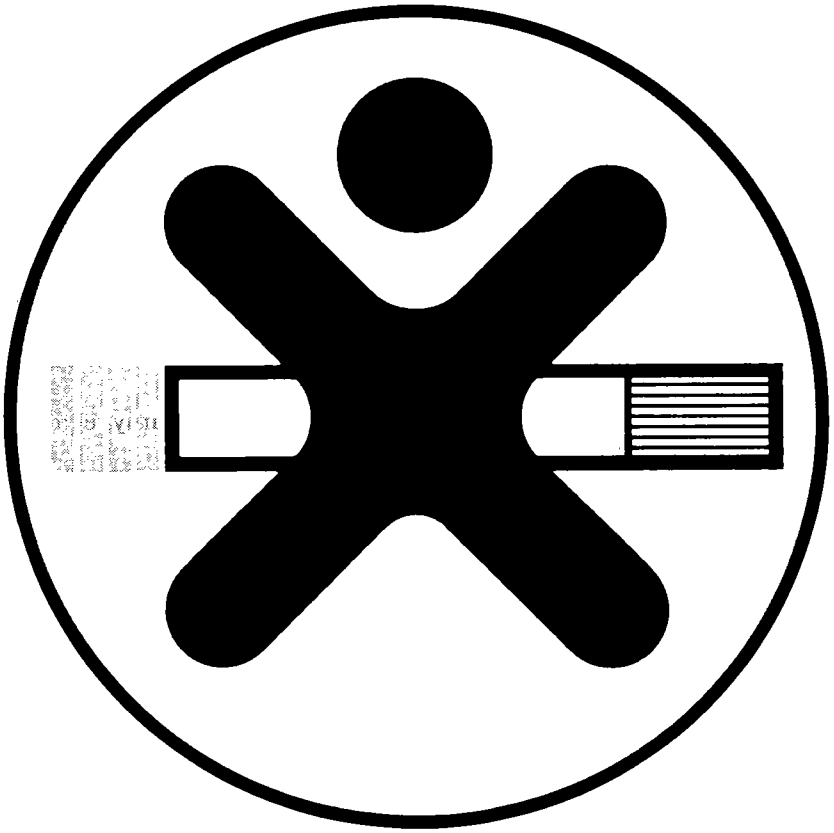
Tobacco or Health

Warning: Tobacco causes cancer and other fatal diseases



Smoke-free Europe: 4

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Sources

This document is closely based on the following sources, which are quoted and paraphrased freely.

Doll, R. Tobacco: an overview of health effects. *In*: Zaridze, D. & Peto, R., ed. *Tobacco. A major international health hazard.* Lyon, International Agency for Research on Cancer, 1986 (IARC Scientific Publications, No. 74), pp. 11-22.

Hoffmann, D. & Wynder, E.L. Chemical constituents and bioactivity of tobacco smoke. *In*: Zaridze, D. & Peto, R., ed. *Tobacco. A major international health hazard.* Lyon, International Agency for Research on Cancer, 1986 (IARC Scientific Publications, No. 74), pp. 145-165.

Murphy, J.F. The effects of maternal smoking on the unborn child. *In*: Studd, J., ed. *Progress in obstetrics and gynaecology.* Edinburgh, Churchill Livingstone, 1984, pp. 36-51.

O'Neill, I.K. et al., ed. Environmental carcinogens. Methods of analysis and exposure measurement, Vol. 9. *In*: *Passive smoking.* Lyon, International Agency for Research on Cancer, 1987 (IARC Scientific Publications, No. 81).

Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon, International Agency for Research on Cancer, 1987 (IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Supplement 7).

Paffenbarger, R.S. Jr et al. Cigarette smoking and cardiovascular diseases. *In*: Zaridze, D. & Peto, R., ed. *Tobacco. A major international health hazard.* Lyon, International Agency for Research on Cancer, 1986 (IARC Scientific Publications, No. 74), pp. 45-60.

Peach, H. Smoking and respiratory disease excluding lung cancer. *In*: Zaridze, D. & Peto, R., ed. *Tobacco. A major international health hazard.* Lyon, International Agency for Research on Cancer, 1986 (IARC Scientific Publications, No. 74), pp. 61-72.

Saracci, R. & Riboli, E. Passive smoking and lung cancer: current evidence and ongoing studies at the International Agency for Research on Cancer. *Mutation research* (in press).

Sasco, A.J. *Rapport préliminaire sur la législation en vigueur pour l'étiquetage des produits du tabac et la limite en goudrons des cigarettes dans les pays de la Communauté Economique Européene.* Lyon, International Agency for Research on Cancer, 1987.

Stellman, S.D. Influence of cigarette yield on risk of coronary heart disease and chronic obstructive lung disease. *In*: Zaridze, D. & Peto, R., ed. *Tobacco. A major international health hazard.* Lyon, International Agency for Research on Cancer, 1986 (IARC Scientific Publications, No. 74), pp. 237-249.

Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines. Lyon, International Agency for Research on Cancer, 1985 (IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 37).

Tobacco smoking. Lyon, International Agency for Research on Cancer, 1986 (IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 38).

Wald, N. et al. *UK smoking statistics.* Oxford, Oxford University Press (in press).

1

Tobacco Products

Tobacco has been used in various forms for centuries and possibly for millenia. Since its discovery by European explorers who landed in the Americas, tobacco has played an important role in agricultural economics and international trade. In the early 1600s, commercial cultivation of tobacco began in Virginia, and throughout the colonial period the Anglo-American tobacco colonies supplied the fast-spreading tobacco market. The form of tobacco consumption used predominantly in western countries since the beginning of this century is cigarettes; however, in response to growing concern about the adverse health effects of tobacco, the consumption of ''smokeless'' tobacco has increased markedly.

Production and use

Smoking tobacco

Tobacco was first smoked by the native populations of North America; however, after tobacco was brought to Europe in the middle of the sixteenth century, smoking spread throughout the world, particularly after the expansion of the cigarette industry beginning in 1918.

By the early 1980s, over 4 million hectares were under cultivation with tobacco worldwide, with a total production in 1982 of over 6.5 million tonnes. In Europe, 510 046 hectares of tobacco were cultivated in 1982, yielding 760 086 tonnes. International trade in unmanufactured tobacco was then about 1.5 million tonnes annually.

Cigarettes are the form of smoking tobacco used most widely in developed countries, although cigars and pipe tobacco constitute more of the tobacco used in the early lives of most of the population at risk today. Cigarettes are made from fine-cut tobaccos blended with varying proportions of different grades of Virginia and other tobaccos. In northern Europe cigarettes made entirely of Virginia tobacco are preferred, whereas in France and southern Europe cigarettes filled with dark, air-cured tobaccos are more popular.

Cigarette design has changed significantly over the past few decades, largely in response to demands for lower yields of certain smoke components (especially total particulate matter and nicotine), due to a growing concern about the adverse health effects associated with tobacco smoking. The major changes in cigarette design include more specific blend selection, variations in length and circumference, addition of filters, the use of reconstituted tobacco sheet and of expanded tobacco, and the development of ventilation techniques.

The standard laboratory methods for determining the yields of particulate matter ("tar", which is defined on p. 6, and nicotine) cannot faithfully represent human smoking practices and thus have limited relation to specific human dosage. However, the major reduction in the measured levels of tar has been achieved by altering the design of filter tips. The popularity of filter-tipped cigarettes increased markedly from the early 1950s, after the publication of studies demonstrating a causal relationship between smoking and lung cancer. In 1982 filter cigarettes accounted for 90% or more of the cigarette market in many countries. In Europe exceptions to this trend are seen in the USSR, where only 30% of cigarettes sold are filter-tipped, Poland with 45%, France with 47% and the Netherlands with 67%. Filtered types have significantly less dry particulate matter than non-filter cigarettes, although carbon monoxide delivery may be higher.

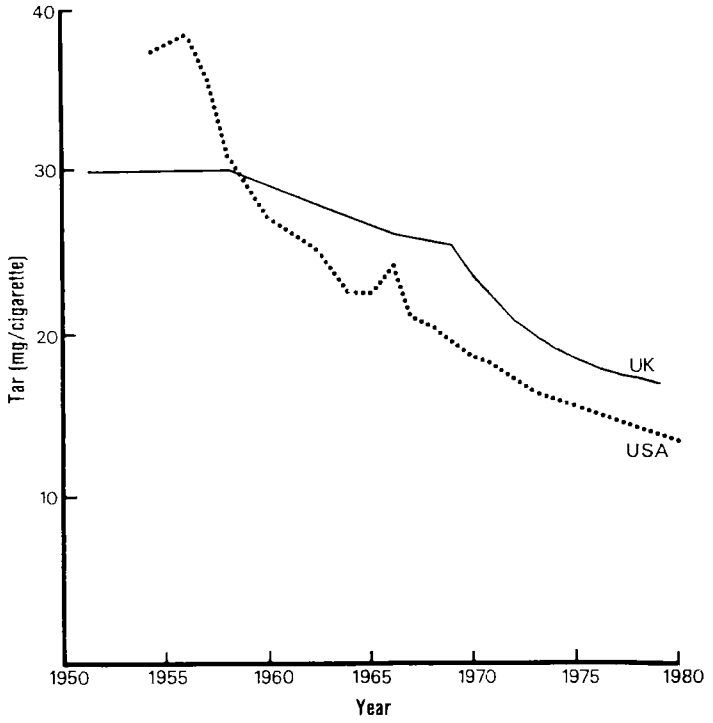
Before filter tips began to be widely used, typical tar deliveries were generally more than 30 mg per cigarette in many countries. Even in countries where no systematic effort has yet been made to reduce tar deliveries, values in the range 20-30 mg are now typical; whereas in countries where substantial reductions have been deliberately engendered, the average tar delivery is now likely to be under 15 mg.

The decline in tar and nicotine levels in British and US cigarettes between 1950 and 1980, as a result of the technical modifications, is shown in Fig. 1. However, tar and nicotine yields of commercial cigarettes vary widely around the world. In 1983 cigarettes delivering more than 30 mg of tar were sold in many countries, for example Austria, China, France, Hong Kong, India, Indonesia, Italy, Kenya, the Philippines, Scotland, South Africa and the USSR.

In 1987, in the European Economic Community, the following measures were directed at tar content:

- *Belgium*: tar and nicotine content given on packets;

Fig. 1. Sales-weighted average tar yields of UK and US cigarettes by year of manufacture



Source: Wald et al. (1981a) and Norman (1982).

- *Denmark*: cigarettes classified as *light*, *strong* and *very strong* (>20 mg); the latter was to have been reduced by 10% beginning in September 1986, with a steady decrease in tar content for several years thereafter;

- *Federal Republic of Germany*: tar content is 6-14 mg (minimum = 2 mg);

- *France*: tar and nicotine content given on packets; average tar content is 18 mg, with 3.5-8 mg in "ultra-light" cigarettes and >40 mg in "maize-paper" cigarettes;

- *Greece*: no legislation; average tar content is 18-20 mg;

- *Ireland*: the aim is for 0 mg; aim to avoid categorizing cigarettes on the basis of tar content;

- *Italy*: an upper limit of 15 mg was aimed for by 1987;

- *Luxembourg*: no legislation;

- *the Netherlands*: no legislation;

- *Portugal*: tar level given on packet; aiming for 15-20 mg limit;

- *Spain*: new brands with >24 mg cannot be sold;

- *United Kingdom*: no legislation, but an agreement with the industry aiming for an average of 13 mg by the end of 1987; no advertising allowed for cigarettes >18 mg.

Estimates of world tobacco consumption reveal rising consumption in most countries between 1920 and the 1960s, interrupted in certain cases by major events such as war or financial depression and reports by health bodies, such as the US Surgeon General and the Royal College of Physicians in the United Kingdom. In some countries, such as Finland, the United Kingdom and the United States, cigarette consumption per person has been declining in recent years. Smokers generally represent between one third and one half of the male population of a country, Japan being one of the few exceptions with a higher proportion in the developed world. In most countries, about one third of the women smoke. Smoking rates among adolescents, although of considerable importance to public health as an indication of future trends, are extremely difficult to measure accurately. It is usual for smoking habits to become established during adolescence, and smoking rates of people in their late teens may approximate or be greater than those of adults.

Smokeless tobacco

Faced with a threat of potentially declining sales of cigarettes, as a result of wider knowledge of the health consequences of smoking and of public concern about risks due to passive smoking, the tobacco industry has expressed a renewed interest in so-called "smokeless" tobacco products.

The predominant use of smokeless tobacco is in the mouth, although it may be taken in via the nose. In Europe and the United States, the smokeless tobacco products used are mainly chewing tobacco and snuff. The categorization of products into one of these two classes is not clear, and there appears to be considerable overlap, depending on national legislation. For instance, in the United States, some types of fine-cut smokeless tobacco classified as chewing tobacco before 1981 are now categorized as moist/fine-cut snuff.

Chewing tobaccos are, as the name implies, usually chewed, or portions are placed between the inside of the lip and the gums for varying periods. Most snuff used today has a relatively high moisture content and is finely cut rather than pulverized. Like chewing tobacco, snuff is used orally and is placed between the inside of the lip and the gums. Dry, pulverized forms of snuff are also predominantly used orally, although nasal sniffing is still practised.

A 1978 estimate indicated 700 000 to 800 000 snuff users in Sweden, constituting 17% of the population; almost all of these users were men. Among Swedish schoolchildren aged 13-16 years, 11-15% of boys took snuff regularly. Use of oral snuff is also widespread in Denmark. Estimates of the number of current users of smokeless tobacco worldwide range from 7 million to 22 million.

Recently, oral tobacco products such as *Skoal Bandits* have appeared on the market. These fine-cut, moist tobacco mixtures are placed in tea-bag-like containers and are sold in varying strengths of nicotine, from mild to strong, with a choice of flavourings. The packagings, logos and advertising of these products are directed toward young male users, although this intention is denied by the industry. These products are aggressively advertised, and their use associated with sports figures, thereby implying that they pose no threat to health and may be a good substitute for cigarette smoking in areas where smoking is prohibited.

The tobacco industry promotes tobacco chewing as a recreational activity by sponsoring spitting contests, shirts and clubs. A "Western cowboy" image of masculinity is projected in advertising that links tobacco chewing and western clothes. Free samples of

chewing tobacco are distributed at colleges, and commercial advertisements feature celebrities extolling the virtues of chewing tobacco.

Use of oral tobacco has increased rapidly among young males in the United States, mainly in the south, with estimates of up to 17% of boys aged 11-15 years regularly using this type of tobacco product. In some countries, imports of these products are prohibited; for example, smokeless tobacco products cannot be sold in Hong Kong.

In most countries, however, the legal definition of tobacco products is loose enough to include any product made, at least in part, from *Nicotiana tabacum* L. Of the countries of the European Economic Community, only Ireland has instituted a ban on sales of oral smokeless tobacco products.

Constitutents of tobacco smoke

The burning of tobacco products yields mainstream smoke and sidestream smoke. Mainstream smoke is generated in the burning cone and hot zones during puff-drawing, travels through the tobacco column and exits from the mouthpiece. Sidestream smoke forms in between puff-drawing and is emitted into the air freely from the smouldering tobacco product.

Tobacco smoke contains more than 3900 chemical constituents. Examples of smoke components from various chemical classes that have been found in tobacco smoke and studied in the laboratory for toxicity, including carcinogenicity, are listed in Annex 1; concentrations may range from nanograms to milligrams per cigarette. Many of these components have been evaluated for carcinogenicity by IARC working groups (Annex 2).

Tobacco smoke's major toxic effects, other than cancer, are caused by the presence in tobacco smoke of carbon monoxide, nitrogen oxides, ammonia, hydrogen cyanide and acrolein.

The majority of the mutagenic and carcinogenic agents reside in the particulate phase. Tar is not a separate agent but is defined as that portion of cigarette smoke retained on a special filter, minus water and nicotine. Tar is a complex mixture of hundreds or thousands of chemicals, many of which can cause cancer in laboratory animals. Some of these are listed in Annex 2.

Nonsmokers are exposed, during involuntary smoking, to effluents comprising both sidestream smoke and mainstream smoke expelled by active smokers. Although sidestream smoke is considerably diluted in the air, and mainstream smoke is inhaled almost undiluted, sidestream smoke has been shown to contain greater amounts of identified carcinogens than mainstream smoke. Table 1 gives the ratio of the relative distribution of selected compounds in sidestream:mainstream smoke. Although Table 1 is based on data for nonfilter cigarettes, comparable tar and nicotine levels have been found in sidestream smoke from medium-tar, low-tar, and ultra-low-tar cigarettes.

Constituents of smokeless tobacco

At least 2500 chemical constituents have been identified in unburnt tobacco. This number includes the tobacco constituents themselves, as well as chemicals applied to tobacco during cultivation, harvesting and processing. The classes of compounds identified in tobacco include all of the major types of organic chemical. Some of the compounds reported in unburnt processed tobacco have been evaluated by IARC working groups (Annex 3). The concentrations of these constituents vary widely, depending on the tobacco product.

The tobacco-specific *N*-nitrosamines — *N'*-nitrosonornicotine (*NNN*), *NNK*, *N'*-nitrosoanatabine (*NAT*) and *N*-nitrosoanabasine (*NAB*) — are the only identified carcinogens that occur in mg/kg concentrations. Microgram per kilogram levels of some carcinogenic polynuclear aromatic hydrocarbons and metal compounds and of the α-emitting polonium-210 have also been detected.

Processed tobacco contains 27 volatile amines, 11 aromatic amines and more than 50 *N*-heterocyclic compounds, such as pyrroles, pyrrolidines, imidazoles, pyridines and pyrazines. Of special relevance to tobacco carcinogenesis are secondary amines, which can give rise to *N*-nitrosamines during curing, fermentation and aging. Nitrogen-containing compounds, including nitrates, amines, amides and proteins, comprise up to 24% of cured and fermented tobaccos, from which many smokeless tobacco products are made. Some of these compounds are known precursors of *N*-nitrosamines. A large number of studies have shown that, during the aging, curing, fermentation and processing of tobacco, nicotine and other alkaloids give rise to carcinogenic, tobacco-specific *N*-nitrosamines. The concentration of these compounds in tobacco exceeds by at least 100-fold the concentrations found so far in other products, such as cured meat, whisky and beer. It has been calculated that, in the United States, cigarette smoking gives rise to at least a 20-fold greater daily exposure to *N*-nitroso compounds than any other product.

Table 1. Ratios of the relative distribution in sidestream:mainstream smoke of selected compounds in nonfilter cigarettes

Compounds	Sidestream:mainstream
Vapour phase	
Acetic acid	1.9-3.9
Acetone	2-5
Acrolein	8-15
Ammonia	40-170
Benzene	10
Carbon dioxide	8-11
Carbon monoxide	2.5-4.7
Carbonyl sulphide	0.03-0.13
Dimethylamine	3.7-5.1
Formic acid	1.4-1.6
Formaldehyde	0.1-≃50
Hydrazine	3.0
Hydrogen cyanide	0.1-0.25
Methylamine	4.2-6.4
Nitrogen oxides	4-10
N-Nitrosodimethylamine	20-100
N-Nitrosophyrrolidine	6-30
Pyridine	7-20
Toluene	6-8
3-Vinylpyridine	20-40
Particulate phase	
Particulate matter	1.3-1.9
4-Aminobiphenyl	31
Anatabine	0.1-0.5
Aniline	30
Benz[*a*]anthracene	2.2-4
Benzoic acid	0.67-0.95
Benzo[*a*]pyrene	2.5-3.5
γ-Butyrolactone	3.6-5.0
Cadmium	3.6-7.2
Catechol	0.6-0.9
Cholesterol	0.9
Glycolic acid	0.6-0.95
Harman	0.7-1.9
Hydroquinone	0.7-0.9
Lactic acid	0.5-0.7
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	1-4
2-Naphthylamine	30
Nickel	0.2-30
Nicotine	1.8-3.3
N-Nitrosodiethanolamine	1.2
N-Nitrosonornicotine	0.5-3
Phenol	1.6-3.0
Polonium-210	1.06-3.7
Quinoline	8-11
Succinic acid	0.43-0.62
ortho-Toluidine	19
Zinc	0.2-6.7

However, since the relative concentration of *NNN*, *NNK* and *NAT* in chewing tobacco is much higher than in cigarette smoke, and since the average chewer consumes 10 g of tobacco versus >1 g tar inhaled by the smoker, tobacco chewing appears to be the greatest exogenous source of exposure to *N*-nitrosamines.

Methods for analysing tobacco smoke

Biochemical methods make it possible to measure exposure to tobacco smoke by determining the levels of certain tobacco smoke constitutents in physiological fluids (e.g. blood, urine) of active smokers and of passive smokers. At present, the best available method for monitoring passive smoking is the measuring of cotinine, the major metabolite of nicotine, in urine. Efforts to standardize methods for measuring tobacco smoke in indoor air have been intensified in recent years, due to the need for accurate data on exposure levels, especially in epidemiological studies of the possible carcinogenic effects of passive smoking (see p. 21). A manual in which all such methods are collected is found in the publication by O'Neill et al.

2

Tobacco Use and Cancer in Humans

Tobacco smoking and cancer

In 1950 five papers appeared in the United Kingdom and the United States describing studies in which the smoking habits of large numbers of patients with cancer of the lung or, in some studies, with cancers of the mouth, pharynx or larynx, were compared with the smoking habits of control patients. One of these studies (Doll & Hill, 1950) concluded that "smoking is a factor, and an important factor, in the production of carcinoma of the lung". At that point the modern era of the study of the health effects of tobacco had begun.

The obvious way to check the conclusions drawn from these studies was to record the smoking habits of large numbers of men and women who smoked different amounts and to follow these subjects over several years to find whether the recorded habits would serve to predict the risk of developing disease. This method, moreover, allowed for study not only of the relationship between smoking and lung cancer, but also of that between smoking and other types of cancer and all other diseases common enough for a substantial number of cases to have occurred within the period of observation.

Many such studies have now been carried out, eight of which cover enough individuals for a long enough period for useful information to be obtained about a wide range of diseases. The design of these studies is summarized in Table 2. On the basis of these and of other smaller studies, conclusions can be drawn about the strength of the association between smoking and cancers at different sites.

Lung cancer

Lung cancer is believed to be the most common fatal neoplastic disease in the world today, and the overall pattern is one of rapid increase. Three factors contribute to this continuing increase. First, especially for old people, increased access to diagnosis and progressive improvements in the accuracy of certification of cause of death mean that an increasing proportion of fatal lung cancers are recognized as such. Second, the absolute

Table 2. Main characteristics of major cohort studies on the relationship between smoking and cancer

Study	Year of enrolment	Sample size: initial samples[a]	Duration of follow-up and number of deaths	Completeness of follow-up for mortality
American Cancer Society nine-state study	1952	204 547 men [187 783]	44 months 11 870 deaths	98.9%
Canadian study	1955-1956	207 397 subjects (aged 30+) [92 000]	6 years 9491 deaths in men; 1794 deaths in women	Not available
British doctors study	1951	34 440 men (aged 20+)	20 years 10 072 deaths	99.7%
		6194 women (aged 20+)	22 years 1094 deaths	99%
American Cancer Society 25-state study	1959-1960	1 078 894 subjects First follow-up: 440 558 men, 562 671 women (aged 35-84); second follow-up: 358 422 men 483 519 women	4.5-5 years 26 448 deaths in men; 16 773 deaths in women	97.4% women 97.9% men in first follow-up
US Veterans study	1954	293 958 men (aged 31-84) [248 046]	16 years 107 563 deaths	almost 100% ascertainment of vital status; 97.6% of death certificates retrieved
California study	1954-1957	68 153 men (aged 35-64)	5-8 years 4706 deaths	Not available
Swedish study	1963	27 342 men, 27 732 women (aged 18-69)	10 years 5655 deaths (2968 autopsies)	Not available
Japanese study	1965	122 261 men, 142 857 women (aged 40+)	16 years 51 422 deaths	Total

[a] Figures in square brackets are population figures for follow-up.

Source: IARC (1986).

size of the world population of adults old enough to be at risk of developing the disease is increasing rapidly. Finally, and most importantly, large increases in the numbers of people smoking cigarettes have produced - and are producing - large, real increases in age-specific lung cancer rates. Most of this increase is the delayed result of the large growth in cigarette smoking by young adults occurring in the second half of this century.

Tobacco smoking causes most cases of lung cancer and, in populations where prolonged widespread cigarette smoking began several decades ago, generally accounts for more than 80% of this disease (and for more than 90% in men). In populations in which the effect of smoking has yet to peak - among young adults and most female populations - the proportion may currently be lower.

The high proportion of lung cancer cases due to smoking does not preclude the possibility that other carcinogenic factors also contribute to the total burden. For example, in populations which experienced heavy industrial development during this century, joint exposure to tobacco smoke and occupational carcinogens may account for up to 10-30% of all cases of lung cancer.

The observed relationship between tobacco smoking and the incidence of lung cancer appears to depend on four factors.

1. *The daily dose of tobacco.* Findings consistently show that, among otherwise similar cigarette smokers, a direct, often linear, relationship exists between the daily dose and the excess risk of lung cancer in both men and women. This relationship is illustrated for men by the results of the major studies shown in Table 3.

2. *The duration of regular smoking.* Because damage to the lung accumulates with continual smoking, the incidence of lung cancer depends strongly on the duration of smoking. So, people who start to smoke in adolescence and who continue to smoke as adults are at the greatest risk of developing lung cancer in adult life. The relationship between age of starting regular cigarette smoking and lung cancer death rates at the age of 55-64 years is shown in Fig. 2 for men in the United States. Studies in many countries show a delay of several decades between the widespread adoption of cigarette smoking by young adults and the emergence of its full effects on national lung cancer rates.

Even among people who have been smoking for many years, those who have not already developed lung cancer (or some other disease) can, by ceasing to smoke, avoid most of their subsequent lifelong risk of tobacco-induced lung cancer. When smoking ceases, the annual excess risk of developing lung cancer appears to remain (to within a factor of about two) roughly constant for many years thereafter. Thus, after 15 years'

Table 3. Dose-response relationship between the amount smoked and risk of lung cancer in men in some cohort studies

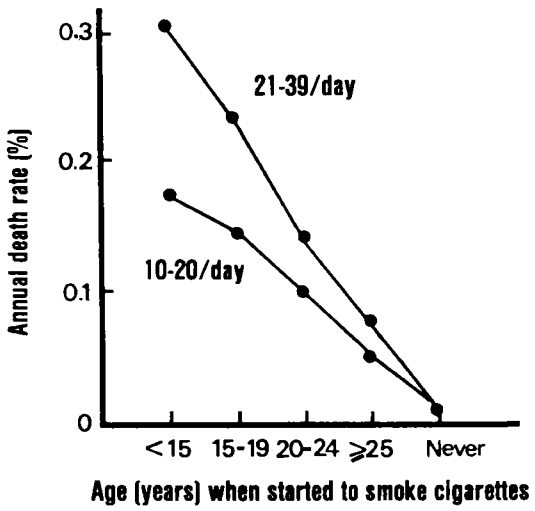
Study	Smoking category	Relative risk	Death rate per 100 000	No. of cases
American Cancer Society nine-state study	(No of packs/day)		[a]	
	0	1.0	12 8	15
	0.5	7.4	95.2	24
	0.5-1	8.4	197.8	84
	1-2	17.9	229.2	90
	2	20.6	264.2	27
Canadian study	(No. of cigarettes/day)	[a]		
	0	1.0		
	1-9	10.0		57
	10-20	16 4		204
	21+	17.3		63
British doctors study	(No. of cigarettes/day)	[a]		
	0	1.0	10	
	1-14	7.8	78	
	15-24	12.7	127	
	25+	25.1	251	
American Cancer Society 25-state study	(No of cigarettes/day)	[a]	[a]	
	0	1.0	12	49
	1-9	4.6	56	26
	10-19	7.5	90	82
	20-39	13.1	159	381
	40+	16.6	201	82
US Veterans study	(No of cigarettes/day)	[a]		
	0	1.0		
	1-9	3.9		
	10-20	9.6		
	21-39	16.7		
	40+	23.7		
California study	(No. of packs/day)	[a]		
	0	1.0		
	about 1/2 or less	3.7		
	about 1	9.1		
	about 1 1/2 or more	9.6		
Swedish study		[a]		
	nonsmokers	1.0		7
	cigarettes only:			
	1-7 per day	2.3		4
	8-15 per day	8.8		11
	16+ per day	13.9		13
	pipe tobacco only:			
	<6 g per day	2.9		4
	>6 g per day	9.1		27
Japanese study	(No. of cigarettes/day)	[a]		
	0	1.0	23.0	80
	1-9	2.3	49.6	74
	10-19	4.0	93.2	486
	20-29	5.9	137.0	464
	30-39	6.1	141 3	52
	40-49	7.2	170.0	28
	50+	15.2	352.6	12
Norwegian study	(No. of cigarettes/day)	[a]		
	0	1.0		7
	1-9	6.0		19
	10-19	9.9		31
	20+	18.2		20

[a] Figures given in original report

Source: IARC (1986).

smoking, the annual excess incidence of lung cancer is approximately 0.005%, or 5 per 100 000; after 30 years' smoking, it is about 0.1%, or 1 per 1000; and after 45 years' smoking, it is about 0.5%, or 5 per 1000. If a smoker stops after 30 years' smoking, 15 years later the annual excess risk may still be about 0.1%, instead of 0.5% if smoking had continued. Stopping avoids about 80% of the excess risk that would have accrued with continued smoking.

Fig. 2. Relationship between age of starting regular cigarette smoking in early adult life and lung cancer death rates at age 55-64 (mean 60) for men in the United States; data presented separately for heavy and for moderate smokers



Source: Doll and Peto (1981).

3. *The form in which tobacco is smoked (cigarettes, cigars, pipes).* Findings generally show that, among otherwise similar smokers, those who used only cigarettes have lung cancer risks much higher than those who used only pipes and/or cigars, although pipe and cigar smoking cause some appreciable risk. The estimated risk in pipe and cigar smokers appears to be intermediate between the risks in cigarette smokers and those in nonsmokers. These findings are illustrated in Table 4.

4. *The type of cigarette smoked.* Soon after the lung cancer risks from smoking (especially cigarette smoking) were first established during the 1950s, substantial modifications in cigarette manufacturing were introduced in some countries. At present, only about 20 years after introducing these modifications, no direct comparison of the health effects of lifelong use of modified and unmodified cigarettes is possible. Therefore, other types of evidence relating to this question are examined. However, although adequate cohort studies are not yet available to assess whether changes in the composition of cigarettes (e.g. use of filters, reduction in tar level) have modified the risk of lung cancer from *prolonged* use of such cigarettes, some conclusions can be drawn from available data.

Thus, in one large cohort study, cigarettes delivering less than 17.6 mg of tar were associated with a lower risk for lung cancer than were those delivering more than 25.7 mg of tar. In other epidemiological studies, there was a fairly consistent tendency for lung cancer risks to be lower among users of filter than of nonfilter cigarettes. The reduction seen in the largest and most recent study was about 40-50%, which was statistically highly significant. In that study, tar yields were also recorded and found to be positively associated with lung cancer risk.

In a few countries where changes in cigarette design and composition began in the late 1950s or early 1960s, cigarette smoking by young men had been established so many years previously that some of the lung cancer rates in men in early middle age had largely or wholly completed their rise by 1960, and might have been expected to remain approximately constant thereafter if the risk per cigarette had remained constant. However, a few years after the significant changes in cigarette manufacturing (associated with reductions in tar levels), a decrease in lung cancer rates began to appear in these particular age groups.

Cancer of the urinary tract

Cancers of the lower urinary tract (renal pelvis, ureter, bladder and urethra), and specifically of the bladder and renal pelvis, have been consistently associated with cigarette smoking in the major cohort studies described in Table 2 and in many case-control

Table 4. Relative risk of lung cancer in some large cohort studies among men smoking cigarettes and other types of tobacco

Study	Smoking category	Relative risk	Death rate per 100 000	Number of cases
American Cancer Society nine-state study			a	
	Never smoked	1.0	12.8	15
	Only occasionally	1.5	19.2	8
	Cigarettes only	9.9	127.2	249
	Cigars only	1.0	13.1	7
	Pipe only	3.0	38.5	18
	Cigarettes and other	7.6	97.7	148
	Cigars and pipe	0.6	7.3	3
Canadian study	Nonsmokers	1.0	10	
	Cigarettes only	14.9		325
	Cigars only	2.9		2
	Pipes only	4.4		18
	Ex-smokers	6.1		18
British doctors study	Nonsmokers	1.0		7
	Current smokers	10.4	104	
	Cigarettes only	14.0	140	
	Pipe and/or cigar only	5.8	58	
	Cigarettes and other	8.2	82	
	Ex-smokers	4.3	43	
American Cancer Society 25-state study			a	a
	Never smoked	1.0	12	49
	Cigarettes only	9.2	111	719
	Cigars only	1.9	22	23
	Pipe only	2.2	27	21
	Cigarettes and other	7.4	89	336
	Cigars and pipe	0.9	11	11
US Veterans study		a		
	Nonsmokers	1.0		
	Cigarettes	11.3		2609
	Cigarettes only	12.1		1095
	Cigars only	1.7		41
	Pipe only	2.1		32
	Ex-smokers (cigarettes)	4.0		517
Swedish study		a		
	Nonsmokers	1.0		7
	Cigarettes only	7.0		28
	Cigarettes and pipe	10.9		27
	Pipe only	7.1		31
	Cigars only	9.2		6
	Ex-smokers	6.1		12
Norwegian study		a		
	Nonsmokers	1.0		7
	Cigarettes	9.7		88
	Cigarettes only	9.5		70
	Pipe or cigars only	2.6		12
	Ex-smokers	2.8		11

[a] Figures given in original report.

Source: IARC (1986).

studies in various parts of the world. These studies generally show a dose-response relationship for men, with risks for those smoking the largest number of cigarettes per day being about five times greater than those for nonsmokers. Such conclusions could not be drawn with regard to women, due to smaller case numbers and less prolonged smoking.

Duration of cigarette smoking was shown to be directly related to the risk for bladder cancer in men in the few studies in which this aspect was examined. When cancers of the renal pelvis and of the ureter were considered separately, a dose-response relationship with daily or cumulative consumption of tobacco was found, with risks generally higher than those for cancer of the bladder. Pipe smoking and cigar smoking probably also increase the risk for bladder cancer, but at lower levels than the risk due to cigarette smoking.

As for cancer of the lung, a lowering of risk for cancers of the lower urinary tract after stopping smoking has been seen in cohort studies carried out in many countries. The risk of ex-smokers thus approximates that of nonsmokers more than 15 years after giving up smoking.

Several studies have also shown an association between cancer of the kidney and cigarette smoking.

The proportion of bladder cancers in the general population that can be attributed to cigarette smoking has been calculated in several countries' studies. These studies show that, in most countries with a history of prolonged cigarette use, 50% of male cases and 25% of female cases of bladder cancer are attributable to smoking. No other factor, such as occupation, which has been independently important, has been shown to account for this association.

Cancers at other sites

Tobacco smoking is an important cause of oral, oropharyngeal, hypopharyngeal, laryngeal and oesophageal cancers, and the risk increases with increasing tobacco use. The risk grows substantially when cigarette smoking is combined with heavy consumption of alcohol. Pipe smoking and cigar smoking appear to increase the risk for these cancers to approximately the same extent as cigarette smoking does. Tobacco smokers also appear to run increased risks of cancer of the lip.

Epidemiological studies of various types consistently point to tobacco smoking as an important cause of pancreatic cancer. No other factor that could explain this relationship has been identified.

The higher risks seen among tobacco smokers for cancers of the stomach, liver and cervix cannot be attributed with certainty to smoking, since in none of the studies has it been possible to rule out the possibility of confounding that other factors that are associated with smoking and responsible for the increase.

For cancer of the endometrium, many studies have shown slightly lower risks for women who smoke cigarettes. This weak negative association may be related to the detrimental effect of smoking in reducing the age at which menopause occurs, and does not provide any material advantage to smokers. With regard to breast cancer, a number of studies have shown no consistent effect of smoking on risk.

Interactions with other factors in causing cancer

Studies of tobacco smokers exposed also to certain other agents show that tobacco-smoking segments of the population run risks of cancer substantially greater than risks experienced by the general population. Most prominent among these groups are alcohol drinkers, workers exposed to asbestos and persons exposed to ionizing radiation in uranium mines. For each of these agents, exposures have been shown to interact almost multiplicatively with smoking increasing the risk for cancer.

The enhancement of risk by alcohol drinking is dose-dependent, and the risk, relative to that for nonsmoking nondrinkers, increases almost multiplicatively with an increasing level of alcohol consumption. This relationship is observed for cancer of the oral cavity, oropharynx, hypopharynx and oesophagus.

The pattern that emerges from studies of asbestos workers is of an interaction between occupational exposure to asbestos varieties and tobacco smoking. In insulators, the joint effect is multiplicative. A multiplicative effect with cigarette smoking was also seen for uranium miners exposed to radioactive alpha emissions in underground mines in the United States.

Tobacco habits other than smoking

The oral and nasal use of tobacco, either finely powdered as snuff or in leaf form for chewing, is as old as its use for smoking in pipes, cigars and cigarettes. In the first half

of the twentieth century, the use of chewing tobacco and snuff in the western hemisphere was overtaken by a huge increase in the use of smoking tobacco. In some parts of the world, however, including the Indian subcontinent, south-east Asia and much of the Middle East, smokeless tobacco is still widely used. Additionally, chewing tobacco and snuff have enjoyed a renaissance in western countries during recent years.

Epidemiological studies carried out in Europe and North America clearly show that the use of smokeless tobacco products is associated with an increased risk for contracting cancer of the mouth. Since the design of these studies differs widely, it would be cumbersome to try to tabulate them using the method applied to the studies of tobacco smoking. However, certain clear associations emerge. Although in most of the studies no distinction was made between chewing tobacco and snuff, it must be remembered that the difference between the two is blurred, as noted above, relating mainly to the fineness of the product. Moreover, categorization of the two types has changed recently, at least in the United States. Thus, chewing tobacco is described as such in only a few studies. Oral use of snuff, on the other hand, has been related consistently with cancers of the oral cavity and pharynx. In addition, cancers frequently developed at the site at which snuff was habitually applied.

Studies that have not distinguished snuff from chewing tobacco are informative for three reasons, when considered with the other studies. Reports of series of oral cancer cases confirm the high relative frequency of use of smokeless tobacco products among such patients; other studies report that use of smokeless tobacco is moderately to strongly associated with oral cancer. A dose-response relationship was found in one large study, in which the risks for oral cancer in men ranged from four-fold for moderate use of smokeless tobacco to more than six-fold with heavy use. Two large studies provide evidence of a positive association with cancer. One study showed a two-fold to three-fold increase in risk of death from oral, pharyngeal and oesophageal cancer; the second study indicated a similar increase from oesophageal cancer.

Two large studies from Pakistan and India report substantial increases in the risk for oral cancer related to the chewing of tobacco mixed with lime (*khaini*). The chewing of similar preparations in the Middle East (*shammah* and *nass*) was found to be associated with the development of oral cancer at the site at which the preparation was habitually placed. Numerous studies have identified an association between oral cancer and the habit of chewing betel quid (a mixture of betel leaf and areca nut) containing tobacco. The association has been consistent across many countries, including Bangladesh, China (Taiwan), India, Malaysia, Pakistan, the Philippines, Singapore, Sri Lanka and Thailand. Sri Lanka reported a significant association between the chewing of betel quid containing tobacco and oesophageal cancer.

Involuntary smoking and cancer

Tobacco smoke affects not only people who smoke but also people who are exposed to the combustion products of other people's tobacco. As described above, the constituents of smoke vary according to its source. Three main sources exist: mainstream smoke, sidestream smoke and smoke exhaled into the general atmosphere by smokers. Smokers are exposed to all three to a greater extent than are nonsmokers. However, toxic and carcinogenic agents have been identified at higher concentrations in sidestream smoke than in mainstream smoke, and such agents have also been identified in the ambient air of indoor environments. Any effect seen in passive smokers will of course reflect larger similar effects in smokers. Correspondingly, effects not seen in smokers will not be seen in passive smokers. That passive smoking gives rise to an increased risk of cancer is a conclusion based on the nature of sidestream and mainstream smoke, the materials absorbed during passive smoking and the quantitative relationships between dose and effect commonly observed after exposure to carcinogens.

This conclusion is also supported by several epidemiological studies indicating that a causal relationship between passive smoking and cancer is likely to exist, although the size of the effect under different circumstances of exposure remains to be estimated accurately. The currently available evidence is composed of 11 case-control and three cohort studies. The main characteristics of these studies are outlined in Table 5. All the studies involve subjects reported to be lifelong nonsmokers who were either exposed involuntarily or not exposed to tobacco smoke. The exposure was defined in terms of the subject living with a smoker, usually a smoking spouse. The studies involved observation of 1145 lung cancer cases, most of whom (1010, 88%) were women.

The combined results of the 14 reports show a statistically significant increase in risk for lung cancer among nonsmokers involuntarily exposed to tobacco smoke. In six studies, data are given on the quantitative relationships between number of cigarettes per day smoked by the spouse and the risk for lung cancer. In four of the six studies, a positive trend is visible. Moreover, positive trends have appeared for other indexes of exposure, such as total number of cigarettes or pack-years smoked by spouse and number of hours per day of involuntary exposure to tobacco smoke. The best estimate that the available studies provide for the increased risk of lung cancer in nonsmoking women involuntarily exposed to smoke, as compared with unexposed nonsmokers, is in the range 20-55%.

Both the widespread distribution of the exposure and its involuntary nature argue in favour of regulatory and legislative action, in line with accepted public health principles for the management of involuntary risks.

Table 5. Main characteristics of epidemiological studies on the relationship between involuntary smoking and lung cancer in nonsmokers

Case-control studies

Reference	Study country	Sex	Lung cancers		Controls		Respondent	Histology/Cytology	
			Exposed	Not exposed	Exposed	Not exposed		% Confirmed	% Adenocarcinoma
Chan & Fung (1982)	Hong Kong	F	34	50	66	73	Self	82	45
Correa et al. (1983)	USA	F	14	8	61	72	Self or proxy	97	54 (F)
		M	2	6	26	154	Self or proxy		
Trichopoulos et al. (1983)	Greece	F	38	24	81	109	Self	65	none
Buffler et al. (1984)	USA	F	33	8	164	32	Self or proxy	100	?
		M	5	6	56	34		100	55
Kabat & Wynder (1984)	USA	F	13	11	15	10	Self	100	74 (F)
		M	5	7	5	7	Self		54 (M)
Garfinkel et al. (1985)	USA	F	91	43	254	148	Self or proxy	100	65
Akiba et al. (1986)	Japan	F	73	21	188	82	Self or proxy	57	?
		M	3	16	9	101	Self or proxy		
Lee et al. (1986)	England	F	22	10	45	21	Self & spouse	?	?
		M	8	7	14	16	Self & spouse		
Koo et al. (1986)	Hong Kong	F	51	35	66	70	Self	97	59
Pershagen et al. (1986)	Sweden	F	33	34	150	197	Self or proxy	99	57
Humble et al. (1987)	USA	F	15	5	91	71	Self or proxy	?	?
Overall			440	291	1291	1197			

Cohort studies of ETS

Reference	Study country	Sex	Lung cancers		Controls		Respondent	Histology/Cytology	
			Exposed	Not exposed	Exposed	Not exposed		% Confirmed	% Adenocarcinoma
Garfinkel (1981)	USA	F	88	65	127 164	49 422	Self or proxy	None	?
Gillis et al. (1984)	Scotland	F	6	2	1 388	521	Self	?	?
		M	4	2	306	515	Self	?	?
Hirayama et al. (1984)	Japan	F	146	37	63 287	21 858	Self	None	?
		M	7	57	1 003	19 222	Self	None	?
Overall			251	163	193 148	91 538			

Source: Saracci & Riboli (1988).

3

Cigarette Smoking and Cardiovascular Diseases

Cigarette smoking is a major cause of cardiovascular diseases among men as well as women. Numerous investigations carried out since the mid-1950s have documented higher rates of these diseases and earlier mortality among cigarette smokers than among nonsmokers. Cigarette smoking contributes to the development of atherosclerotic lesions, the predominant underlying cause of cardiovascular diseases, and to the clinical manifestations of atherosclerotic vascular disease - coronary, cerebral, aortic and peripheral vascular disease, and sudden death.

Representative world studies on cardiovascular diseases

The major epidemiological studies that have implicated cigarette smoking in exacerbating the risk for coronary heart disease in various countries are summarized in Table 6.

The study of US military veterans spans a period when both cigarette smoking and the incidence of coronary heart disease were rising. The risk of dying from such disease was 58% higher for smokers than for nonsmokers for the period 1953-1969.

The American Cancer Society studies of huge populations of volunteers (followed for four years) yielded detailed information on types of tobacco used, number of cigarettes smoked daily, age at which smoking began, inhalation practices and other variables that might influence mortality. Compared with death rates among nonsmokers, 46% and 41% more deaths occurred among male and female smokers, respectively.

Canadian veterans and Californians in a wide range of occupations had similar hazards due to smoking.

In the Japanese study, the proportions of mortality from coronary heart disease among smokers were 34.3% for men and 9.5% for women. Among the male British physicians followed for 20 years, the risk for coronary heart disease was found to be 62%

Table 6. Age-adjusted relative risks of death from coronary heart disease in major cohort studies on the effects of tobacco smoking[a]

Study	Number of deaths	Relative risk of death[b]
American Cancer Society nine-state study	34 874 men	1.58
Canadian study	3 405 men	1.60
British doctors study	3 191 men	1.62
	179 women	2.00
American Cancer Society 25-state study	10 771 men	1.24-2.81[c]
	4 048 women	1.19-2.00[c]
US Veterans study	34 874 men	1.58
California study	1 718 men	1.60
Swedish study	916 men	1.70
	457 women	1.30
Japanese study	3 351 men	1.71
	2 653 women	1.78
Swiss doctors study[d]	280 men	1.33-2.18

[a] The design of the studies is outlined in Table 2.
[b] Taking the relative risk for nonsmokers as 1.00.
[c] Two follow-ups.
[d] 3749 men followed up for 18 years.

Source: Paffenbarger et al. (1986).

higher for cigarette smokers. The risk for female British physicians who smoked 15 or more cigarettes daily was more than double that for nonsmokers. In the Swedish study, overall mortality from coronary heart disease was 70% higher for male cigarette smokers and 30% higher for female cigarette smokers than for nonsmokers. Data on Swiss physicians showed that mortality rates increased with dose (cigarettes smoked per day), rising by 33% for up to 10 per day and by up to 118% for 35 or more per day, as compared to the rate for nonsmokers. This pattern is corroborated in each of the studies listed in Table 6.

The dose-response effects are consistent, as indicated not only by the number of cigarettes smoked per day but also by data on inhalation, use of filters, age when starting to smoke, years of smoking, cessation of smoking and risks to nonsmokers in the vicinity of smokers. The dose-dependent influence of cigarette smoking on the risk for coronary heart disease is considered to be strong evidence that the relationship between cigarette smoking and coronary heart disease is causal.

The epidemiological evidence linking cigarette smoking and cardiovascular diseases is reinforced by findings that smoking aggravates and accelerates the development of the underlying lesions and occlusive events in coronary, cerebral and peripheral arteries. Many studies have shown more severe atherosclerotic changes in smokers than in nonsmokers and a concomitant increase in the degree of pathological arterial changes with the amount of cigarette smoking. In addition, some evidence exists to incriminate smoking in altering the serum lipoprotein profile in ways that increase the development of atherosclerosis, such as reduction of the high-density lipoprotein cholesterol. Smoking affects the haemostatic system by decreasing platelet survival time and increasing platelet stickiness and tendency to aggregate. The many gaseous components of cigarette smoke have complex pharmacological and toxic effects that alter metabolism, reduce oxygen transport, lower the threshold of ventricular fibrillation and promote the atherosclerotic process.

Influences of interactions with other factors on cardiovascular disease

Male university graduates

A study of cigarette smoking habits, other living habits and health status among male university graduates in the United States has shown how past and present characteristics relate to risk for cardiovascular disease in middle and later life. Data on 16 936 former students aged 35-74 years and initially free of coronary heart disease who had entered Harvard University in the period 1916-1950 were reviewed for personal characteristics, including cigarette smoking. The data were obtained from the university archives on students' health and from postal questionnaires answered in 1962 and 1966 by these former students. Follow-up data on nonfatal coronary heart disease were obtained from questionnaires posted in 1972, and data for fatal cardiovascular disease from official death certificates through 1978.

During the follow-up intervals 1966-1972 and 1962-1972, the risk for having an attack of coronary heart disease was 68% higher for smokers than for nonsmokers. Follow-up of fatal cases showed that the excess risks of smokers compared to nonsmokers for dying from cardiovascular diseases were 77% for all such diseases, 78% for coronary heart disease, 52% for stroke and 100% (double) for other cardiovascular diseases. The risks were shown to be related to the level of cigarette smoking. For coronary heart disease, as the number of cigarettes smoked per day increases from none to 20 or more, a gradient increase in risk to smokers over nonsmokers is seen, ranging steadily upwards to nearly

double (82%), in an evidently dose-dependent trend. Ex-smokers have a slightly higher risk than nonsmokers.

The relationship between cigarette smoking and other characteristics was also investigated. These characteristics included blood pressure, physical activity, body weight:height ratio and parental history of coronary heart disease.

The risks for coronary heart disease in ten years of follow-up and of fatal cardiovascular disease in 16 years of follow-up, using selected characteristics predisposed to produce these outcomes, are as follows.

- After allowance for each variable, cigarette smokers were found to be at a 67% greater risk of coronary heart disease, nonfatal or fatal, than were nonsmokers.
- Hypertensive men had twice the risk of those with normal blood pressure.
- Sedentary subjects were at a 38% higher risk than men more physically active.
- Heavier men were at a 23% greater risk than leaner men.
- Finally, subjects with an adverse parental history of coronary heart disease had a 20% greater risk of developing the disease themselves than did classmates whose parents had been free from such affliction.

Estimates of the risks for the corresponding characteristics suggest that cigarette smoking might account for 21% of the coronary heart disease among these subjects; hypertension, 8%; sedentary living, 19%; overweight, 8%; and the genetic or familial tendencies implied by parental history of coronary heart disease, a further 7%. If all of these factors could have been avoided, there might have been one half as many attacks of coronary heart disease.

Women smokers

A study of cigarette smoking on nonfatal myocardial infarction in 555 women aged 25-49 years living in north-eastern United States provides new evidence on dose-response and interaction with other personal characteristics known or suspected to predispose to infarction. Estimates of risk increased steadily from 40% for smokers of 1-14 cigarettes per day, to 140% for those using 15-24 cigarettes, to 400% for use of 25-34, to 700% for smokers of 35 or more cigarettes daily. Among former smokers who had abstained for at least one year, the risks were the same as for women who has never smoked.

The risk for myocardial infarction among current users of oral contraceptives was 23 times greater for heavy smokers than for nonsmokers. When compared on the basis of serum cholesterol level, female heavy smokers had five times the risk of nonsmokers with the same level of cholesterol. Furthermore, the risk of myocardial infarction among women was higher for smokers than for nonsmokers, regardless of whether they had such predisposing characteristics as hypertension, agina pectoris, diabetes, obesity, a tendency to time-urgency and competitiveness (so-called type A behaviour) and an adverse history of cardiovascular disease in a parent or sibling.

Elderly smokers

Among 2674 elderly white men in an impoverished urban setting, current cigarette smokers were at 52% higher risk for fatal coronary heart attack during the five years of follow-up. The excess risk for mortality declined within one to five years of giving up smoking.

Filter cigarettes

In a large United States study, men were classified as to whether they smoked filter or nonfilter cigarettes. The 58% of men who used filtered brands had been smoking for a shorter period than the comparison group, but, despite this more favourable history, their incidence rates of coronary heart disease over 14 years of follow-up did not differ from that of users of unfiltered cigarettes. Thus, no evidence exists showing that filter cigarettes of the 1960s and 1970s conferred any protection against coronary heart disease for these men. This may not be unexpected, since smokers may alter their smoking behaviour when they switch to low-yield brands, in order to compensate for nicotine loss. This modified smoking behaviour may induce accelerated atherogenesis through increased uptake of carbon monoxide, hydrogen cyanide and nitrous oxides.

Passive smoking and cardiovascular disease

Nonsmoking patients with angina pectoris exposed in a confined space to the cigarette smoke of others have been shown to experience increased serum levels of carboxyhaemoglobin, coronary symptomatology and electrographic changes indicative of myocardial ischaemia. In ten years of follow-up of nonsmoking wives of former and current

smokers, an elevated death rate from coronary heart disease was seen when compared to nonsmoking wives of men who have never smoked. A dose-response relationship was shown for the number of cigarettes smoked by the husband.

Cessation of smoking and cardiovascular disease

Several studies show a consistent gradient in reduction in risk for coronary heart disease as the interval since cessation of cigarette smoking increases. Men who have abandoned cigarettes for a decade or more have little if any excess risk over men who have never smoked. This benefit is seen in all age groups and for both light and heavy smokers who have dropped the habit. Among men aged 65 years and over, the percentage reduction appears to be less impressive than for younger men, aged 30-54 years; however, in view of the relationship between age and mortality from coronary heart disease, the numbers spared would be substantial. In general, the greater the risk attached to cigarette smoking, the greater the benefit, or reduction in risk, achieved by quitting the habit.

4

Tobacco Smoking and Lung Diseases other than Cancer

Comparing men smoking 20 or more cigarettes per day and lifelong nonsmokers, all of the major epidemiological studies outlined in Table 2 show ten-fold to 40-fold differences in risk of death due to chronic bronchitis and emphysema (now preferably called chronic obstructive lung disease), respiratory heart disease and aortic aneurysm. The evidence leaves no room for doubt that cigarette smoking is one of the principal causes of chronic obstructive lung disease and, in view of its relation to the latter, it must also be regarded as a cause of respiratory heart disease. Cigarette smokers of all ages also have more chest illnesses than nonsmokers; cough, expectoration and recurrent respiratory infections result in considerable absenteeism from work.

Chronic obstructive lung disease (often referred to as chronic obstructive airways disease or chronic obstructive pulmonary disease) is a significant morbidity and mortality factor in many economically developed countries. Chronic mucus hypersecretion, chronic productive cough independent of airflow limitation and previously called simple and mucopurulent bronchitis, may not itself lead to death but is important in terms of morbidity.

Chronic obstructive lung disease is as specifically related to smoking as is lung cancer. One measure of lung function, the FEV_1 — the forced expiratory volume in one second — can be reliably used to predict chronic obstructive lung disease. This measure falls gradually and irreversibly over several decades in both nonsmokers and smokers, but the range of rates of loss of FEV_1 is much wider among smokers than nonsmokers. Some smokers suffer such unusually rapid rates of loss of FEV_1 that, if they continue to smoke, they first become disabled once their FEV_1 falls to about one litre (as compared to four litres in normal subjects) and then die of their obstructive lung disease. If such people stop smoking, their subsequent rate of decline of FEV_1 usually reverts to about that seen in nonsmokers. Thus, if susceptible smokers stop smoking well before they are disabled, they can prevent much of their risk of dying from chronic obstructive lung disease.

Thus, in the study of 100 000 British doctors, the death rates (per 100 00 subjects per year) for those who smoked 1-14, 15-24 and 25 or more cigarettes per day were 51, 78 and

114 respectively. Use of filter cigarettes and low-tar levels were consistently related to lower production of sputum or phlegm in five epidemiological studies of chronic obstructive lung disease, to reduced prevalence of cough in three studies, and to less shortness of breath in two studies. Wheeze and dyspnoea were more frequent in smokers of nonfilter citgarettes than in smokers of filter cigarettes in two analyses, but were unrelated to tar level in a third. Lung function (as measured by forced vital capacity, or FEV_1) was lower on average (that is, worse) in smokers of higher-tar or nonfilter cigarettes in two studies, but was unrelated to tar level in another.

Finally, mortality from chronic bronchitis was no different in smokers of filter and nonfilter cigarettes in one study and was about the same in smokers of high-tar, high-nicotine cigarettes as compared to smokers of low-tar, low-nicotine cigarettes in another extremely large study.

In summary, there is good evidence that smoking low-yield cigarettes leads to lower phlegm production, reduced cough and less shortness of breath. Evidence is, however, conflicting for an effect of use of filter cigarettes on lung function, and no evidence supports an effect on mortality from chronic obstructive lung disease.

Cigarette smokers cough more often and produce more phlegm than do nonsmokers. Even teenagers who smoke more than five cigarettes a day cough almost as much as adult smokers. The risk increases with the number of cigarettes smoked, with an earlier starting age for smoking and with depth of inhalation. The fact that cough and phlegm usually disappear or diminish when cigarette smoking is given up shows that smoking is the main cause of these symptoms. Airways obstruction during an infective episode is often more severe in smokers than in nonsmokers. Morning phlegm has been found to be more common in smokers of nonfilter cigarettes than in smokers of filter-tipped cigarettes. Pipe and cigar smokers, however, are much less afflicted than are cigarette smokers with cough, phlegm and recurrent chest infection.

5

Effects of Cigarette Smoking on the Fetus

The deleterious effects of smoking during pregnancy have been studied and reported extensively. Some authors have found an impact of smoking on fertility, with a longer delay to conception among smoking women and a higher proportion of sperm abnormalities among smoking men.

Smoking by women during pregnancy has been associated repeatedly with an increased risk for low birth weight. Reductions of 40 g to over 400 g in mean birth weight have been reported among infants of smokers as compared with infants of nonsmokers. Two mechanisms are involved in this effect: retardation of intrauterine growth and an increased risk for premature birth. A modest increase in the risk for spontaneous abortion is also present.

Lowered intrauterine weight may be brought about in several ways. Maternal smoking reduces fetal oxygenation by increasing the blood levels of carbon monoxide and carbon dioxide, decreasing blood oxygen tension, altering blood flow patterns and inhibiting respiratory enzymes. Another factor might be reduced maternal nutrition, since cigarette smoking is known to diminish the appetite. Further, nicotine is a powerful vasoconstrictor, which crosses the placental barrier rapidly to depress cellular metabolism in the placenta and block the active transport of amino acids from the maternal to the fetal circulation. Nicotine also causes bradycardia and changes in the central nervous system of the fetus, while increasing maternal adrenaline and noradrenaline concentrations.

More recently, passive exposure of pregnant women to tobacco smoke has also been associated with a small reduction in birth weight due to retardation of intrauterine growth.

Low birth weight is itself associated with increased perinatal morbidity and mortality. Among the long-term sequelae are persistent effects on physical development and delays in intellectual and emotional development.

Studies on germ cells and on the products of smokers' conception provide equivocal results as to whether or not cigarette smoking results in heritable mutations that are transmitted to progeny. The evidence concerning an increased prevalence of morphologically abnormal sperm in smokers is conflicting.

6

Chromosomal Effects of Tobacco

In humans, tobacco smoking results in genetic damage to somatic cells: cigarette smokers have significantly raised levels of chromosomal damage (structural aberrations, sister chromatid exchanges and micronuclei) in somatic cells. There is some evidence that the prevalence of chromosomal aberrations in blood cells of smokers is a function of the number and the tar yield of cigarettes smoked. More positive evidence for a dose-response relationship is provided by studies on the prevalence of sister chromatid exchanges in somatic cells of smokers.

Chromosomal damage to somatic cells has also been reported in humans who use smokeless tobacco products. Thus, an increased incidence of micronuclei was observed in exfoliated epithelial cells from chewers of *khaini* and *nass*. In addition, saliva collected from chewers of Indian tobacco induced chromosomal aberrations in mammalian cells in vitro.

7

Experimental Studies

Studies in experimental animals

Tobacco smoke

Although the evidence for the carcinogenicity of tobacco smoking emerged first in humans, there was a need for an inhalation model in experimental animals in which the carcinogenic and other toxic effects of different types of tobacco and tobacco products could be studied and compared.

The finding that inhalation of tobacco smoke causes cancer of the larynx in hamsters established such a model system. Few assays have been conducted, however, in longer-lived mice, rats and dogs because of low priority and high cost; therefore, the spectrum of possible tumour responses in animals to inhalation of tobacco smoke is little known.

In order to study the response of animals to smoke inhalation, it was necessary to develop methods and equipment to deliver smoke in a standardized, effective way. A number of devices have been employed, some involving whole-body exposure and some nose-only exposure. However, animals which are being forced involuntarily to inhale the smoke have avoidance reactions and change their breathing patterns to shallow, hesitant inspirations with reduced air intake. This affects the doses delivered to the different parts of the respiratory system. Because rodents are obligatory nose-breathers and because rodents and dogs have more convoluted and intricate patterns of nasal passages than humans, the dynamics of particle deposition in the upper respiratory tract are probably different. Inhalation of tobacco smoke is irritating and toxic to animals: they can adapt to many short exposures over time, but require varying periods of recovery between exposures, depending somewhat on the species. Despite these problems, useful information has been obtained concerning the toxic effects of whole smoke and its gaseous phase.

Experiments in which mice and rats were exposed to tobacco smoke by inhalation produced tumours of the respiratory tract, and, as mentioned above, laryngeal tumours

were seen in hamsters. The available studies in rabbits and dogs, however, were inadequate for any conclusions to be drawn. A large number of studies on the carcinogenicity of cigarette-smoke condensate on mouse skin have consistently demonstrated the induction of benign and malignant skin tumours. Other studies have shown that cigarette-smoke condensate and its constituents have tumour-initiating, tumour-promoting and other cocarcinogenic activities. Direct injection of cigarette-smoke condensate into the lungs of rats caused carcinomas of the lung, and topical application to mouse oral mucosa resulted in the induction of lung tumours. Exposure of hamsters and rats to both polynuclear aromatic hydrocarbons and cigarette smoke resulted in more tumours than with smoke alone, confirming the cocarcinogenic effect. The same was true for concomitant exposure to radon decay products.

Animals chronically exposed to tobacco smoke generally gain weight more slowly than unexposed animals. They also show other cellular and biochemical responses, including increased levels of carboxyhaemoglobin in blood (indicating exposure to carbon monoxide), higher levels of certain tissue enzymes in lung lavage fluid, and decreases in pulmonary function. Fibrotic changes have been observed in dogs.

Many of these functional and pathological changes, however, disappeared after cessation of exposure to smoke. The enzyme changes mentioned above have been studied in detail. The results show that: they are induced in the lungs of all rodents tested, except guinea-pigs; the inducing components are found in the particulate phase of tobacco smoke; the changes are dependent on RNA and protein synthesis; the induced enzymes alter the metabolism of many chemical carcinogens; and, as a result, levels of metabolites bound to DNA are changed.

Smokeless tobacco

Various chewing tobaccos, unburnt cigarette tobaccos and extracts of tobacco have been tested in experimental animals by different routes of administration. However, none of the studies was entirely satisfactory with regard to design. In studies in which tobacco extracts were tested for initiating or promoting activity on mouse skin, positive results were obtained.

Genetic and related effects

Tobacco smoke, extracts of particulate matter collected on filters in rooms containing cigarette smoke and tobacco-smoke condensates were all found to be mutagenic to the

bacterium *Salmonella typhimurium*. Differences in tar content and the presence of a filter did not change the mutagenic activity significantly.

Tobacco smoke has also been shown to inhibit the repair of DNA damage in mice, to cause genetic changes in yeast strains and in the fruit fly (*Drosophila melanogaster*) and to increase the frequency of chromosomal changes (sister chromatid exchange) in isolated human lymphocytes and in the bone-marrow cells of rodents exposed to tobacco smoke.

Cigarette-smoke condensates caused genetic changes in bacteria, yeasts and fruit flies and caused mutation, chromosomal changes and neoplastic transformation in mammalian cells in culture. The urine of rats and of baboons exposed to cigarette smoke showed mutagenic activity in *S. typhimurium*.

Various extracts of chewing tobacco have induced mutation in *S. typhimurium* and in cultured mammalian cells, and caused chromosomal changes in and neoplastic transformation of cultured cells and micronuclei in rodents treated in vivo.

Annex 1

Examples of Biologically Active Agents in Cigarette Mainstream Smoke

Smoke constituents

Total particulate matter

Carbon monoxide
Nicotine
Nitrogen oxides
2-Nitropropane
Hydrogen cyanide

Ammonia and volatile amines

Ammonia
Dimethylamine
2,5-Dimethylpyrazine
Ethylamine
Methylamine
Methylpyrazines
2-, 3- and 4-Methylpyridines
1-Methylpyrrolidine
Pyridine
Pyrrolidine
Trimethylamine
Hydrazine

Volatile aldehydes and ketones

Acetaldehyde
Acetone
Acrolein
Crotonaldehyde
Formaldehyde
Furfural

Other volatile compounds

Benzene
Urethane
Vinyl chloride

Polynuclear aromatic compounds

Anthanthrene
Anthracene
Benzo[*a*]antracene
Benzo[*b*]fluoranthene
Benzo[*j*]fluoranthene
Benzo[*k*]fluoranthene
Benzo[*ghi*]fluorene
Benzo[*b*]fluorene
Benzo[*c*]fluorene
Benzo[*ghi*]perylene
Benzo[*c*]phenanthrene
Benzo[*e*]pyrene
Carbazole
Chrysene
Coronene
Dibenz[*a,h*]acridine
Dibenz[*a,j*]acridine
Dibenz[*a,c*]anthracene
Dibenz[*a,h*]anthracene
Dibenz[*a,j*]anthracene
7 *H*-Dibenzo[*c,g*]carbazole
Dibenzo[*a,e*]pyrene
Dibenzo[*a,h*]pyrene
Dibenzo[*a,i*]pyrene
Dibenzo[*a,l*]pyrene
Dimethylphenanthrene
Fluoranthene
Fluorene
Indeno[1,2,3-*cd*]pyrene
1-, 2-, 3-, 4-, 5- and 6-Methylchrysenes
2- and 3-Methylfluoranthenes
1-Methylphenanthrene
Perylene
Phenanthrene
Pyrene
Triphenylene

Alcohols

Butanol-1
Butanol-2
Ethanol
Methanol
2-Methylpropanol-1
Propanol-1

Phenolic compounds and quinones

Catechol
ortho-, *meta*- and *para*-Cresol
4-Ethylcatechol
Ethylphenols
Eugenol
Guaiacol
Hydroquinone
3'-Hydroxyisoeugenol
Isoeugenol
3- and 4-Methylcatechol
1-Naphthol
2-Naphthol
Phenol
Resorcinol
4-Vinylcaechol
4-Vinylguaiacol
2-, 3- and 4-Vinylphenols
Xylenols

Carboxylic acids

Acetic acid
Benzoic acid
n-Butyric acid
Formic acid
Lactic acid
Phenylacetic acid
Propionic acid
Succinic acid

Lactones

Coumarin
γ-Butyrolactone

Aromatic amines

2-, 3- and 4-Aminobiphenyls
Aniline
2,3-, 2,4-, 2,5- and 2,6-dimethylanilines
2-, 3- and 4-Ethylanilines
2-methyl-1-naphthylamine
1- and 2-Naphthylamines
ortho-, *meta*- and *para*-Toluidines

Pyridines and pyrazines

2,3-Dimethylpyrazine
2,4-, 2,5- and 2,6-Lutidines
2-Methylpyrazine
3-Methylpyridine
2-, 3- and 4-Picolines
Pyridine
3-Vinylpyridine
N-Nitrosamines
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
N'-Nitrosoanabasine
N'-Nitrosoanatabine
N-Nitrosodi-*n*-butylamine
N-Nitrosodiethanolamine
N-Nitrosodiethylamine
N-Nitrosodimethylamine
N-Nitrosodi-*n*-oropylamine
N-Nitrosomethylethylamine
N'-Noricotine
N-Nitrosopiperidine
N-Nitrosopyrrolidine

Metals

Aluminium
Antimony
Arsenic
Bismuth
Cadmium
Caesium
Chromium
Cobalt
Copper
Gold
Iron
Lanthanum
Lead
Magnesium
Manganese
Mercury
Nickel
Potassium
Scandium
Selenium
Silver
Sodium
Telluriam
Zinc

Polnium-210

Agricultural chemicals

Captan
Carbaryl
para, *para'*- and *ortho*, *para'*-DDD
para, *para'*- and *ortho*, *para'*-DDT
Endrin
Malathioin
Maleic hydrazide
Thiodan

Annex 2

Chemicals in Tobacco Smoke Associated with Cancer

Chemicals identified in tobacco smoke that are causally associated with cancer in humans

4-Aminobiphenyl
Arsenic
Benzene
Chromium (hexavalent compounds)
Nickel
Vinyl chloride

Chemicals identified in tobacco smoke that are probably carcinogenic to humans

Benzo[*a*]pyrene
Cadmium
Dibenz[*a,h*]anthracene
Formaldehyde
N-Nitrosodiethylamine
N-Nitrosodimethylamine

Chemicals identified in tobaco smoke for which there are inadequate or no data on carcinogenicity in humans, but for which sufficient evidence exists of carcinogenicity in experimental animals

Acetaldehyde
Benzo[*b*]fluoranthene
Benzo[*j*]fluoranthene
Benzo[*k*]fluoranthene
para-cresol
DDT
Dibenz[*a,h*]acridine
Dibenz[*a,j*]acridine
7 *H*-Dibenzo[*c,g*]carbazole
Dibenzo[*a,e*]pyrene
Dibenzo[*a,h*]pyrene
Dibenzo[*a,f*]pyrene
Dibenzo[*a,i*]pyrene
Hydrazine
Indeno [1,2,3-*cd*]pyrene
Lead (inorganic)
5-Methylchrysene
2-Nitropropane
N-Nitrosodi-*n*-butylamine
N-Nitrosodiethanolamine
N-Nitrosodi-*n*-propylamine
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone
N-Nitrosomethylethylamine
N'-Nitrosonornicotine
N-Nitrosopiperidine
N-Nitrosopyrrolidine
ortho-Toluidine
Urethane

Annex 3

Chemicals in Unburnt Processed Tobacco Associated with Cancer

Chemicals identified in unburnt processed tobacco that are causally associated with cancer in humans

Arsenic
Chromium (hexavalent compounds)
Nickel

Chemicals identified in urburnt processed tobacco that are probably carcinogenic to humans

Benzo[*a*]pyrene
Cadmium

Chemicals identified in unburnt processed tobacco for which there are inadequate or no data on carcinogenicity in humans, but for which sufficient evidence exists of carcinogenicity in experimental animals

α-Hexachlorocyclohexane
Lead (inorganic)
N-Nitrosodiethanolamine
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone
N-Nitrosomorpholine
N'-Nitrosonicotine
N-Nitrosopieridine
N-Nitrosopyrrolidine