicides, DDT, dichloroacetic acid, glass, polychlorinated biphenyls and styrene [5]. 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 [5]. 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 [6], 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, benzo[a]pyrene diol epoxide and dibenz[a, h]anthracene. However, humans are almost always exposed to mixtures of PAHs (several of which are listed in Tables 2.13.1 and 2.13.2 e.g. coals, soots, creosoted), and an assessment of the carcinogenicity of individual PAHs 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.

Table 2.13.1: Agents, groups or mixtures classified as established human carcinogens, for which exposure is mainly occupational. While some risk is due to non-occupational exposure, for the majority reliable risk estimates are possible.

<table>
<thead>
<tr>
<th>Agent/Group</th>
<th>Target Organ</th>
<th>Exposure</th>
<th>Main industry or use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylamide</td>
<td>Bladder</td>
<td>Rubber</td>
<td></td>
</tr>
<tr>
<td>Arsenic and arsenic compounds</td>
<td>Lung, skin</td>
<td>Glass, metals, pesticides</td>
<td></td>
</tr>
<tr>
<td>Benzene</td>
<td>Lung, pleura</td>
<td>Insulation, construction</td>
<td></td>
</tr>
<tr>
<td>Benzo(a)pyrene</td>
<td>Lung</td>
<td>Solvent, fuel</td>
<td></td>
</tr>
<tr>
<td>Benzo(a)pyrene diol epoxide*</td>
<td>Lung</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Benzo(b)fluoranthene*</td>
<td>Lung</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Benzo(k)pyrene*</td>
<td>Lung</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Carbazole</td>
<td>Lung, skin, lung</td>
<td>Cancer, surgery, pigment</td>
<td></td>
</tr>
<tr>
<td>Carbon black</td>
<td>Skin, lung</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>Skin</td>
<td>Fuel</td>
<td></td>
</tr>
<tr>
<td>Coal-tar pitches</td>
<td>Formaldehyde</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Cotton dust</td>
<td>Formaldehyde</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Cyclododecane</td>
<td>Gallium arsenide</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Dieldrin</td>
<td>Gallium arsenide</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Fluorine</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Methyl methacrylate*</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Mineral oils, untreated and mildly treated</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Mustard gas (sulphur mustard)*</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Nickel compounds</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Radion-222 and its decay products</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Radon</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Silica, cristobalite</td>
<td>Glass, metals, pesticides</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Strong inorganic acid mists containing sulphuric acid</td>
<td>Lung, skin</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Talc containing substantial fibrous thbers</td>
<td>Lung</td>
<td>Paper, paint</td>
<td></td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Lung</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Wood dust</td>
<td>Nails</td>
<td>Glass, metals, pesticides</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2.13.1: Chemicals
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, attention has focused on the possible contribution of work-related exposure to breast cancer risk. 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.

### Table 2.13.2: Agents, groups or agents and mixtures classified as probable human carcinogens

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Suspected target organ</th>
<th>Main industry or use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylamide</td>
<td>Plastic</td>
<td></td>
</tr>
<tr>
<td>Benzidine-based dyes</td>
<td>Bladder</td>
<td>Plastic</td>
</tr>
<tr>
<td>Capital</td>
<td>Pigment, leather</td>
<td></td>
</tr>
<tr>
<td>Chlorinated hydrocarbons</td>
<td>-</td>
<td>Paint, chemical</td>
</tr>
<tr>
<td>Coke</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Diesel engine exhaust</td>
<td>Lung</td>
<td>Hard metal production</td>
</tr>
<tr>
<td>Diethyl sulfate</td>
<td>-</td>
<td>Chemical</td>
</tr>
<tr>
<td>Dimethylcarbonamide chloride</td>
<td>-</td>
<td>Chemical</td>
</tr>
<tr>
<td>DMSO</td>
<td>-</td>
<td>Research</td>
</tr>
<tr>
<td>Dimethyl sulfite</td>
<td>-</td>
<td>Chemical</td>
</tr>
<tr>
<td>Epichlorohydrin</td>
<td>-</td>
<td>Plastic</td>
</tr>
<tr>
<td>Ethylene dichloride</td>
<td>Fungus</td>
<td></td>
</tr>
<tr>
<td>Indium phosphate</td>
<td>-</td>
<td>Semiconductors</td>
</tr>
<tr>
<td>Lead compounds, inorganic</td>
<td>Lung, stomach</td>
<td>Metals, pigments</td>
</tr>
<tr>
<td>Methyl methanesulfonate</td>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Non-arsenical insecticides</td>
<td>Leukaemia</td>
<td>Agriculture</td>
</tr>
<tr>
<td>Polychlorinated biphenyls</td>
<td>Liver, lymphoma</td>
<td>Electrical components</td>
</tr>
<tr>
<td>Styrene-human-made</td>
<td>Plastic</td>
<td></td>
</tr>
<tr>
<td>Tetrachlorophthalic acid isomer</td>
<td>Oxophosphates, lymphoma</td>
<td></td>
</tr>
<tr>
<td>Tri-toluolene</td>
<td>Bladder</td>
<td>Pigment</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>Liver, lymphoma</td>
<td>Solvent, dry cleaning</td>
</tr>
<tr>
<td>1,2,3-Trichloropropene</td>
<td>-</td>
<td>Solvent</td>
</tr>
<tr>
<td>Tris(2,3-dibromopropyl) phosphate</td>
<td>-</td>
<td>Plastic, textile</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>-</td>
<td>Plastic, textile</td>
</tr>
<tr>
<td>Vinyl fluoride</td>
<td>-</td>
<td>Chemical</td>
</tr>
</tbody>
</table>

### Table 2.13.3: Agents, groups or agents and mixtures classified as probable human carcinogens

<table>
<thead>
<tr>
<th>Industry/occupation</th>
<th>Target organs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum production</td>
<td>Lung, bladder</td>
</tr>
<tr>
<td>Aerospace, manufacture of</td>
<td>Bladder</td>
</tr>
<tr>
<td>Boat and shoe manufacture and repair</td>
<td>Nasal cavity, leukaemia</td>
</tr>
<tr>
<td>Chimney sweeping</td>
<td>Skin, lung</td>
</tr>
<tr>
<td>Coal gasification</td>
<td>Skin, lung, bladder</td>
</tr>
<tr>
<td>Coal tar distillation</td>
<td>Skin</td>
</tr>
<tr>
<td>Coke production</td>
<td>Skin, lung, kidney</td>
</tr>
<tr>
<td>Furniture and cabinet making</td>
<td>Nasal cavity</td>
</tr>
<tr>
<td>Cosmetics mixing (underground) with exposure to radon</td>
<td>Lung</td>
</tr>
<tr>
<td>Iron and steel founding</td>
<td>Lung</td>
</tr>
<tr>
<td>Isopropanol manufacture (strong-acid process)</td>
<td>Nasal cavity</td>
</tr>
<tr>
<td>Magnesium, manufacture of</td>
<td>Bladder</td>
</tr>
<tr>
<td>Printer</td>
<td>Lung, bladder</td>
</tr>
<tr>
<td>Powdering and rolling with coal tar pitch</td>
<td>Lung</td>
</tr>
<tr>
<td>Rubber industry</td>
<td>Bladder, leukaemia</td>
</tr>
<tr>
<td>Petroleum refining</td>
<td>(Skin, skin)</td>
</tr>
</tbody>
</table>

### Table 2.13.4: Agents, groups or agents and mixtures classified as probable human carcinogens

<table>
<thead>
<tr>
<th>Industry/occupation</th>
<th>Target organs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum production</td>
<td>Lung, bladder</td>
</tr>
<tr>
<td>Aerospace, manufacture of</td>
<td>Bladder</td>
</tr>
<tr>
<td>Boat and shoe manufacture and repair</td>
<td>Nasal cavity, leukaemia</td>
</tr>
<tr>
<td>Chimney sweeping</td>
<td>Skin, lung</td>
</tr>
<tr>
<td>Coal gasification</td>
<td>Skin, lung, bladder</td>
</tr>
<tr>
<td>Coal tar distillation</td>
<td>Skin</td>
</tr>
<tr>
<td>Coke production</td>
<td>Skin, lung, kidney</td>
</tr>
<tr>
<td>Furniture and cabinet making</td>
<td>Nasal cavity</td>
</tr>
<tr>
<td>Cosmetics mixing (underground) with exposure to radon</td>
<td>Lung</td>
</tr>
<tr>
<td>Iron and steel founding</td>
<td>Lung</td>
</tr>
<tr>
<td>Isopropanol manufacture (strong-acid process)</td>
<td>Nasal cavity</td>
</tr>
<tr>
<td>Magnesium, manufacture of</td>
<td>Bladder</td>
</tr>
<tr>
<td>Printer</td>
<td>Lung, bladder</td>
</tr>
<tr>
<td>Powdering and rolling with coal tar pitch</td>
<td>Lung</td>
</tr>
<tr>
<td>Rubber industry</td>
<td>Bladder, leukaemia</td>
</tr>
<tr>
<td>Petroleum refining</td>
<td>(Skin, skin)</td>
</tr>
</tbody>
</table>

### References

1. Pott P (1775). Chirurgical observations relative to the cures of the evils, the cases of thereceipt, the different kinds of stages, and the mortification of the toes and feet. London: T.J. Carnegy.
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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 tests 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. 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 cancer of human in the workplace (see Occupational exposures, Chapter 2.13). The carcinogenic hazard associated with asbestos fibres has been recognised 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 asbestos-rich 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 residential exposure is evident among inhabitants of villages in Turkey where houses and natural surroundings contain the mineral asbestos.

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, polycyclic aromatic hydrocarbons (PAHs) and nitrogen oxides.

Emissions of traditional industrial air pollutants such as sulphur dioxide and particulate matter have decreased in developed countries over the past decades. However, 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 from 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].

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 industrialisation, 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 benz(a)pyrene, polynuclear aromatic hydrocarbons 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 was observed in the vicinity of foundries from the mid-1950s to the mid-1970s and later subsided in parallel with emission reductions of 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.

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Environmental exposure to tobacco smoke has emissions from high-temperature frying may and experimental evidence that cooking-oil coarse, fine, and ultrafine particles and many the components of this indoor smoke include 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 various organics, including carcinogens such as benzo[a]pyrene, formaldehyde, and benzene. There is also strong epidemiologic and experimental evidence that cooking-of 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 syn-
drome in children [11,12]. Among the most prominent pollutants of indoor air are radon and formaldehyde. Outdoor air pollutants can also occur at levels above WHO standards, and 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 season, geography of the soil and water bodies, where the action of chloroform is often reduced from agriculture and industry. The greatest concern relates to infectious diseases. 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]. Chloriform and other haloforms are among the 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]. The main source of environmental exposure to arsenic for the general population is through ingestion of contam-
nated 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 con-
tamination [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 concentrations or exposures in the past. The risks of lower arsenic concentrations (e.g., above 5 μg/l) are not established, but an estimated excess bladder cancer in the order of 50% is plausible.

Several other groups of pollutants of drink-
ing water have been investigated as possible sources of cancer risk in humans [15]. These include organic pollutants (such as chlorinated solvents and pesticides) derived from industrial, commercial and agricultural sources, and in particular from waste sites. Organic pollutants that persist in the environment and accumulate in fish (such as polychlorinated dibenz-p-dioxins, polychlorinated biphenyls (PCBs), and organochlorine pesticides) are of particular concern, as well as nitrate and nitrite, radionuclides, hormonally-active com-
pounds, and asbestos. For most pollutants, the epidemiologic studies are inconclusive, however, an increased risk of stomach cancer has been repeatedly reported in areas with higher concentrations of asbestos, and an increased risk of leukemia has been observed in studies of asbestos-exposed workers. Whether asbestos at lower levels of intake is carcinogenic remains uncertain. There is some evidence that asbestos found in water may be associated with increased risks of cancer [15].

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 pollutants [2,17]. These reviews generally considered only man-made carcinogens, most of which were identified through occupational studies several decades ago and are less present in today’s environment than previous reports have suggested. Environmental pollution levels may be higher in newly-industrialised countries with less strin-
gent regulations or enforcement, and there is not as much information about cancer risks in less-
studied groups such as women, children, and the elderly. Another 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 cancer poten-
tial. Little is known about risks from combinations of exposures at levels found in the environment or from exposures during critical time windows in development or in susceptible populations. Cancer may have multiple causes, so that belief in the existence of a factor that is causally related to cancer is rare. The complex interactions between exposure to chemicals, smoking and alcohol may contribute to the idea that individual cancers may have multiple causes.

Finally, it is important to remember that environ-
mental pollution is not only a cancer problem. Much environmental pollution can be pre-
vented, 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.

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Genetic Susceptibility

Cancer genetics comprises of two main subfields: genetic susceptibility and somatic cell genetics. Genetic susceptibility focuses on an inherited [constitutional or germinal] genetic variation in cancer susceptibility genes, and the effects of these inherited genes 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 these mutations play during tumour initiation and progression.

What kinds of genes can be cancer susceptibility genes? In general, oncogenes and tumour suppressor genes are grouped into three types, and a number of molecular genetic approaches. In a descriptive sense, these classes of studies have delivered three important pieces of information about genetic susceptibility to breast cancer. For most of the common cancers, about 25% of the difference in risk between individuals is attributable to genetic variation.##

To assist this discussion of cancer susceptibility genes and deleterious sequence variants, we have prepared two graphs of genotype relative risk by cancer frequency. The first, Figure 2.15.i, is annotated with contour lines of gPAF, providing a frame of reference familiar to molecular epidemiologists. The second, Figure 2.15.ii, is annotated with contour lines of FRR, a reference frame more familiar to genetic epidemiologists. On these graphs, risk and frequency are expressed as odds ratios (ORs). In the next few years, any high-risk variants with carrier frequencies in the range of 10% for ORs of 1.5, and studies that use early-onset or familial cases should achieve sufficient power at ORs of 1.5. We do not currently know how much risk is attributable to variants in this frequency range. For example, genetic association studies are beginning to find replicable 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.i and 2.15.ii provide another view of both potential importance and likelihood of the nine risk and frequency sectors. Individual deleterious sequence variants can be represeted...
sent 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 tell us? Under the common disease/common variant (CD/CV) hypothesis, we would expect the density distribution to be skewed towards the frequency high risk of the graph, or at above a certain frequency of 10%, unless most of the risk is in minor allele homozygous carriers. 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 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 common modest-risk SNPs 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, we can not yet specify the shape and density distribution of the aforementioned cloud of points in risk frequency space, we can only 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 carry carriers (see Genetic Testing, Chapter 4.14).

REFERENCES

Medical and Iatrogenic Causes

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 leukocytes in necrotic tissue and made a connection between inflammation and cancer. Most of the early data were derived from descriptions of chronic inflammatory lesions, such as ulcers, burn scars or draining sinus tracts [12]. Since then, the association between chronic inflammation and pancreatic cancer has now been linked 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. In the UK, smoking is the major cause of chronic pancreatitis, with smoking rates among patients with chronic pancreatitis usually twice that of the general population. In the USA, chronic pancreatitis is more common in men than in women, in southern and western states, and in Mexican Americans; in the UK, in Ireland, among Jewish people, and in India, among Hindus. In the USA, 90% of patients with chronic pancreatitis are heavy smokers, with the average daily intake of cigarettes exceeding 15. The frequency of smoking in patients with chronic pancreatitis is low in light and moderate drinkers, but increases sharply in heavy drinkers.

Chronic pancreatitis has been related to hyperinsulinaemia, 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 possibly 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].

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, notably alcohol. Subjects with cirrhosis have a gross excess (over 10-fold) of subsequent primary liver cancer (see chapter 5.4). Indeed, cirrhosis is considered a pathogenic step in liver carcinogenesis [10]. History of cirrhosis has been related to excess risk of oral, pharyngeal and esophageal cancers [11], but incomplete allowance for alcohol drinking remains an open issue for causal inference.

Diabetes (and particularly type II diabetes) is related to hyperinsulinaemia, 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 possibly pancreatic cancer risk [13].

Unlike 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]. Kras mutations, found in nearly all pancreatic cancers, have also been detected in patients with chronic pancreatitis [9].

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 nuclear-plash linked with chemotherapy treatment is leukemia; 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 3.8, hormone replacement therapy in menopause (HRT) increases the risk of breast, endometrial and ovarian cancers, and oral contraceptives increase the risk of breast cancer.

REFERENCES

CANCER EFFORTS IN THE WHO WESTERN PACIFIC REGION

Cancer is now 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.

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