

Tobacco use and cancer causation: association by tumour type

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Abstract. Kuper H, Boffetta P, Adami H-O (London School of Hygiene and Tropical Medicine, London, UK; Karolinska Institutet, Stockholm, Sweden; and International Agency for Research on Cancer, Lyon, France). Tobacco use and cancer causation: association by tumour type (Review). *J Intern Med* 2002; **252**: 206–224.

In the second part of our review we describe the association between tobacco use and risk of specific cancer types. There is evidence for an established association of tobacco use with cancer of the lung and larynx, head and neck, bladder, oesophagus, pancreas, stomach and kidney. In contrast,

endometrial cancer is less common in women who smoke cigarettes. There are some data suggesting that tobacco use increases the risk for myeloid leukaemia, squamous cell sinonasal cancer, liver cancer, cervical cancer, colorectal cancer after an extended latency, childhood cancers and cancer of the gall bladder, adrenal gland and small intestine. Other forms of cancer, including breast, ovarian and prostate cancer, are unlikely to be linked to tobacco use.

Keywords: cancer, carcinogenesis, smoking, tobacco.

Introduction

In the first part of this review the global pattern of tobacco consumption was described, as well as the mechanisms by which tobacco use causes cancer. The second part of the review will focus on specific cancer types and their association with tobacco use. The strength of evidence supporting the association will be assessed for different cancer types. We will also discuss evidence for the existence of a dose–response pattern for the association between tobacco use and cancer risk, as well as for a beneficial effect of cessation of tobacco use, and variation in risk by type of tobacco product.

Cancer types that are established to be associated with smoking

For a summary of cancers for which tobacco use has a definite effect on risk, see Table 1.

Lung cancer

Lung cancer was a rare disease until the beginning of the twentieth century, but since then it has become the most common nonskin malignancy worldwide, in terms of both incidence and mortality [1]. It accounts for an estimated 772 000 new cases each year in men (18% of all nonskin

Table 1 Summary of cancers for which tobacco use has a definite effect on risk

	Relative risk for ever smoking	Attributable risk	Dose-response	Cessation	Tobacco types
Lung	1.5 for small cell and squamous cell carcinoma and 3–5 for adenocarcinoma	85% in men and 46% in women [21]	Intensity and duration, possibly stronger effect of duration	Sharp decline in risk on quitting, particularly for young people, but some excess risk remains	All smoking tobacco products and passive smoking linked to lung cancer, but not smokeless tobacco
Larynx	10–15	67% in men and 28% in women [21]	Intensity and duration	Risk decreases after quitting to near that of never-smokers	All forms of tobacco
Bladder	3	37% in men and 14% in women [21]	Intensity and duration	Risk decreases up to 60% after quitting	Cigarettes more deleterious than cigars or pipes and no effect of smokeless tobacco
Oesophagus	2–5 for squamous cell carcinoma and <2 for adenocarcinoma	45% in men and 11% in women [21]	Intensity and duration	Risk decreases after quitting, but significant increased risk persists	Smoking tobacco, but not smokeless tobacco
Pancreas	2–4	27% in men and 11% in women [21]	Intensity and duration	Risk halved after quitting	Cigarettes and cigars
Kidney	2 for renal cell carcinoma and 3 for cancer of the renal pelvis	38% in men and 4% in women [21]	Intensity and duration	Up to 25% risk reduction in long-term quitters	Cigarettes, but not cigars, pipes or smokeless tobacco
Oral cavity, pharynx	2–3	41% in men and 11% in women [21]	Intensity and duration	Long-term quitters have risks close to never-smokers	All forms of tobacco
Endometrium	0.5	–	Not always a clear effect of intensity and duration	Long-term quitters have risks close to never-smokers	Cigarettes only
Stomach	1.5–1.6 Risk highest for adenocarcinoma and intestinal rather than diffuse variants	13% in men and 7% in women [79]	Intensity and duration	Ex smokers have a third of the excess risk of current smokers	All forms of tobacco

cancers) and 265 000 new cases amongst women (7%), less than half (42%) of which occur in developing countries. The main histological types of lung cancer are squamous cell carcinoma, small cell carcinoma, adenocarcinoma and large cell carcinoma.

The geographical and temporal patterns of lung cancer incidence are largely determined by tobacco consumption patterns that took place two or more decades earlier. Populations with a high incidence of lung cancer are therefore those where tobacco consumption has been high during the last decades (e.g. USA, Canada and UK) and lung cancer incidence is low in countries where tobacco consumption has recently declined (e.g. Sweden) or consumption has only increased lately (e.g. China, India, Africa). As men took up tobacco use earlier than women, the increase in lung cancer incidence in men generally precedes that in women by several decades.

There is a vast body of evidence supporting a causal association between tobacco smoking and risk of lung cancer, but few data showing an effect of smokeless tobacco. Relative risks (RR) in the region of 10–15 are frequently quoted for the effect of smoking on lung cancer risk, although this reflects the contribution of different aspects of tobacco smoking. Doll and Peto [2] analysed the data of the classical British Physicians prospective study, initiated already in 1951. They concluded that the excess lung cancer risk raises in proportion to the square of the number of cigarettes smoked per day but to the fourth or fifth power of the duration of smoking. Other studies, however, suggest a comparable effect of amount and duration of smoking [3]. Furthermore, the results of a recent large case-control study conducted in several western European countries suggest a plateau in the excess risk above 15–20 cigarettes per day [4], although others have not found evidence for this [5] (Fig. 1).

An important aspect of tobacco-related lung carcinogenesis is the effect of cessation of smoking. As compared with continuous smokers, the excess risk sharply decreases in ex-smokers after approximately 5 years since quitting. Although in some studies the risk after 20 years since cessation approaches that of never smokers, an excess risk probably persists throughout life [6]. Age at the start of regular tobacco smoking is also important; smokers who started before age 15 had a four-

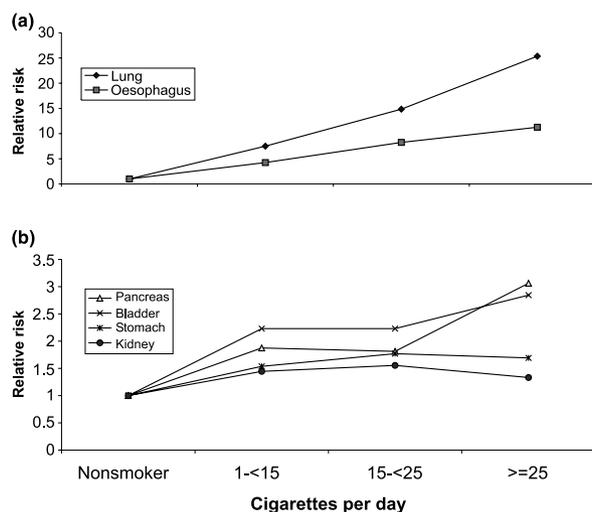


Fig. 1 Cancer mortality rates by intensity of smoking [5]. (a) Lung and oesophageal cancer, (b) Pancreas, bladder, stomach and kidney cancer.

fivefold higher risk of lung cancer than smokers who started at age 25 or later [6]. However, as periods of temporary quitting tend to be short, there is a strong relationship between age, age at start, duration of smoking and time since quitting, which makes it difficult to assess the independent effect of each temporal variable on lung cancer risk.

The risk of lung cancer is lower amongst smokers of low-tar and low-nicotine rather than high-tar/nicotine cigarettes [3, 7–9], smokers of filtered rather than unfiltered cigarettes [10], and smokers of blond rather than black tobacco [11]. It is difficult to separate these effects as tar content, presence of filter and type of tobacco are not independent, as cigarettes are often high tar because they are unfiltered and/or made of black tobacco. Other tobacco products, including cigars, cigarillos, pipes [12–14], hooka or bidis [15–17] and Chinese water pipes [18] also increase lung cancer incidence, probably at a similar order of magnitude to cigarettes for comparable levels of consumption.

Following the first reports in the early 1980s [19], an association between exposure to passive smoke and lung cancer risk in nonsmokers has been shown in a number of case-control and cohort studies, with RR in the early studies estimated to be in the order of 1.4 [20]. This evidence has been challenged on the basis of

possible confounding by active smoking, diet or other factors and of possible reporting bias. However, two large multicentre case-control studies undertaken to address these criticisms confirmed the increase in risk from passive smoke exposure [21, 22], although the magnitude of the excess risk amongst those exposed might be smaller than previously estimated, in the order of 20–25% [23].

Although tobacco smoking induces all major histological types of lung cancer, the strongest associations are with squamous cell and small cell carcinoma: the RR for adenocarcinoma are four- to fivefold lower than for other histological types [3]. The frequency of different histological types of lung cancer has changed over the last two decades in the USA and Europe, so that squamous cell carcinoma has become less common and adenocarcinoma more frequent [24, 25]. This potentially reflects changes in patterns of tobacco consumption, such as deeper inhalation of low nicotine and tar tobacco smoke [26].

Laryngeal cancer

An estimated 140 000 new cases of laryngeal cancer occurred worldwide in 1990, 120 000 of which were amongst men [1]. The incidence of laryngeal cancer in men is particularly high in Southern and Central Europe, South America and amongst Blacks in the United States, whilst the rates are low in South-east Asia and Central Africa [27]. More than 90% of cancers of the larynx are squamous cell carcinomas.

The increased risk of laryngeal cancer amongst cigarette smokers is substantial. Risks in smokers are in the order of 10 relative to nonsmokers and in excess of 15 for heavy smokers [28], and risks seem to be stronger for glottic than for supraglottic neoplasms [29]. Indeed, most cases of laryngeal cancer in Western countries are attributable to tobacco smoking, alcohol drinking and the interaction between these two factors [30]. Studies in several populations have shown a dose-response relationship for intensity and duration of smoking [28], and risk decreases after quitting smoking to approach that of a never-smoker after 15 years [31].

Smoking black tobacco cigarettes entails a stronger risk for laryngeal cancer than smoking blond tobacco cigarettes [32], and use of filters provides some protection. Tobacco smoking in the form of

cigars [14, 33] or bidis [34] have also been linked to increased laryngeal cancer risk, as has the use of smokeless tobacco [33, 34].

Bladder cancer

Bladder cancer is diagnosed in 261 000 people annually [1]. It is more frequent in men than in women and is most commonly found in Europe and North America, as well as in Northern Africa and Western Asia where it is caused by *Schistosoma mansoni* infestation. The most common histological type of bladder cancer is transitional cell carcinoma and true squamous cell carcinomas are relatively rare.

Cigarette smoking is the primary risk factor for bladder cancer [6]. Data from the British Physicians cohort, amongst others, suggest an approximate threefold increase in risk comparing heavy cigarette smokers with nonsmokers [5] (Fig. 1). In a combined analysis of 11 case-control studies from six European countries, risk for bladder cancer increased with duration and intensity of smoking [35, 36]. RR declined immediately after smoking cessation and continued to fall with time from cessation; RR decreasing more than 30% after 1–4 years and up to 60% after 25 years. The rapid benefit of smoking cessation in protecting from bladder cancer indicates a late effect of smoking in bladder carcinogenesis, although the residual excess risk could indicate an initiation effect of cigarettes.

Risk depends on the method of tobacco smoking; pure cigarette smokers were at higher risk (RR = 3.5, 95% confidence interval (CI) = 2.9–4.2) than pure pipe smokers (1.9, 1.2–3.1) or pure cigar smokers (2.3, 1.6–3.5) [37], although the effect of cigar smoking may be limited to people who inhale [14]. In addition, one study suggests that users of black tobacco are at two to three times higher risk than users of blond tobacco [38]. However, limited data do not suggest an effect of smokeless tobacco use [39], Egyptian waterpipe or hashish smoking [40] on the risk of bladder cancer.

Oesophageal cancer

Oesophageal cancer occurs in 316 000 people per year, and as it is highly fatal, it causes a similar number of deaths annually [1]. Oesophageal cancer

is particularly common in Africa, China and Southern Asia, and South America. Oesophageal cancer is found in two histological types: squamous cell carcinomas and the less common adenocarcinomas that may develop from Barrett's oesophagus. To date, most epidemiological studies do not clearly distinguish these histopathological types, although there is increasing evidence that they have different aetiologies.

Evidence from both cohort and case-control studies strongly support a role for smoking in the aetiology of oesophageal cancer. Epidemiological studies generally report a two- [41] to fivefold [42, 43] increase in risk of oesophageal cancer amongst smokers, although a Swedish population-based case-control study reported a nearly tenfold increased risk of oesophageal squamous cell carcinoma amongst current smokers [44]. A dose-response increased risk of squamous cell carcinoma of the oesophagus with intensity and duration of smoking [5, 42, 44] (Fig. 1) and a decline in risk after smoking cessation have been repeatedly demonstrated [42, 44, 45], although a significant increased risk persists [44].

Risk of cancer varies by type of cigarettes and tobacco used. Risk of squamous cell carcinoma of the oesophagus is related to use of strong tobacco, dark tobacco and nonfilter-tipped cigarettes [42, 44, 46] as well as cigar [14], bidi [47] and South African pipe smoking [48]. The data for smokeless tobacco use are more mixed: snuff use in Sweden appears unrelated to risk of oesophageal cancer [44], but betel-tobacco chewing in India [49] and Taiwan [50] increased risk.

Smoking is also responsible for a two- to threefold increased risk of adenocarcinoma of the oesophagus, and risk relates to the intensity of smoking [51-54]. There is, however, convincing evidence that smoking is associated more strongly with squamous cell cancer than with adenocarcinoma of the oesophagus [44] (Fig. 2).

Pancreatic cancer

Pancreatic cancer is globally the thirteenth most common cancer in terms of incidence, but ninth in terms of mortality, on account of its poor prognosis, and it has been increasing in incidence over the past 40 years [1]. Pancreatic cancer is approximately equally frequent in men as in women, and most

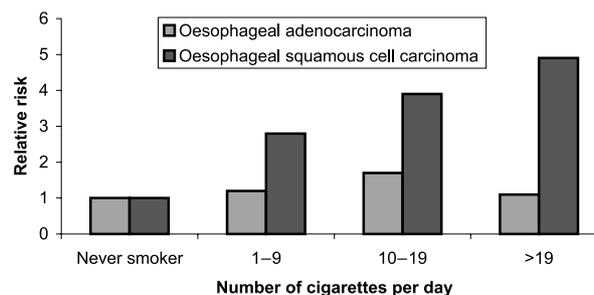


Fig. 2 Effect of intensity of smoking on risk for oesophageal cancer [44].

cases occur in high-income countries. Pancreatic cancer is usually an adenocarcinoma.

Smoking has been recognized as a cause of pancreatic cancer [6]. Overall, smoking is associated with an approximate two- to fourfold increased risk of pancreatic cancer [5, 55-57]. A joint analysis from the Nurses Health Study and Physicians Follow-up study estimated that 25% of pancreatic cancers were attributable to cigarette smoking [55]. In another study, risk for pancreatic cancer was increased almost threefold amongst cigar smokers who inhaled their smoke, but not for cigar smokers overall [14].

Several studies, including the joint analysis of the Nurses Health Study and Physicians Follow-up study, found a significant dose-response increased risk with increasing pack years of exposure [5, 55] (Fig. 1). Compared with people who continued to smoke, quitters halved their risk of pancreatic cancer within 2 years [55], and this reduced risk of pancreatic cancer after smoking cessation has been confirmed in case-control studies [56, 57].

Kidney cancer and cancer of the renal pelvis

Kidney cancer is responsible for 150 000 new cancer cases annually and 78 000 cancer deaths [1]. It is generally a disease of high-income countries, and incidence is low in Africa and Asia. Adenocarcinoma of the renal parenchyma arising from tubular epithelial cells accounts for more than four-fifths of malignant tumours of the kidney. In adults, transitional cell carcinoma of the renal pelvis accounts for the remaining approximately 15%.

All case-control studies including more than 100 cases have found an increased risk amongst smokers compared with nonsmokers, with smoking typically

doubling risk [58]. In an international, population-based, case-control study, risk increased with the duration of smoking and number of cigarettes smoked per day but there was no effect of cigar or pipe smoking or smokeless tobacco use [59]. Although this study reported that long-term quitters (>15 years) experienced a 15–25% reduced risk compared with current smokers, others have not always found a clear dose-response effect [5] (Fig. 1).

Similarly, smoking has been shown to be associated with a more than threefold increased risk of cancer of the renal pelvis [60–61]. Risk was particularly high amongst heavy smokers and smokers of long duration and declined with time since smoking cessation [61].

Oral and pharyngeal cancer

Cancers of the mouth and pharynx are a heterogeneous group of cancers, responsible for 363 000 annual new cases and 200 000 deaths globally [1]. Incidence is particularly high in men, but there is no clear pattern across high- and low-income countries. The vast majority of cancers in the oral cavity are squamous cell carcinomas.

Smokers are at dramatically increased risk for oral carcinoma, particularly squamous cell cancer [28]. These associations hold for cancer of the lip, tongue, mouth and pharynx, whilst no effect on the salivary gland has been substantiated. RR for current smoking (adjusting for alcohol consumption) are generally about two to three in most studies [28], although tenfold increased risks have been reported in hospital-based studies [62]. Risk appears to fall on cessation of smoking, so that 10 years after quitting risk is close to the level of never smokers, suggesting a late stage effect for cigarette smoking. Studies have also demonstrated a dose-response effect on risk of intensity and duration of smoking [62].

Users of black, rather than blond, tobacco and smokers of hand-rolled cigarettes were at greater risk than filter cigarette smokers [62]. Risk is also elevated amongst cigar [14], pipe [63] and bidi smokers [16] and potentially also in reverse chutta smokers [64]. Oral smokeless tobacco use, whether shamma in Saudi Arabia [65], tobacco quid [16] or betel-tobacco [66] in India, areca nut (with tobacco) in South Africa [67], or toombak in Sudan [68], but

not the inhalation of snuff [69], is also related to risk of oropharyngeal cancer. The carcinoma seems to occur most commonly at the site of administration of tobacco [6, 70].

Endometrial cancer

Endometrial cancer is diagnosed in 142 000 women per year and results in 42 000 deaths annually [1]. It is most frequent in high-income countries where it is the most commonly occurring gynaecological cancer. Most endometrial tumours are adenocarcinomas.

Endometrial cancer has been shown repeatedly to be inversely associated with cigarette smoking, with risk amongst heavy smokers up to half that of never smokers [71–76]. There is, however, not always a clear effect of duration or intensity of smoking [75], but the similar risks in former smokers as compared with never smokers suggests a detrimental effect of cessation [74, 76]. The protective effect of smoking appears to be stronger amongst postmenopausal women [72, 73, 75, 76] and women with high levels of oestrogen (e.g. heavier women with diabetes who use Hormone Replacement Therapy) [75, 77], and may even be confined to this group. This suggests that smoking may reduce the risk of endometrial cancer through its antioestrogenic effects [78].

Stomach cancer

Stomach cancer is the second most frequent cancer globally, with 798 000 new cases and 628 000 deaths estimated per year [1]. The high incidence in Eastern Asia, Eastern Europe and South America, is likely because of a higher prevalence of *Helicobacter pylori*, the primary cause of stomach cancer. Gastric cancers are overwhelmingly adenocarcinomas (>90%), which may be either gastric cardia cancer or distal gastric cancer, and either of the intestinal or diffuse variant.

Cohort and case-control studies converge to show that risk of gastric cancer is smallest in nonsmokers, higher in current smokers and particularly high in heavy smokers [58]. A meta-analysis revealed that overall smoking increases risk of gastric cancer 1.5–1.6-fold [79]. In addition, risk increases with intensity and duration of smoking [5, 79] (Fig. 1). Risk is lower in ex-smokers; in the meta-analysis ex-smokers

had an RR of 1.2 [79], although risk may persist more for gastric cancer of the intestinal type than of other histologies [80].

The association with smoking is possibly stronger for adenocarcinoma of the gastric cardia than at other stomach sites [52, 81–83]. Furthermore, smoking may be more closely related to intestinal than diffuse variants [84], which is in line with current thinking that intestinal variants are more influenced by environmental factors. Bidi smokers may be at particularly high risk of gastric cancer [85], and risk has also been associated with pipe and cigar use [86] as well as smokeless tobacco use [87].

Confounding by poor diet and socio-economic status may explain some of the excess risk in smokers. However, the effect of smoking persisted after controlling for diet and it was noted amongst both the socially homogenous British Physicians [5] as well as the American veterans [88] who came from a variety of socio-economic backgrounds. Additionally, chemicals present in tobacco smoke can cause gastric cancer in animals further supporting a causal role of tobacco use in the aetiology of stomach cancer [58].

Cancer types that are possibly associated with smoking

For a summary of cancers for which tobacco use has a possible effect on risk, see Table 2.

Leukaemia

Leukaemias account for 231 000 new cases of cancer each year and 184 000 cancer deaths [1]. Rates are highest in North America and Australia/New Zealand, and lowest in sub-Saharan Africa.

Leukaemias are classified on the basis of the cell type involved and the state of maturity of the leukaemic cells, so that acute leukaemias (very immature cells) are distinguished from chronic leukaemias (mature cells), and lymphocytic from myelogenous types.

In 1993 a meta-analysis was conducted to evaluate the possible role of smoking in the aetiology of adult leukaemia. Based on seven prospective cohort studies and eight case-control studies [89], a small yet significant increased risk of leukaemia associated with smoking was noted in both cohort studies (RR = 1.3, 95% CI = 1.3–1.4) and case-control studies (1.1, 1.0–1.2). The meta-analysis suggested that risk of myeloid leukaemia was particularly closely related to smoking. Studies published since then have generally confirmed the increased risk of myeloid leukaemia, but not lymphocytic leukaemia, amongst smokers [5, 90, 91], although null studies have also been published [92, 93].

Liver cancer

Primary liver cancer is the fifth most common cancer worldwide, but fourth in terms of mortality on account of its poor survival rates [1]. Eighty per cent of cases are in developing countries, particularly West and Central Africa, Eastern and South-east Asia and Melanesia, because of the high prevalence of hepatitis B and C virus in these areas. Most liver cancer arises from hepatocytes and so is called hepatocellular carcinoma.

Data on smoking and risk for hepatocellular carcinoma are contradictory. A number of studies found no statistically significant relationship or dose-response relation between tobacco smoking and hepatocellular carcinoma, although some elevation in risk was frequently noted [5, 94–96].

Table 2 Summary of cancers for which tobacco use has a possible effect on risk

	Relative risk	Comments
Leukaemia	1.1–1.3	Risk may be limited to myeloid types
Liver	2	Effect may be limited to people chronically infected with HBV, but not HCV
Cervix	2	Unclear whether association is the result of residual confounding by sexual behaviour
Colorectal	1.5	Elevated risk only becomes apparent 30–40 years after smoking initiation, and risk may be higher for rectal than colon cancer
Gall bladder	1.3	Too few studies have been published for a consensus to be reached
Adrenal gland	2–5	Too few studies have been published for a consensus to be reached
Small intestine	0.5–4	Too few studies have been published for a consensus to be reached
Sinonasal	2–3	Effect may be limited to squamous cell carcinoma rather than adenocarcinoma
Childhood cancers	1.2–2	Effect may be limited to paternal smoking

Conversely, other studies reported a statistically significant positive relationship and a dose–response relationship between cigarette smoking and risk for hepatocellular carcinoma, with risks approximately doubled amongst current smokers [97–101]. One possible explanation for this lack of consistency is that the effect of smoking on hepatocellular carcinoma causation could be limited to people who are chronically infected with the hepatitis B virus, but without hepatitis C virus chronic infection [97, 100]. An effect of smoking on the development of hepatocellular carcinoma is biologically plausible given that the liver plays a role in the metabolism of carcinogens in tobacco smoke.

Cervical cancer

Cervical cancer is the third most common cancer in women globally, and is particularly frequent in low-income countries where 78% of the cases occur [1]. The most important cause of cervical cancer is human papillomavirus (HPV), and it is unlikely that cervical cancer can occur in its absence. About 80–95% of cervical cancers are squamous cell carcinomas, which usually arise from cervical intraepithelial neoplasia, and a small minority are adenocarcinomas.

The study of the effect of cigarette smoking on cervical cancer is complicated by the possible confounding by sexual practice, a factor strongly linked to smoking [102, 103]. Most studies report an approximate doubling in risk amongst smokers, and this association is always reduced, as would be expected, by controlling for the presence of HPV and/or sexual behaviour [58]. However, some studies report an enduring excess risk of smoking after adjustment for sexual behaviour [104]. Moreover, mutagens have been found in the cervical mucus of smokers, but not nonsmokers, and there is a reduction in the proportion of Langherhans' cells in the cervical mucosa of smokers [58].

Colon and/or rectal cancer

Colon and rectal cancer accounted for 10% of all new cancer cases in 1990 and 8% of all cancer deaths [1]. The incidence of colon and rectal cancer is higher in high-income countries and is up to 30 times less frequent in India, South America and Africa. Colorectal cancer is approximately equally

frequent in men as in women and is usually adenocarcinoma.

Early studies in the 1950s and 60s investigating the association between smoking and colorectal cancer risk were generally null [105–109]. With extended follow-up, however, some studies appeared showing an increased risk amongst smokers. The Nurses' Health Study, for instance, found that cigarette smoking was unrelated to colorectal cancer when the uptake of smoking was less than 35 years ago, but 35–39 years after initiation smokers of at least 10 cigarettes per day had a 50% increased risk compared with nonsmokers [110]. Similarly, in the Health Professionals Follow-up Study smoking was related to risk for colorectal cancer only after an induction period of more than 35 years [111]. Overall all published studies assessing the role of smoking in colorectal cancer causation in men after 1970 and women after 1990 (i.e. 40 years after smoking became common) showed statistically significant positive associations [112]. Furthermore, risk of colorectal cancer depends on the intensity and duration of use, and the Cancer Prevention II cohort study showed that risk may fall with time since smoking cessation [113]. The long induction period, together with the consistently found association between smoking and risk of colorectal adenomas [112], suggest that smoking may act as a tumour initiator for colorectal cancer.

Smoking may be more closely related to rectal than colon cancer, as testified by data from the male British Physicians cohort [5] and a cohort of young male Swedish construction workers [114]. Risk of colorectal cancer is also related to cigar and pipe smoking [113, 115], and rectal cancer may relate to chewing tobacco and snuff use [115].

Gall bladder cancer

Gall bladder cancer is rare, only the fifth most common cancer of the digestive tract, and has a poor prognosis. Gall bladder cancer incidence increases with age and it is more common in women than men. Most carcinomas of the gall bladder are adenocarcinomas.

Because of the rarity of this cancer few studies have investigated its aetiology, and those studies that do exist are generally small. Although two USA case–control studies supported a role for smoking in the aetiology of gall bladder cancer [116, 117], a

multicentre case-control study found no increased risk amongst cigarette smokers (odds ratio = 1.3, 95% CI = 0.8–1.9) [118]. Despite the equivocal epidemiological data, there is a biological rationale supporting the association between smoking and gall bladder cancer, as there is evidence that smoking increases the risk of gall bladder disease [119], which, in turn, is a risk factor for gall bladder cancer [118].

Cancer of the adrenal gland

Adrenal cancer is a heterogeneous group of rare endocrine tumours that arise from the medulla on the cortex. There are few data on risk factors for adrenal carcinoma. The US veterans study reported a fivefold increase in risk for adrenal carcinoma (most of which were adrenocortical carcinomas) amongst current cigarette smokers during 26 years of follow-up, with risk being particularly high amongst those who smoke most intensively [120]. Other forms of tobacco use were associated with a nonsignificant increased risk. A case-control study in the USA found a doubled risk for adrenal cancer amongst heavy smokers in men, but not in women [121].

Cancer of the small intestine

The small intestine represents 75% of the length of the alimentary canal, but is the source of only 3–6% of gastrointestinal tumours [122]. Small intestinal adenocarcinomas and carcinoids, the most common type of cancer in the small intestine, are approximately equally incident and both types are more common in men.

Three case-control studies were weakly supportive of an association between smoking and cancer of the small intestine, two showing a three- to fourfold increased risk amongst smokers [123, 124], and the third indicating a 90% increased risk [125]. In contrast, two case-control studies, one conducted in the USA and the other in Italy, found no evidence for an effect of smoking on cancer of the small intestine [126, 127].

There are strong similarities between small intestinal and colorectal cancers in their relationship to various risk factors. It is therefore possible that there truly is an effect of smoking, but that the studies have been too small to detect it. Alternatively an

association with smoking may appear because of the confounding effect of, for instance, dietary factors that differ between smokers and nonsmokers and influence risk of cancer in the small intestine [127].

Sinonasal cancer

Cancers of the nasal cavity and nasal sinuses, or sinonasal cancer, are rare, representing less than 1% of all cancers. They usually arise as either squamous cell carcinomas or adenocarcinomas.

Epidemiological studies suggest that cigarette smoking is related to a two- to threefold increased risk of nasal cancer and that there is a reduction in risk amongst long-term quitters [128–134]. This effect may be limited to squamous cell carcinoma rather than adenocarcinoma [128, 131, 132, 134].

Childhood cancer

There are clear international differences in the incidence and types of childhood cancer. In the USA, cancer is the second leading cause of death, after accidents, amongst children between 1 and 14 years of age [135]. The most commonly occurring cancers in children are leukaemias (especially acute lymphocytic leukaemia), tumours of the central and sympathetic nervous systems, lymphomas, soft-tissue sarcomas and renal tumours.

The Collaborative Perinatal Project, a cohort of 54 795 liveborn children in the USA followed until the age of eight, detected no effect of maternal smoking during pregnancy on childhood risk of cancer [136]. Similarly, in a large cohort of Swedish children born 1982–87 followed through 1987, there was no effect of maternal smoking during pregnancy on cancer risk [137]. In contrast, a number of case-control studies have noted an effect of paternal smoking on childhood cancer. The Oxford Survey of Childhood Cancers found that paternal, but not maternal, cigarette smoking was related to risk of childhood cancer [138, 139] and the UK interregional epidemiological study of childhood cancer found a positive association between paternal smoking at the time of conception and childhood cancer risk [140]. The effect of paternal smoking preconception has also been noticed in a Chinese case-control study [141] and the Children's Cancer Group case-control study [142]. Conversely, other studies reported that parental smoking

was not related to an increased risk of childhood neuroblastoma [143], childhood brain tumours [144, 145], childhood leukaemia [146, 147], and total childhood cancer [136].

The epidemiological evidence therefore shows either no effect of parental smoking on childhood cancer risk, or an effect limited to paternal smoking. As the biological pathway for an effect of paternal smoking cannot be through passive smoking, as then maternal smoking would be important, it must be limited to preconception, perhaps through an effect of cigarette smoking on oxidative DNA damage in human sperm cells [148]. However, the lack of cohort evidence and the restriction of case-control evidence to an effect of paternal smoking is more indicative of recall bias than true biological causation. Despite the lack of consistent epidemiological evidence for an effect of parental smoking, biological evidence for an association exists. Some components of cigarette smoke have been shown to cross the placenta and enter the foetal bloodstream in humans [149], and transplacental carcinogenesis has been demonstrated in animals [150]. Further, the potential role of passive smoking must not be neglected amongst the children of smokers.

Cancer types unlikely to be associated with smoking

Skin cancer

Melanoma. Malignant melanoma of the skin is caused by high levels of sun exposure and people with fair skin are particularly susceptible. This type of cancer is therefore most common amongst Caucasian people in sunny areas, such as Australia and New Zealand [1]. Survival in high-income countries is generally good, but not in low-income countries on account of later stage at diagnosis.

A number of case-control studies have shown no difference in the prevalence of tobacco smoking between cases with malignant melanoma and controls [151–154]. What is more, a case-control study conducted in Australia and Scotland reported that current cigarette smoking was significantly inversely related to acral melanoma (RR = 0.6, 0.4–0.9) [155]. Although there may be no effect of smoking on the incidence of melanoma, cigarette smoking might increase the metastatic potential of melanoma

[156, 157], although this effect was reduced once the thickness of the melanoma lesion was taken into account [157].

Non-melanoma skin cancer. Basal cell carcinoma and squamous cell carcinoma are the most common forms of non-melanoma skin cancer. Although these forms of cancer are reasonably common in the southern latitudes of the Northern hemisphere, causing approximately 1 million new cases of cancer per year in the USA alone, they are rarely fatal.

Tobacco smoking has been linked to the incidence of squamous cell carcinoma in a prospective follow-up study of patients with prior skin cancer [158] and in the Nurses Health Study [159], as well as in case-control studies [153, 154, 160]. In contrast, neither cohort studies [158, 161, 162] nor case-control studies [153, 154, 163] show an effect of smoking on the incidence of basal cell carcinoma.

Breast cancer

Breast cancer is by far the most common cancer for women, but rare amongst men [1]. Survival is relatively good, so although breast cancer accounts for 21% of cases in women, it results in 14% of female cancer deaths [1]. Incidence is especially high in richer countries, excepting Japan.

A review of 14 case-control studies and five cohort studies found that RR for heavy smokers compared with never smokers generally ranged from 0.9 to 1.2 [164]. There was no evidence for an effect of long-term or high-intensity smoking on risk of breast cancer, nor an effect of age at smoking initiation or years of smoking. Although results have been published that are weakly supportive of an effect of smoking [165], there are also weakly negative results [166]. Studies that assess whether there is an effect of smoking in post or premenopausal women, or for oestrogen-receptor positive or negative tumours are contradictory, possibly implying no association. Limited data suggest an effect of passive smoking on increasing breast cancer risk [167]. It is difficult, however, to justify a lack of direct effect of smoking on breast cancer risk, but an association with passive smoking, and therefore these data may be because of confounding or chance.

Although an association has rarely been found by epidemiological studies, a role of cigarette smoking in

the aetiology of breast cancer is biologically plausible [28]. Smoking has anti-oestrogenic effects [78] and menopause occurs at an earlier age in smokers [168], supporting a protective effect on breast cancer risk. In contrast, substances, such as 7,12-dimethylbenz[a]anthracene, similar to those contained in cigarette smoke have been shown to act as breast carcinogens in animal models [169] and mutagens from cigarette smoke have been detected in the breast fluid of nonlactating women [170].

Prostate cancer

Prostate cancer is the sixth most common cancer globally and fourth in terms of mortality, annually affecting 396 000 men and causing 165 000 deaths [1], and it is particularly common in the elderly and in high-income countries. Prostate carcinomas are adenocarcinomas.

Amongst 22 prospective cohort studies, only four found some positive relationship between prostate cancer and smoking [171]. In the USA veterans cohort study, an effect of smoking cigarettes and smokeless tobacco use was found on prostate cancer mortality, but not incidence [172]. Similarly, an effect of smoking on fatal prostate cancer was found in the Lutheran Brotherhood Cohort Study [173] and the Cancer Prevention Study II [174]. Another prospective study showed that although smoking was unrelated to overall prostate cancer incidence, current smokers and recent quitters were at higher risk for distant metastatic prostate cancer and fatal prostate cancer [175]. Of 30 case-control studies that evaluated the role of smoking in the aetiology of prostate cancer, only two reported a significant positive association [171].

The effect of smoking on fatal prostate cancer, but not incidence of prostate cancer, is of note. This pattern could arise if cigarette smoking induces prostate cancer to become more aggressive or rapidly progressing [175].

Lymphoma

Non-Hodgkin's lymphoma. Globally non-Hodgkin's lymphoma (NHL) is responsible for 221 000 new cancer cases and 126 000 new cancer deaths annually [1]. NHL is relatively common in the USA, fifth in incidence in both men and women [135], and is increasing in frequency.

Six cohort studies have reported on the association between NHL and smoking. In five of these no increased risk amongst smokers was evident [88, 92, 107, 176, 177]. However, in one prospective study, men who had ever smoked cigarettes had a doubling in risk of NHL, and risk was higher still amongst the heaviest smokers [178]. In general data from case-control studies also do not support a large effect of smoking on NHL incidence [93, 179].

After stratification by histological subtype of NHL, however, various patterns emerged. In a cohort of 41 837 women followed for 11 years smoking was associated with an increased risk of follicular NHL [177]. In corroboration of this, in two studies there was a weak positive association between smoking and risk for follicular lymphoma, but no effect on other histological types [93, 176]. Biological support for an association between smoking and follicular NHL relies on drawing analogy with the increased risk for this subtype in patients with HIV infection and immunosuppression as a result of chronic antigenic stimulation.

Hodgkin's lymphoma. Hodgkin's lymphoma is most frequent in the upper socio-economic strata of Western populations, although even there it is relatively rare, responsible for an estimated 7400 new cancer cases and 1300 deaths in the USA in 2001 [135].

In general, studies do not support the hypothesis that smoking increases the risk of Hodgkin's disease [93, 180, 181]. A large cohort study found a suggestion of a positive association between smoking and the risk of developing Hodgkin's lymphoma, but the elevated RR only reached statistical significance for young current smokers [92]. Furthermore, two case-control studies reported some increased risk amongst smokers [182, 183].

Multiple myeloma

In multiple myeloma, a systemic malignancy of plasma cells, the case fatality rate is very high, so that in 1999 about 13 700 new cases of multiple myeloma were estimated to arise in the USA, and there were 11 400 deaths [184]. Epidemiological evidence converges impressively in showing that the association between smoking and risk of multiple myeloma is null. Support for this comes from cohort

studies [92, 178, 185, 186] and case-control studies [93, 187, 188]. Only one relatively small cohort study of Seventh Day Adventists reported an increased incidence of multiple myeloma amongst ever smokers [189].

Ovarian cancer

Ovarian cancer is the sixth most incident cancer in women, but the second most common gynaecological cancer [1]. It is a cancer found most commonly in high-income countries. Tumours in the ovary consist of a range of pathological entities, as they can arise from the epithelial cells (most common), germ cells or stromal cells. Epithelial ovarian tumours include serous tumours, mucinous tumours, which have an epithelium consisting of mucin-secreting cells, and endometrioid tumours that develop from the wall of an endometriotic cyst.

A strong effect of smoking on ovarian cancer risk is unlikely as few studies have shown an association [108, 190] and most studies were null [191–195]. Recent interest in separating histological types of ovarian cancer has prompted researchers to report associations separately. Two studies showed that ever smokers were at excess risk for mucinous epithelial ovarian cancer, but not other histological types [190, 196], but a third study did not support this finding [195].

Soft tissue sarcoma

Soft tissue sarcomas are malignant tumours that arise in the mesodermal tissues of the extremities (50%), trunk and retroperitoneum (40%), and the head and neck (10%). Cancers of the soft tissue are responsible for an estimated annual 7800 new cases of cancer and 4400 deaths from cancer in the USA [184].

The few data that exist on the association of tobacco use and risk of soft tissue sarcoma preclude a strong effect. One cohort study found an effect of cigarette smoking (whether former or current) and former use of snuff and chewing tobacco on the incidence of soft tissue sarcoma after 25 years of follow up [197]. The effect of chewing tobacco or snuff use on increasing the incidence of soft tissue sarcoma was confirmed in a population-based case-control study in Kansas [198]. However, no effect of cigarette smoking was detected in an Italian hospital-based case-control study [199].

Cancer of the central nervous system

A number of neoplasms are included under the general heading of cancer of the central nervous system and they are classified as either gliomas (for instance astrocytomas or glioblastomas) or nonglial tumours (such as meningiomas).

The scarcity of studies investigating the role of tobacco use in the aetiology of tumours of the brain and central nervous system and the lack of consistency in the data make it difficult to draw firm conclusions. The incidence of gliomas has been linked to smoking in men, but not in women [200–202], and an association between an increase in incidence of meningioma in women and passive smoking from their spouse has also been reported [203]. In contrast, other studies have shown a lack of effect of tobacco use on tumours of the central nervous system [204–207].

Testicular cancer

Testicular cancer is extremely responsive to treatment, so that although it is diagnosed in 7700 men per year in the USA (mainly aged 15–34), it kills only approximately 300 [184]. Testicular cancer is extremely heterogeneous. Studies have consistently failed to show an association between cigarette smoking and risk of testicular cancer [208–210]. Data on the effect of other forms of tobacco on testicular cancer risk are lacking. It has, however, been hypothesized that smoking by the mother during pregnancy may increase risk for testicular cancer in her male offspring [211].

Thyroid cancer

Thyroid cancer is a relatively rare form of cancer with a good prognosis, responsible for 87 000 new cancer cases annually [1]. Thyroid cancer is three times more common in women than in men and is most often found in the Pacific islands, Central America and East Asia. There are several major subtypes of thyroid carcinomas, the most common of which is papillary carcinoma.

There is a lack of consensus on the association between cigarette smoking and risk of thyroid cancer. The majority of studies have reported a protective (often dose-response) effect of smoking

on risk of thyroid cancer [212–214]. Other studies have reported no association [215, 216] or even a deleterious effect of smoking [217, 218].

Conclusions

There is strong evidence for an association between tobacco use and cancer of the lung, larynx, oral cavity and pharynx. Risk of bladder cancer is also associated with tobacco use, as is oesophageal, pancreatic, stomach and kidney cancer, whether of the renal parenchyma or renal pelvis. In contrast, the incidence of endometrial cancer is lower in women who smoke cigarettes. For most of these associations a dose–response effect of tobacco use on cancer risk is evident, as is a decline in risk on cessation of tobacco use.

Data indicate that myeloid leukaemia, but not other forms of leukaemia, may be associated with smoking. Similarly, smoking may increase risk of squamous cell sinonasal cancer, but not sinonasal adenocarcinoma. Liver cancer risk may be elevated in smokers who are chronically infected with the hepatitis B virus. Whether cervical cancer incidence is higher in smokers, or whether this apparent association is the result of residual confounding by sexual behaviour, remains open for debate. Colorectal cancer may be associated with tobacco use, but only after a very extended time since the initiation of tobacco use. The evidence for an association between tobacco use and cancer of the gall bladder, adrenal gland or small intestine is equivocal. The evidence for an association between parental smoking and childhood cancer is very inconsistent and may be subject to bias, but suggests a possible effect of paternal smoking.

Skin cancer overall shows little association with smoking, although there may be some increased risk for squamous cell carcinoma of the skin. Breast cancer, ovarian cancer and prostate cancer incidence are unlikely to be linked to tobacco use, although fatal prostate cancer may be higher in smokers. Non-Hodgkin's lymphoma, excepting the follicular type, Hodgkin's lymphoma and multiple myeloma show little relationship with tobacco use. The few data on the association between tobacco use and risk of soft tissue sarcoma, testicular cancer, thyroid cancer and cancer of the brain and central nervous system, preclude a strong effect.

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