

Highly Confidential

V
Final draft

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V. Conclusions and Evaluations

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1. Conclusions

Usage and trends

Smoking of tobacco is practised worldwide by hundreds of millions of people. In 1982, 6.7 million tonnes of tobacco were produced, and annual per-capita consumption ranged up to more than 3500 cigarettes. In developing countries, cigarette smoking is increasing, and many cigarettes and other products, including bidi, have very high tar (up to 73 mg per cigarette) and nicotine yields. In many developed countries, sizeable decreases in total consumption, sales and smoking rates have occurred. Generally, about one-third and one-half of men smoke, with some countries having notably higher rates. In most developed and some developing countries, about one-third of women smoke, although in some countries fewer than 10%.

Sales-weighted average tar and nicotine contents (as measured by standard laboratory methods) have declined significantly since the 1950s in some parts of the world. The chemical composition of smoke depends on (a) the type of tobacco; (b) cigarette design, including filtration, blend selection (e.g., reconstituted sheet, expanded tobacco), ventilation, paper and additives; and (c) the smoking pattern.

Tobacco is smoked principally in cigarettes, with pipes, cigars, bidi and other forms being used either to a minor extent or only in

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certain regions. Combustion of tobacco products delivers mainstream and sidestream smoke which differ in physicochemical nature. In addition, sidestream smoke contains greater amounts of identified carcinogens than mainstream smoke. Passive smoking is a universal phenomenon where smoking is common. The uptake of smoke constituents by smokers and by passive smokers has been studied in only a few countries, although extensive analysis of smoke shows cigarette smoking to be a major source of exposure to tobacco-specific nitroso compounds, polynuclear aromatic compounds, aromatic amines and some other carcinogens.

Carcinogenicity in animals

Cigarette smoke has been tested for carcinogenicity in experimental animals by inhalation and by topical application of condensates and in other ways. Exposure of hamsters and rats to whole smoke results in the induction of malignant respiratory-tract tumours. Cigarette smoke condensates induce skin cancers in mice and rabbits after application to the skin, and lung cancers in rats after intrapulmonary injection. Cigarette smoke contains many chemicals known to produce cancer in animals and/or humans.

An increase in carcinogenicity occurs in animals exposed both to cigarette smoke and to 7,12-dimethylbenz[a]anthracene, benzo[a]pyrene or radon daughters, as compared to animals exposed to any one of these materials alone.

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No study was available that was designed specifically to investigate the carcinogenicity of passive smoking to experimental animals.

Genetic activity and short-term test results

Tobacco smoke and smoke condensate are mutagenic and cause chromosomal damage in various test systems with multiple genetic endpoints. Exposure to these complex mutagenic mixtures results in mutagenic urine in smokers and in increased chromosomal damage in the somatic cells of smokers compared to nonsmokers. Cigarette-smoke condensates induce neoplastic transformation in mammalian cells in vitro.

Overall assessment^a of data from short-term tests on cigarette smoke

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi, green plants		+	+	
Insects		+		
Mammalian cells (in vitro)			+	
Mammals (in vivo)			+	
Humans (in vivo)			+	
Degree of evidence in short-term tests for genetic activity: Sufficient				Cell transformation: No data

^aThe groups into which the table is divided are defined on pp. 16-17 of the Preamble; the degrees of evidence are defined on pp. 17-18

^bGas phase of smoke only

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Overall assessment^a of data from short-term tests on cigarette-smoke condensate

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungus/plants		+	+	
Insects		+		
Mammalian cells (in vitro)		+	+	
Mammals (in vivo)			+	
Humans (in vivo)				
Degree of evidence in short-term tests for genetic activity: Sufficient				Cell transformation: Positive

^aThe groups into which the table is divided are defined on pp. 16-17 of the Preamble; the degrees of evidence are defined on pp. 17-18

Human exposure

Smokers of cigarettes with low tar yields tend to inhale to a greater extent than do smokers of cigarettes with high-tar yields, but, in general, their intake of smoke components is reduced.

Certain biochemical markers of smoke intake, i.e., nicotine in urine or saliva and cotinine in plasma, urine or saliva, are sufficiently sensitive and specific to identify passive smokers. Passive smokers who have been examined in western Europe and North America generally have levels between about 0.1% to 1% of these markers as compared to active smokers. The precise quantitative relationship between the measured levels of these markers and the intake of carcinogenic compounds in tobacco smoke is not known.

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Approximately 80% of inhaled particles from cigarette mainstream smoke is deposited in the respiratory tract, the majority in the tracheobronchial region. Wide variation is found, however, among individuals. The distribution of particulate matter in the lung is similar in smokers of high- and low-tar cigarettes. The pattern of deposition of sidestream smoke is very different: the proportion deposited is smaller and is likely to occur mainly in the periphery of the lung.

Genetic host factors

Genetic polymorphism in microsomal monooxygenases exists in humans. Lung cancer patients with a history of smoking are more often extensive metabolizers of the drug debrisoquine or have high induced levels of aryl hydrocarbon hydroxylase than unaffected smokers. It remains to be established whether this association implies that individuals with such genotypes are at increased risk of tobacco smoke-associated cancer.

Cancer in humans

Lung cancer is believed to be the most important cause of death from cancer in the world, with estimated total deaths in excess of 1 million annually. The major cause of the disease is tobacco smoking, primarily of cigarettes. Risk of lung cancer is particularly dependant on duration of smoking; therefore, the earlier the age at initiation of smoking, the greater the individual risk. Further, the longer the time

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period during which a major proportion of adults in a population have smoked, the greater the incidence and mortality from the disease in that population. Risk of lung cancer is also proportional to the numbers of cigarettes smoked, increasing with increasing cigarette usage. In populations with a long duration and heavy intensity of cigarette usage, the proportion of lung cancer attributable to smoking is of the order of 90%. This attributable proportion applies to men in most western populations; in populations in which women are increasingly using cigarettes, the attributable proportion in women is also approaching this level.

In smokers who have smoked for any length of time, the annual lung cancer risk incurred persists at approximately the same level after cessation of smoking, so that the increasing risk that would have been incurred by continuation of smoking is prevented.

Although cigarettes are the predominant cause of lung cancer, some increased risk also results from pipe and/or cigar smoking.

Smokers of other types of tobacco, particularly in Asia (e.g. of bidis in India), also appear to be at an increased risk of lung cancer. At present it is not possible to determine whether prolonged bidi smoking increases the risk of lung cancer to the same extent as does prolonged smoking of cigarettes.

Cigarettes appear to increase the risk of squamous-cell (epidermoid) and small-cell carcinomas of the lung to a greater extent

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than that of adenocarcinomas. However, each of these three main histological types of lung cancer are caused by tobacco smoking.

The risk of lung cancer associated with cigarette smoking is substantially increased in conjunction with high-dose exposures to radon daughters or asbestos.

Tobacco smoking (particularly of cigarettes) is an important cause of bladder cancer and cancer of the renal pelvis. The proportion of these diseases attributable to smoking in most countries with a history of prolonged cigarette usage is of the order of 50% in men and 25% in women. The relationships of risk with duration and intensity of smoking are similar to those for lung cancer, although the risks of smoking pipe and/or cigar smoking probably also increases the risk of bladder cancer, but at lower levels than the risk caused by cigarette-smoking.

Tobacco smoking is an important cause of oral, oropharyngeal,

hypopharyngeal, laryngeal and oesophageal cancers. Pipe and/or cigar

smoking appears to increase the risk of these cancers to approximately the same extent as cigarette smoking. The risks of these cancers associated with cigarette smoking are substantially increased in conjunction with high-dose exposure to alcohol. Tobacco smokers also appear to have increased risks for cancer of the lip.

Cigarette smoking is an important cause of pancreatic cancer and perhaps of renal adenocarcinoma. The proportion of these diseases that is attributable to smoking is not possible to quantify with the same

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smoking and stomach and liver cancers do not at present permit a conclusion that the associations noted in some studies are causal.

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Although the risk of cancer of the cervix is increased in tobacco smokers, it is not possible to conclude that the association is causal. Further, although in some studies a reduction in risk of endometrial cancer has been found in smokers as compared to non-smokers it cannot be concluded that smoking protects against cancer at this site.

The cigarettes that are currently sold differ, in many countries, from those that were sold prior to the general recognition of the hazards associated with their use. When the newer cigarettes are smoked under standard laboratory conditions, the yield of some components - particularly of tar and nicotine - is, in consequence, reduced. It is difficult, however, to deduce from this how hazardous such cigarettes are likely to be as they tend to be smoked differently, and the differences observed with laboratory testing may not be reproduced when they are smoked by people. It is difficult, too, to detect their effect on a national scale, as the harmful effects of smoking accumulate over many years and the risk of developing cancer attributable to smoking depends on both recent and past exposure.

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Nevertheless, the Group noted that:

- (a) Although smokers of low tar-level cigarettes tend to compensate for lower yields of nicotine and perhaps other smoke components, chiefly by changing the manner of smoking, they do not in general compensate fully for lower tar yields.
- (b) Case-control and cohort studies suggest that prolonged use of nonfilter and 'high-tar' cigarettes is associated with greater lung cancer risks than prolonged use of filter and 'low-tar' cigarettes.
- (c) In a few countries, in which smoking had been established for many years, a substantial reduction in mortality from lung cancer has been observed in young and middle-aged men, which is greatest in the youngest age groups. This has occurred at a time when the number of cigarettes smoked by young men in these countries has remained approximately constant. No substantial cause or (cofactor) has so far been identified that offers a plausible explanation for the observed magnitude of the reduction of risk for lung cancer noted in (b) and (c) above, other than changes in cigarette design which include reduction in tar content.

It was concluded that the risk of lung cancer associated with the types of cigarettes commonly smoked before the middle 1950s is greater

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than that for modified cigarettes with low tar levels now generally available in some countries.¹

The health benefits from the cessation of smoking, however, greatly exceed those to be expected from changes in cigarette composition.

Tobacco smoke affects not only people who smoke but also people who are exposed to the combustion products of other people's tobacco. The effects produced are not necessarily the same, as the constituents of smoke vary according to its source. Three main sources exist: (i) mainstream smoke, (ii) sidestream smoke, and (iii) smoke exhaled to the general atmosphere by smokers. Smokers are exposed to all three to a greater extent than are nonsmokers. It follows that it is unlikely that any effects will be produced in passive smokers that are not produced to a greater extent in smokers and that types of effects that are not seen in smokers will not be seen in passive smokers. Examination of smoke from the different sources shows that all three types contain chemicals that are both carcinogenic and mutagenic. The amounts absorbed by passive smokers are, however, small, and effects are unlikely to be detectable unless exposure is substantial and very large numbers of people are observed. The observations on nonsmokers that have been made so far are compatible with either an increased risk from 'passive' smoking or an absence of risk. Knowledge of the nature of sidestream

¹See 'General Remarks' for a discussion of effects on other tobacco-related diseases.

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and mainstream smoke, of the materials absorbed during 'passive' smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens leads to the conclusion that passive smoking gives rise to some risk of cancer.

2. Evaluation

There is sufficient evidence that inhalation of tobacco smoke as well as topical application of tobacco smoke condensate cause cancer in experimental animals.

There is sufficient evidence that tobacco smoke is carcinogenic to humans.

The occurrence of malignant tumours of the respiratory tract and of the upper digestive tract is causally related to the smoking of different forms of tobacco (cigarettes, cigars, pipes, bidis). The occurrence of malignant tumours of the bladder, renal pelvis and pancreas is causally related to the smoking of cigarettes.

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