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REVIEW

Tobacco use, cancer causation and public health impact

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Abstract. Kuper H, Adami H-O, Boffetta P (University College London, Torrington Place, London, UK; Karolinska Institutet, Stockholm, Sweden; and International Agency for Research on Cancer, Lyon, France). Tobacco use, cancer causation and public health impact. *J Intern Med* 2002; **251**: 455–466.

This review describes global patterns of tobacco use and the mechanisms by which tobacco use is involved in carcinogenesis. A second part will discuss the association between tobacco use and risk of specific cancer types. To bacco use has traditionally been a practice of high-income countries, but it has recently been taken up in low-income countries and it is particularly common in men. A wide variety of tobacco products exist, of which cigarettes are most frequently consumed. Tobacco products contain more than 50 established or identified carcinogens and these may increase risk of cancer by causing mutations that disrupt cell cycle regulation, or through their effect on the immune or endocrine systems. Certain factors such as genes, diet and environmental exposures may alter susceptibility to cancer in tobacco users. Today at least 15% of all cancers are estimated to be attributable to smoking, but this figure is expected to increase because of the uptake of tobacco use in low-income countries.

Keywords: tobacco, smoking, cancer, carcinogenesis

Introduction

Tobacco use, particularly tobacco smoking, is so firmly established in the public consciousness as a cause of cancer that in many ways it serves as the prototype of a disease risk factor. Smoking is the leading cause of death from cancer, and at least 15% of all cancers are estimated to be attributable to smoking [1]. Although this proportion is higher in men (25%) than in women (4%), and higher in high-income countries (16%) than low-income countries (10%) [1], the uptake of smoking by women and people in low-income countries may eventually eliminate these differences [2]. In addition, the risk of death associated with cigarette smoking has risen over time as the average duration of smoking has increased [3]. All is not doom and gloom however; stopping smoking substantially reduces mortality risks even amongst long-term smokers [3] and large numbers of smokers, mainly men from industrialized countries, have quit the habit in recent decades [2].

Epidemiological studies about tobacco have been important not only because they have revealed the devastating health effects of tobacco use, but also because they have paved the way and gone hand in hand with the development of modern epidemiology from the middle of the last century. The first convincing report showing an association between smoking and lung cancer was published by Doll and

Hill in 1950 [4] and became the prototype for case–control studies whilst their prospective study amongst doctors [5], initiated only 1 year later, has remained an archetype for longitudinal studies with repeat exposure measurements.

In the first part of this review we will discuss the characteristics of different types of tobacco products and the geographical distribution of their use. The various mechanisms by which tobacco products cause cancer will be described, and supporting evidence will be given. Not all smokers will go on to develop cancer, and in an effort to explain this we will explore factors that increase susceptibility to tobacco-related cancer. Finally, projections for the future in terms of tobacco use and tobacco-related diseases will be given. In the second part of the review we will discuss the association between the use of tobacco products and the causation of specific cancer types.

Tobacco products and their distribution

Tobacco products

Many tobacco products exist, and their use varies both geographically and over time [6]. Cigarettes are shreds of tobacco wrapped in paper as compared to cigars, where the shredded tobacco is wrapped in tobacco leaf. Local variants of cigars and cigarettes exist, such as bidis (tobacco hand-rolled in the dried leaf of various plants) or chuttas (small cigars smoked with the burning end held in the mouth), and they often have very high nicotine and tar content. And, of course, tobacco can be smoked using a pipe. Manufactured cigarettes and hand-rolled cigarettes are most intensively consumed, accounting for over 85% of global tobacco consumption, and so they will be the main focus of this review [7].

Noncombustive use of tobacco, or smokeless tobacco use, comes in the form of chewing tobacco and snuff (ground or powered tobacco, either moist or dry) which is inhaled nasally or placed in the mouth, although nasal use has become rare in industrialized countries [8, 9]. Smokeless tobacco use is particularly common in South and South-East Asia, and in this context tobacco is usually chewed together with another product, such as betel quid, ash, lime, cotton or sesame oil [8, 9]. The average consumption in regular users is 10–15 g per day and this is kept in the oral cavity for several hours per day [8, 9].

Composition of tobacco

Most tobacco products are made from the species *Nicotiana tabacum* [6]. Over 2000 chemical compounds have been identified in tobacco leaf, some of which are released through smoking, and 55 of these have been evaluated by the International Agency for Research on Cancer (IARC) as showing 'sufficient evidence for carcinogenicity' in either laboratory animals or humans [6]. These carcinogenic substances include, inter alia, *N*-nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), numerous polycyclic aromatic hydrocarbons (PAHs) (e.g. benzo[*a*]pyrene), radioactive polonium and benzene. Tar is the material that remains on a glass filter (after removing the water and nicotine) through which a machine has smoked a cigarette.

The carcinogen content varies by type of tobacco product; for instance, black (air-cured) tobacco has a higher content of tobacco-specific nitrosamines than blond (flue-cured) tobacco, and hand-rolled cigarettes have a higher tar content than filter cigarettes. Cigarettes have undergone a dramatic transformation between the 1950s and 1980s: filter use has increased and the average tar and nicotine yields per cigarette has fallen [10]. Regrettably, smokers of low tar cigarettes tend to inhale more deeply than do smokers of high tar cigarettes to compensate for lower yields of nicotine [6] so that the tar yield of a cigarette may not relate closely to the amount of smoke components consumed [11]. However, the mortality from smoking-related diseases is consistently lower in smokers of low than high tar cigarettes [12].

Nicotine makes up 0.05–4% of the weight of tobacco leaves and smokers extract about 1–2 mg of nicotine per cigarette [6, 13, 14]. This nicotine is absorbed in seconds throughout the body, and then metabolized to form, principally (±80%), cotinine [6]. Nicotine is the constituent of tobacco that is responsible for addiction and the resultant maintenance of smoking behaviour, exerting its addictive effect by activating the brain's mesolimbic dopaminergic reward system [15]. Individual susceptibility to nicotine addiction varies because it is affected by polymorphisms that influence dopamine availability [16].

The combustive use of tobacco results in the production of smoke, which consists of mainstream smoke and sidestream smoke. Mainstream smoke, an aerosol made up of a vapour phase and a particulate phase containing carcinogens (e.g. PAHs, aromatic amines, and aldehydes), is generated during inhalation through the butt end of a lit cigarette [17, 18]. Of all inhaled particles from cigarette mainstream smoke 80% are deposited on the respiratory tract, in particular the tracheobronchial region [6]. Sidestream smoke is the mixture emitted directly into the ambient environment, between puffs, from a smouldering cigarette. Sidestream smoke is unfiltered and therefore contains a higher concentration of many tobacco smoke products than mainstream smoke, although this is diluted in the ambient air. A smaller proportion of particles from sidestream smoke than mainstream smoke is deposited mainly on the periphery of the lung. Environmental tobacco smoke, or passive smoke, is a combination of exhaled mainstream smoke and sidestream smoke produced from the burning cigarette.

Biomarkers of exposure

Epidemiologists usually obtain information on patterns of tobacco use through questionnaires or interviews; however, self-reports may be inaccurate, potentially leading to bias. For this reason biomarkers of exposure to tobacco products are also used to assess patterns of tobacco use and these biomarkers also give a measure of exposure to tobacco and in particular to environmental tobacco smoke. Cotinine, the main metabolite of nicotine, is the most commonly used biomarker for tobacco exposure. It can be measured in the blood, urine and saliva, and, less often, in semen and hair. Although cotinine can measure both passive and active smoking with relatively high sensitivity and specificity, it cannot adequately address the variation produced by individual differences in the rates of metabolism of nicotine [19, 20]. Carbon monoxide and thiocyanate are also by-products of smoking that can serve as biomarkers for tobacco use, but are poor measures of low levels of smoke inhalation [21]. Adducts to tobacco products, that is, metabolites that are covalently bound to DNA, can be measured within blood-based proteins, including haemoglobins. Adducts are highly correlated with the intensity of smoking and show exposure to smoke over a relatively long period of time [22, 23]. Biomarkers are not without their limitations; they may lack sensitivity or specificity, and they may only indicate recent exposure to tobacco.

Worldwide patterns of smoking

Native Americans originated the practice of tobacco use, and the colonists later carried this habit back to Europe. Mass manufacturing of cigarettes only started in the 19th century, however, and so the widespread use of tobacco is a relatively recent phenomenon, particularly in low- and middle-income countries who have only taken up this habit in the last 30 years. Globally, about 1.1 billion people (one in three adults) smoke today, of whom approximately 80% live in low- and middle-income countries [7]. The prevalence of smoking is highest in Eastern Europe and Central Asia and lowest in the Middle East and Africa (Table 1), although this pattern is changing rapidly [7]. The total number of smokers is expected to reach 1.6 billion by 2025, partly as a result of increased trade liberalization and the consequent uptake of smoking in the poorer countries in the world, notably in China [7].

Smoking is particularly common amongst men: globally four times as many men smoke as women (Table 1) [7]. The gender difference is more striking in low- and middle-income countries than in high-income countries, because rates of smoking cessation in men in high-income countries are relatively high. There are also socio-economic differences in smoking habits. Within rich countries, the affluent are giving up smoking, whilst poorer people are continuing with their habit and, similarly, in poorer countries men of low socio-economic status are more likely to be smokers [7]. This means that, to some extent, tobacco use provides a marker of deprivation, and so the adverse health effects are concentrated in those who are less well off.

Most smokers start during their teens and early 20s [7]. The age at initiation of smoking has reduced throughout the world, which is of concern, as people who start smoking earlier are less likely to quit and more likely to become heavy smokers. As well as this, the health consequences of smoking are particularly severe amongst those who start smoking early, as illustrated by the fact that people who start smoking before the age of 15 have double the

Table 1 Estimated smoking prevalence by gender and number of smokers in population aged 15 or more, by World Bank region, 1995 [7]

	Smoking prevalence (%)			Total smokers	
	Men	Women	Total	Number (millions)	% of all smokers
World Bank Region					
East Asia and Pacific	59	4	32	401	35
Eastern Europe and Central Asia	59	26	41	148	13
Latin America and Caribbean	40	21	30	95	8
Middle East and North Africa	44	5	25	40	3
South Asia (cigarettes)	20	1	11	86	8
South Asia (bidis)	20	3	12	96	8
Sub-Saharan Africa	33	10	21	67	6
Summary of World Bank regions					
Low/middle income	49	9	29	933	82
High income	39	22	30	209	18
World	47	12	29	1142	100

Reproduced, with permission, from Chaloupka, FJ. *Curbing the Epidemic: Governments and the Economics of Tobacco Control.* Washington, DC: World Bank, 1999. This table was based on data from the WHO report *Tobacco or Health, a Global Status Report (1997).*

risk of lung cancer as those who start smoking when they are older than 20 [3]. This means that because smokers today have on average been smoking for longer than in previous generations, they are at even higher risk of cancer than in the past [3].

The prevalence of smoking increased between 1945 and 1965 in most high-income countries, and remained reasonably stable from 1965 until 1985 after which the prevalence began to fall, stimulated by the extensive reporting of the adverse health effects of smoking [24]. As an illustration of this, in the USA in 1945 on average seven manufactured cigarettes were consumed per day per adult, and this figure rose to 10.5 in 1965 and then fell back to 8.7 in 1985 [24]. However, the high rates of cessation have not been matched in low-income countries, so that only 2% of Chinese men and 5% of Indian men were former smokers in 1993 [7]. This is unfortunate because tobacco users can avoid much of the risk of cancer if they cease their habit. Smoking cessation is particularly advantageous if it occurs at a young age; the cumulative risk of lung cancer by age 75 is 15.9% for men who continue to smoke, but 9.9, 6.0, 3.0 and 1.7% for men who ceased smoking at ages 60, 50, 40 and 30, respectively (Fig. 1) [3].

Tobacco use and disease causation

The large body of epidemiologic evidence supporting an effect of tobacco use on cancer causation is drawn from cohort and case–control studies, as well as ecological data. This evidence will be discussed in greater detail in the second part of this review. Briefly, there is strong evidence supporting a role for tobacco use in the causation of cancers in the respiratory tract, including the oral cavity, pharynx, larynx and lung, as well as in the urinary bladder, pancreas, kidney, and renal pelvis. There is also an established association between endometrial cancer and tobacco use, but in this instance smoking substantially reduces the risk of endometrial cancer. The association between cancers of the digestive tract and tobacco use diminishes as one passes down the alimentary canal, so that there is strong evidence for a link between tobacco use and oesophageal cancer and stomach cancer, but the evidence for colon and rectal cancer and cancers of the small intestines is weaker. An association between leukaemia, gallbladder cancer, cervical cancer, sinonasal cancer, childhood cancers and cancers of the adrenal gland and tobacco use is possible, but remains to be established. Finally, based on current evidence, it is unlikely that an association exists overall between tobacco use and cancer of the breast, prostate, brain, skin, or testicles, or soft tissue sarcoma, lymphoma or melanoma.

A distinct feature of tobacco smoking is that it also increases the risk of many nonneoplastic disease. So, in a given population, the burden of tobacco-related mortality depends on the mortality from chronic diseases: in Europe and North America, most nonneoplastic tobacco related deaths are from cardiovascular disease, whilst in China they are from chronic obstructive pulmonary disease [25] and in India from tuberculosis (Dr C. K. Gajalakshmi,

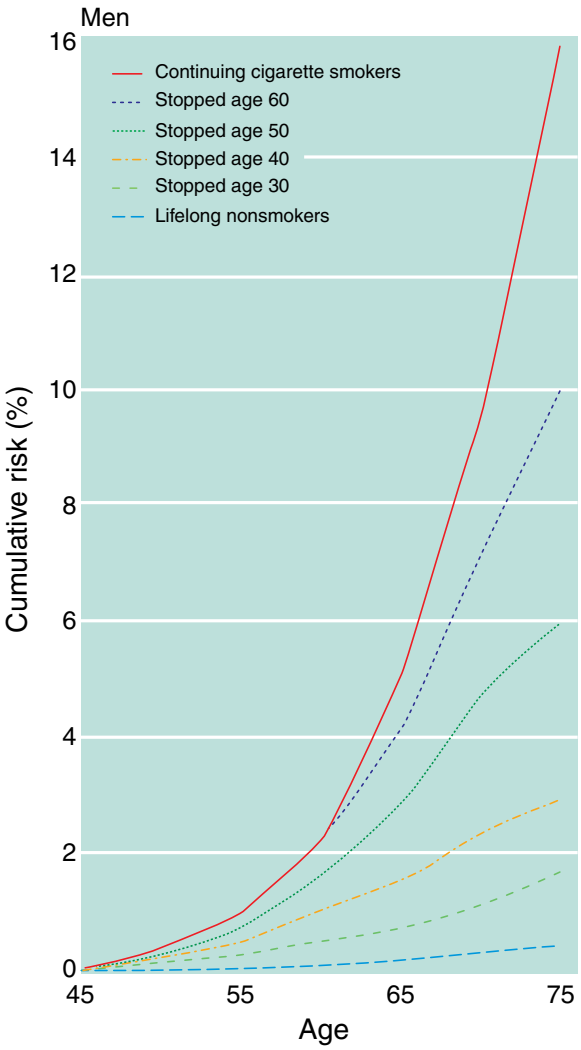

Fig. 1 Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in United Kingdom in 1990. Reproduced with permission from the BMJ Publishing Group, from Peto *et al.* Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 2000; **321**: 323–329.

Chennai, India, personal communication). Specifically, tobacco use increases the risk of heart disease, chronic obstructive pulmonary disease, acute respiratory disease, stroke, peripheral vascular disease, peptic ulcer disease, and osteoporosis. Furthermore, both men and women who smoke may have reduced fertility and the risk of spontaneous abortion is increased in women who smoke. Smoking is also linked to various psychiatric disorders, including depression, anxiety, schizophrenia, agoraphobia, panic disorder and Alzheimer's disease and dementia, but may reduce the risk of Parkinson's disease.

Mechanisms of tobacco-related carcinogenesis

The label 'cancer' encompasses a wide variety of diseases, all of which share the common characteristic of unregulated cell growth. Carcinogenesis, or the development of cancer, is a multistage process. For cells to be free from cell growth regulation mechanisms there must be both enabling of oncogenes (genes that stimulate cell division) and switching off of tumour suppressor genes (genes that prevent cell division), so that the cells are constantly stimulated to divide but there is no control preventing the mitosis. These effects are caused by mutations. Cells with damaged DNA are usually destroyed through apoptosis; however, aberrant cells may escape normal growth control and acquired mutations may alter apoptosis, and thereby allow the development of cancer. Carcinogenesis therefore requires multiple genetic changes, as can occur within the context of long-term, repeated exposure to genotoxic products in tobacco.

Clearly, there is no single mechanism of tobacco-related carcinogenesis. A variety of tobacco products exist, and the methods by which they are consumed influences the release of carcinogens and therefore the link between tobacco use and cancer causation. Furthermore, the complexity of the mixture of carcinogens in tobacco smoke means that in different individuals, different carcinogens might cause different types of damage, and there is also a random component to carcinogenesis. Carcinogens must be metabolically activated to exert their deleterious effects, but this is counteracted by the ongoing detoxification of carcinogens, so that the balance between activation and detoxification determines part of the individual susceptibility to the carcinogenic effects of tobacco. It is important to elucidate these mechanisms, because an understanding of the pathways by which tobacco use causes cancer may allow the course to be blocked at some level, even in people who continue to use tobacco.

The most likely pathway, based on currently available data, by which tobacco use causes cancer is outlined in Fig. 2 [26]. Carcinogens from tobacco products can be taken in directly through inhalation or ingestion (smokeless tobacco) and also may be

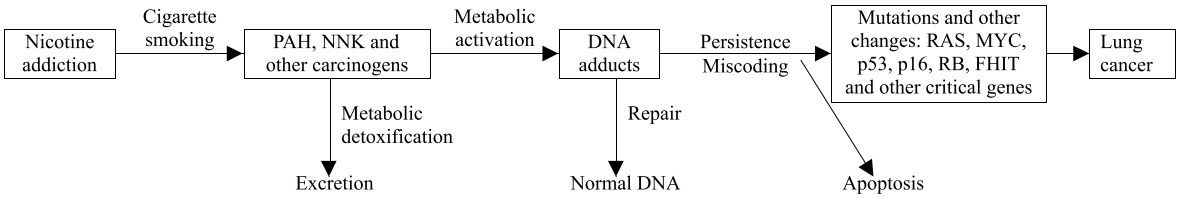

Fig. 2 Scheme linking nicotine addiction and lung cancer via tobacco smoke carcinogens and their induction of multiple mutations in critical genes [26]. Reproduced, with permission from Oxford University Press, from Hecht SS. Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst* 1999; **91**: 1194–1210.

absorbed into the circulation [6]. Many compounds from tobacco are converted into reactive electrophilic metabolites by oxidative (phase I) enzymes, to allow the attachment of a conjugate by inactivating (phase II) enzymes so that the substrate becomes more hydrophilic and can be excreted from the cell more easily. Unfortunately, the substrates produced in phase I have more potential to damage DNA than the precursor chemicals, that is, the carcinogens in tobacco may become metabolically activated by phase I enzymes.

Metabolites formed during the activation of carcinogens may bind covalently with DNA to form DNA adducts, usually at adenine or guanine. As evidence of this, there is a significant association between smoking status and bulky DNA adduct levels: adduct levels are highest in current smokers whilst in former smokers levels decline with years of abstinence from smoking [22, 23]. DNA adducts to metabolites of tobacco can also be detected in tissue not directly exposed to smoke. For instance, DNA adducts formed by benzo[a]pyrene were detected in the colonic mucosa of smokers more frequently and at higher concentrations than for nonsmokers [27].

If DNA adducts escape cellular repair mechanisms they could persist and may lead to miscoding, resulting in a mutation. In addition, cigarette smoke contains free radicals that can induce oxidative damage of DNA in humans and cause mutations [6]. Certain mutations could trigger the activation of an oncogene or the deactivation of a tumour suppressor gene. The *p53* gene is a key regulator of the cell cycle and mutations of the *p53* gene are more common in smokers amongst lung cancer patients [28, 29] and oral cancer patients [30]. These changes may allow a cell to begin dividing uncontrollably, potentially resulting in cancer causation. There is also recent evidence that nicotine might be directly implicated in carcinogenesis, beyond its crucial role in establishing and maintaining dependence, by promoting lesion growth and angiogenesis [31].

In addition to the epidemiologic evidence, experimental evidence from animals supports a role of tobacco use in carcinogenesis. Although this body of data is not without obstacles, a few examples will be given. Exposure to tobacco products, such as extracts of moist oral snuff, can produce mutations, sister chromatid exchange and chromosomal aberrations in a variety of experimental models [6, 32]. Furthermore, specific chemicals extracted from tobacco can be carcinogenic. For instance, some tobacco specific nitrosamines present in smokeless tobacco, such as *N*-nitrosonornicotine, are potent carcinogens in animal tests, producing carcinomas of the upper digestive tract and nasal cavity and the respiratory tract [6]. Benzo[*a*]pyrene, which is a PAH, can also induce lung tumours upon local administration or inhalation [26]. In addition to this, smoke condensate is clearly carcinogenic in animals. In mice and rabbits application of cigarette smoke condensate to skin induces skin cancer, and intrapulmonary injection of smoke condensate induces lung cancer in rats [6]. Whole smoke and its particulate phase can also trigger malignant respiratory-tract tumours in hamsters and rats [6].

Aside from this pathway, smoking may also have an effect on the endocrine system and so influence the occurrence of hormone-related cancers. For instance, smoking may have antioestrogenic effects that could protect women from endometrial, and potentially breast, cancer [33]. Smoking may also act to reduce levels of circulating testosterone [34], potentially reducing the risk of prostate cancer.

Tobacco smoking may result in impairment of the immune system functioning thereby increasing the risk of cancer [35] (Fig. 3). Evidence supporting this assertion comes from both human and experimental models. Smokers have higher rates of infection,

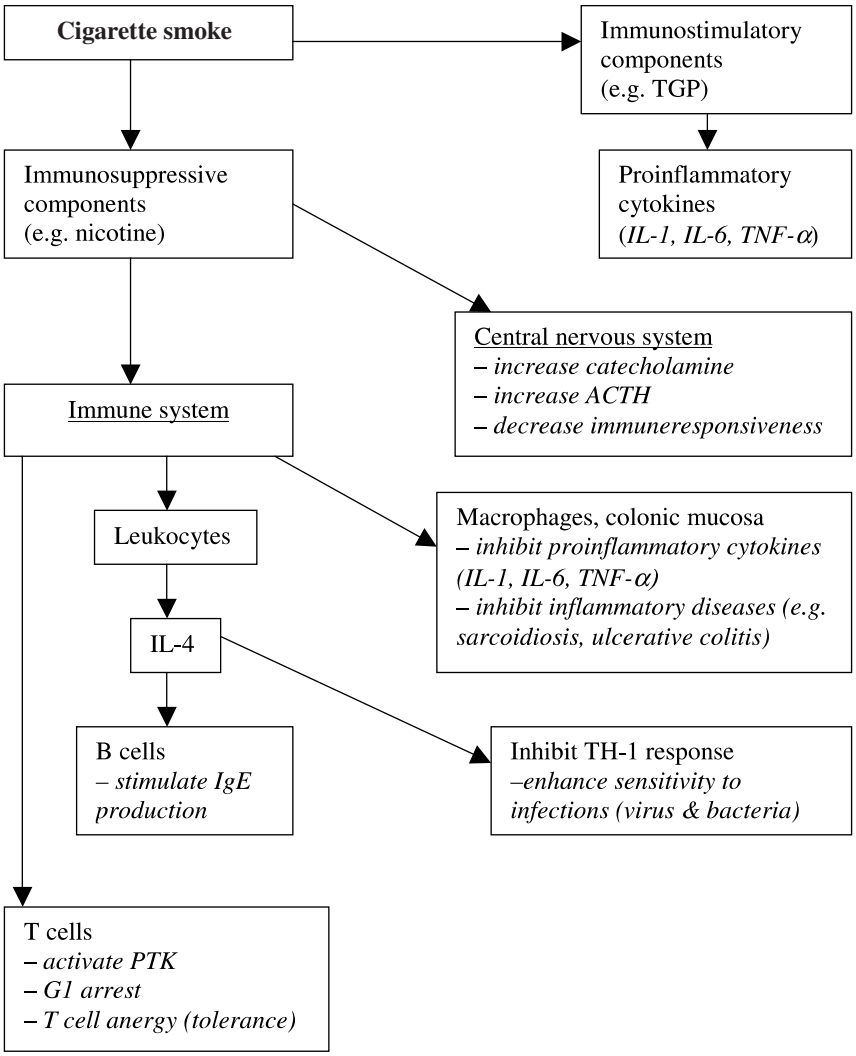

Fig. 3 A simplified model by which cigarette smoke could affect the immune system [35]. Reprinted from *J Neuroimmunol*, 83, Sopori ML & Kozak W, Immunomodulatory effects of cigarette smoke, 148–156, Copyright 1998, with permission from Elsevier Science.

lower serum levels of most immunoglobulin classes (except for IgE) and lower antibody titres when infected [35]. When animals are exposed to smoke they experience a suppression of their primary antibody response as well as an increased susceptibility to infections [35]. There are a number of proposed mechanisms for this immunological effect. Cigarette smoke and/or nicotine may influence the hypothalamo-pituitary-adrenal axis by stimulating the release of catecholamines and ACTH, they may modulate cytokine production and thus change the Th1/Th2 ratio, or they could reduce the responsiveness of T cells [35].

The association between tobacco use and cancer varies by anatomic site. This may be the result of cofactors, such as alcohol and diet, that are present in various parts of the body, or because the duration of contact of specific anatomical sites to tobacco constituents and their metabolites varies, as well as the concentration of this contact. For instance, metabolites are excreted in the urine, and as urine is stored in the bladder substantially longer than in the kidneys this may explain the stronger effect of smoking on bladder than kidney cancer described in the second part of the review. In addition, the variation in proliferative ability of tissues may be important.

Passive smoking

Several sources of evidence suggest that passive smoking, or exposure to environmental tobacco smoke, increases the risk of cancer. Haemoglobin adducts of 4-aminobyphenyl, a carcinogen in

tobacco smoke, have been identified in people exposed to environmental tobacco smoke [36]. Moreover, sidestream smoke contains more carcinogens, although at a lower concentration, than mainstream smoke and no safe limit for carcinogens exists [6]. Epidemiologic studies have repeatedly shown an association between exposure to passive smoke and lung cancer risk in nonsmokers [37–39]. The magnitude of the excess risk amongst those exposed is probably in the order of 20% [40]. There are, of course, difficulties in inferring a causal effect of passive smoking on cancer development, as this exposure is liable to misclassification and there is likely to be confounding by other exposures related to cancer. However, the combination of biological plausibility and epidemiologic evidences makes such an association highly likely [41].

Cofactors and tobacco-related carcinogenesis

The fact that not all tobacco-users develop cancer is frequently used to argue against a role of tobacco in carcinogenesis. The real reason for this (aside from the random element) is that characteristics relating to individual smokers may put them at increased risk of cancer, or indeed, may be protective, and these are called cofactors. The interaction might take place at the stage of external exposure (e.g. the other agent has to be absorbed on the tobacco particles to penetrate into the lung) or at some stage of the carcinogenic process (e.g. induction of common activating or detoxifying enzymes). The potential importance of cofactors must not, however, detract from the primary role of tobacco in cancer causation.

Dietary, occupational and environmental cofactors

Dietary components can modify the role of tobacco in carcinogenesis. As one example, high fruit and vegetable intake may protect from the deleterious effects of smoking with respect to lung cancer [42] and gastric cancer [43]. A cross-sectional study of 63 healthy male smokers revealed that blood levels of vitamin E and vitamin C [44] and retinol, α-tocopherol and β-carotene [45] were inversely associated with PAH–DNA adducts in circulating mononuclear cells. Hence, fruit and vegetables may protect smokers from cancer by reducing the formation of adducts, perhaps by inhibiting DNA and chromosomal damage by carcinogens and altering expression of metabolic enzymes [46].

Alcohol may confound the association between smoking and cancer, but it also acts as an effect modifier. Alcohol consumption appears to interact significantly with tobacco use in the development of oesophageal squamous-cell carcinoma [47, 48], cancer of the oral cavity, pharynx and larynx [10], gastric cancer [49] and liver cancer [50]. The effect modification by alcohol may be because ethanol increases the tissue penetration [51] or metabolic activation of tobacco smoke carcinogens [52]. Microorganisms are important carcinogenic agents, and they may interact with smoking during carcinogenesis, as in the case of infection with *Helicobacter pylori* which interacts with smoking in the development of gastric cancer [49].

Occupational and environmental exposures could influence the carcinogenic effect of smoking. A less than multiplicative interaction for the effect of smoking on risk of lung cancer has been suggested in studies of workers exposed to asbestos or crystalline silica [42, 53, 54]. The results of studies of uranium miners are compatible with a multiplicative interaction between smoking and radon decay products [55]. Furthermore, nickel or arsenic appear to have an additive effect with smoking on risk for lung cancer [10], and smoking has a multiplicative interactive effect with occupational exposure to aromatic amines in the causation of bladder cancer [10].

Host and genetic cofactors

Cancer is more common in older age groups. This is chiefly a function of increased duration of exposure to carcinogens, and partly because of a reduced ability to repair DNA damage with increasing age. Furthermore, risk of cancer amongst smokers may vary between men and women, either because exposure to smoking depends on gender, or because of the interactive effect of hormonal status with smoking in carcinogenesis. For instance, bladder cancer may be more strongly related to smoking amongst women than men [56] and risk of smoking is particularly protective for endometrial cancer amongst women with high levels of oestrogen [57].

There are also established racial differences in tobacco-related diseases; for example, there may be a

closer association between bladder cancer risk and smoking in African Americans than White Americans [58, 59]. Experimental evidence has shown that nicotine intake per cigarette is 30% greater in Black than White smokers, moreover Black smokers clear cotinine at a significantly slower rate [60], possibly because of a poorer potential for detoxification [61].

Hereditary variation in the metabolic pathways through which carcinogens are activated and detoxified appear to influence risk for developing cancer [62, 63]. A good model of this is provided by the Cytochrome P450 (CYP) proteins that comprise many of the phase I enzymes. A number of CYP proteins exist, and polymorphisms in these proteins may relate to cancer risk amongst tobacco users. For example, *CYP1A1* probably plays an important role in the activation of PAHs [64]. Certain *CYP1A1* variants are more efficient at bioactivating procarcinogens, and these variants confer a higher susceptibility to lung cancer [64].

Furthermore, *CYP2A6* activates NNK and certain *N*-nitrosamines [65]. This *CYP2A6* activity varies considerably in humans, partly because variant *CYP2A6* alleles code for the inactive enzyme [66]. The frequency of *CYP2A6* whole deletion was found to be lower in nonsmall cell lung cancer cases than controls [65, 66]. There is, therefore, evidence to suggest that diminished *CYP* activity might decrease the production of carcinogenic metabolites, and thereby reduce the risk of cancer amongst smokers.

Near complete loss of *N*-acetyltransferase 2 (*NAT2*) enzyme activity is caused by at least seven different alleles resulting from single-base substitution [67, 68]. People with two mutant alleles are slow acetylators, with a reduced ability to detoxify aromatic amines, whereas those with at least one normal allele are fast acetylators. Studies have shown that smoking is significantly more deleterious, with respect to risk to bladder cancer [67, 68], and possibly colorectal cancer [69], amongst people with the NAT2 slow acetylation polymorphism.

The glutathione S-transferase μ gene (*GSTM1*) is another genetic susceptibility factor that codes for a phase II detoxification enzyme. Within the group of smokers, PAH–DNA adducts in circulating mononuclear cells were detected less frequently amongst those with an inherited absence of *GSTM1* (the null *GSTM1* genotype) [44]. Indeed, studies have shown that people with the null *GSTM1* genotype may have a significantly higher risk of, inter alia, lung [70], bladder [71] and laryngeal cancer [72], probably on account of their reduced ability to detoxify carcinogens.

A number of genes have been identified that confer highly increased risk for specific types of cancer, and these are known as high penetrance cancer genes. These high penetrance cancer genes could alter the effect of tobacco use in promoting carcinogenesis. For instance, two highly penetrant genes for breast cancer have been identified, the breast cancer 1 (*BRCA1*) and 2 (*BRCA2*) genes, which are associated with a very high risk of breast cancer. In a matched case–control study of female carriers of either *BRCA1* or *BRCA2* mutation, women with breast cancer were half as likely to have smoked cigarettes at any time in their lives as healthy control subjects, and a dose–response protective effect of smoking duration and intensity was observed [73]. This protective effect may be the result of the antioestrogenic effect of smoking [33].

Projections for the future

Although tobacco use has been common in high-income countries for more than half a century, in low-income countries the habit has only been adopted on a large scale in the last 30 years. As the full health effects of smoking are only seen after several decades, the full consequences of the tobacco epidemic on health in the developing world will only appear during the next 20 years. Peto and his colleagues have presented evidence from China showing that in 1990 smoking caused 12% of adult male deaths, but by 2030 this proportion will have grown to one-third [25, 74]. Given that China contains one-fifth of the world's populations, this will have a dramatic impact on global tobacco-related mortality rates, and the situation in China may be typical of what happens in other low-income countries. As a consequence of this, the total number of tobacco-related deaths is estimated to increase from 4 million per year in 2000 to approximately 10 million deaths per year by the year 2030 [75]. Put another way, although tobacco is believed to be responsible for one in 10 adult deaths today, this figure could rise to one in six by the year 2030 [7]. The relative burden of tobacco-

related deaths in the developed versus developing world is expected to shift. Today, 2 million tobacco-related deaths per year occur in the developed world and 2 million in the developing world [75]. By 2030 the majority of tobacco-related deaths will occur in the developing world (7 million) and a smaller proportion in the developed world (3 million) [75].

Reducing the incidence of smoking-related cancer depends either on reducing the uptake of smoking or promoting smoking cessation. The benefits of smoking cessation are clear; smoking cessation reduces the risk of cancer and the earlier a person gives up smoking the more the risk of cancer is reduced [3] (Fig. 1). Furthermore, former smokers live longer than people who continue to smoke, and this decline in mortality rates occurs shortly after smoking cessation and continues for at least a decade [3, 76]. Promoting smoking cessation will therefore help prevent deaths from cancer in the first half of this century. Furthermore, there is scope to reduce smoking prevalence by delaying the uptake of smoking, and this could result in reduced cancer-related mortality in the second half of this century. If we fail to reduce the prevalence of tobacco use today we will invite devastation to population health in low-income countries in the future.

Conclusions

It is established that tobacco use is a primary cause of cancer. We have outlined the main pathways by which tobacco use is involved in carcinogenesis, and we have discussed other agents involved in these pathways. The high prevalence of tobacco use in high-income countries has been of concern since the 1950s, when the health effects of smoking became apparent. The uptake of tobacco use in low-income countries will result in widespread disease over the next 30 years, unless we are successful in promoting smoking cessation.

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