


# CHAPTER 3

**Smoking and Cancer**

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SMOKING AND CANCER

Summary

Previous reports (59, 60, 61) have presented the evidence that cigarette smoking is a major cause of lung cancer and that cessation of cigarette smoking sharply reduces the risk of dying from lung cancer as compared to the risk taken by those who continue to smoke. Cigarette smoking was also shown to be a significant factor in the causation of cancer of the larynx. A strong association between various forms of smoking and cancers of the buccal cavity, pharynx, and esophagus was also shown. Data were presented which indicated that cigarette smoking was associated with cancer of the urinary bladder. Data were also presented which suggested that cancer of the kidney and pancreas may be related to cigarette smoking.

During the past year, both population studies and laboratory studies from various countries have added to the weight of the evidence linking smoking and cancer. A major study of histological changes in the larynx has demonstrated the higher risk of premalignant changes among smokers. More studies have been done to identify those substances in tobacco smoke which take part in carcinogenesis. New animal models for the experimental study of respiratory cancer, which may be helpful in elucidating the mechanisms of respiratory tract carcinogenesis, have been developed and refined.

Epidemiological Studies

It is interesting to note that epidemiological information on cigarette smoking and lung cancer, similar to that which has been collected in the United States and Western European countries, is now being reported from Eastern Europe and Africa as well.

Lung Cancer

In Norway, a study of histologically proven cases of lung cancer by Kreyberg demonstrated the low frequency of lung cancer among nonsmokers. The cases were collected between 1950 and 1964 from two hospitals and a diagnostic laboratory which service all parts of Norway. The author states that the population represented in this study is most probably geographically representative of the whole country. In comparing his results in Norway with those in other European
countries, Kreyberg stated that a nonsmoking Norwegian population today should present lung cancer cases in the same number, with the same sex ratio, and with the same representation of histological types as prevailed in Norway 40 years ago, and in Europe in general at the beginning of this century (24, 25). The risks of developing various histological types of lung cancers among smokers, as contrasted to nonsmokers, are presented in table 1. Two facts are strikingly apparent from the table. First, the preponderance of the higher risk of lung cancer in smokers lies in the categories of epidermoid carcinoma and anaplastic small cell carcinoma. Second, while female smokers have a higher risk of developing lung cancer than female nonsmokers, the relative risks are smaller than those for males. At least part of this difference may be accounted for by differences in smoking habits between men and women. Women tend to smoke fewer cigarettes, to smoke brands lower in tar and nicotine, inhale less and smoke less of each cigarette than do men; therefore, women have lower exposure to cigarette smoke.

TABLE 1.—Tumor prevalence among males and females 35-69 years of age, by type of tumor and smoking category

<table>
<thead>
<tr>
<th>Sex and type of tumor</th>
<th>Smoking category</th>
<th>Expected number among smokers</th>
<th>Risk ratio among smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Smoking all methods</td>
<td>Non-smokers</td>
</tr>
<tr>
<td>Males:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermoid carcinoma</td>
<td>434</td>
<td>431</td>
<td>3</td>
</tr>
<tr>
<td>Small cell anaplastic carcinoma</td>
<td>117</td>
<td>116</td>
<td>1</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>88</td>
<td>83</td>
<td>5</td>
</tr>
<tr>
<td>Bronchiolo-alveolar carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoid</td>
<td>46</td>
<td>39</td>
<td>7</td>
</tr>
<tr>
<td>Bronchial gland tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>685</td>
<td>660</td>
<td>16</td>
</tr>
</tbody>
</table>

Females:

<table>
<thead>
<tr>
<th>Sex and type of tumor</th>
<th>Smoking category</th>
<th>Expected number among smokers</th>
<th>Risk ratio among smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermoid carcinoma</td>
<td>12</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Small cell anaplastic carcinoma</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>50</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Bronchiolo-alveolar carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoid</td>
<td>32</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Bronchial gland tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>108</td>
<td>35</td>
<td>73</td>
</tr>
</tbody>
</table>

1 Number that would be expected if incidence rate among smokers was equal to that of nonsmokers.

Source: Kreyberg, L. (44).
Brett, et al. (8) found that the mortality rate for lung cancer in smokers in England was especially high for the smokers who “drooped” the cigarettes off the lip while they smoked, a habit which may result in the delivery of a greater dose of smoke from each cigarette.

Gelfand, et al. (19) in a study of lung cancer in Rhodesian Africans, reported a preponderance of smokers among the lung cancer patients as compared to a control group. The authors express the opinion that air pollution does not play a role in respiratory cancer in Rhodesia.

In the 1967 Health Consequences Report (59), it was pointed out that the lung cancer risk of ex-smokers declined, relative to those who continued to smoke. It equalled that of nonsmokers about 10 years after stopping smoking, and the rate of decline depended on the number of cigarettes previously smoked and the duration of smoking. Bross, et al. (10) reported that the risk of developing lung cancer is lower among filter cigarette smokers than nonfilter cigarette smokers. Since filter cigarettes are generally lower in tar content than nonfilter cigarettes, this study supports the inference that the tar content of cigarettes is a meaningful measure of exposure to risk.

In view of the fact that practically all lung cancer patients started to smoke nonfilter cigarettes and have smoked filter cigarettes only in recent years and for a variable length of time, a more exact comparison of the risks run by smokers of filter and nonfilter cigarettes must await further studies (67).

The relationship of smoking to lung cancer in women is an area of continuing concern, since we may expect a continued increase of lung cancer in women with the increase in cigarette smoking among them since World War II. Lombard, et al. (32) show a relationship of cigarette smoking to epidermoid lung cancer in women but not to adenocarcinoma. It is generally agreed that the contribution of cigarette smoking to the development of epidermoid and oat-cell lung cancer (Kreyberg Group I) in males is significantly greater than to the development of adenocarcinoma (Kreyberg Group II).

An association of other diseases to cancer of the lung is found in a report by Salzer, et al. (48). Salzer and his colleagues have reported in an autopsy study that lung cancer and scars from stomach ulcers are statistically associated and suggested that cigarette smoking may have contributed to both conditions. A study by Stamler, et al. (53) indicated that male cigarette smokers with elevated cholesterol levels had higher rates of lung cancer than those with lower cholesterol levels. Additional studies are needed to confirm and elucidate these observations.

Programs have been recently established to perform cytological examinations on the sputum of smokers, since they represent a population at a high risk for the development of carcinoma of
the lung. These programs have detected individuals with atypical or frankly malignant cells in their sputum before a shadow has appeared in the lung fields of x-ray (18, 62). Valaitis, et al. (62) reported that some degree of cytological abnormality was found in the sputum of 4.8 percent of the smokers and 0.9 percent of the nonsmokers.

Oral Cancer

In the Soviet Union, Orlovskiy has shown an association between cigarette smoking and lung cancer, as well as an association between the use of "nas" (a mixture of tobacco and ashes) and the development of cancer of the oral cavity (37). Other studies of interest from around the world include one by Pindborg, et al. (39) on the epidemiology and histology of oral leukoplakia and leukoedema among Papuans and New Guineans. They report that smoking may be more closely associated with these conditions than is the chewing of betel nut which previously was considered the obviously associated habit. A study by Wahi (64) reports on the relationship of tobacco chewing to oral and oropharyngeal cancer in a district in India. Pindborg also presents evidence from India indicating that oral submucous fibrosis (38) may be associated with tobacco use and may result in an oral epithelium more susceptible to the carcinogenic substances in tobacco.

In a study of oral malignancies indexed in a large tumor registry in California, Chierici, et al. (13) found that 88 percent of the cancer patients were smokers. The proportion of smokers ranged from 81 to 83 percent for cancers of the gingival and alveolar mucosa, buccal mucosa, hard palate, and lip, to 94 percent or more for cancers of the floor of the mouth, soft palate, tonsil, or oropharynx. Unfortunately, comparable percentages of smokers in a control population are not presented. No new studies have appeared which clarify the relative contributions of other environmental risk factors for oral cancer, such as alcohol consumption, nutritional problems, and poor oral hygiene.

Laryngeal Cancer

Auerbach, et al. (1) studied the histology of the larynx of 942 men, aged 21 to 95, who were autopsied at a single hospital between 1964 and 1967. Cases of primary cancer of the larynx were excluded from the study. Smoking histories for all cases were obtained from family members of the deceased by trained interviewers. The numerous randomized histological sections were graded by one observer. Table 2 shows the percentage of cells with atypical nuclei found in the true vocal cord. Of the men who never smoked, 75 percent had no cells with atypical nuclei, only 4.5 percent had sections with areas containing 60 to 69 percent of cells with atypical nuclei, and none had a higher percentage.
Table 2.—Number and percent distribution by relative frequency of atypical nuclei among true vocal cord cells, of men classified by smoking category

<table>
<thead>
<tr>
<th>Percent atypical nuclei</th>
<th>Never smoked regularly</th>
<th>Ex-cigarette smokers</th>
<th>Cigar/pipe smokers</th>
<th>Current cigarette smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>None</td>
<td>86</td>
<td>100.0</td>
<td>88</td>
<td>90.0</td>
</tr>
<tr>
<td>Less than 50</td>
<td>66</td>
<td>75.0</td>
<td>86</td>
<td>74.1</td>
</tr>
<tr>
<td>50–59</td>
<td>14</td>
<td>15.7</td>
<td>14</td>
<td>16.2</td>
</tr>
<tr>
<td>60–89</td>
<td>4</td>
<td>4.6</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>70–79</td>
<td>0</td>
<td>....</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>80–99</td>
<td>0</td>
<td>....</td>
<td>0</td>
<td>....</td>
</tr>
<tr>
<td>90–99</td>
<td>0</td>
<td>....</td>
<td>0</td>
<td>....</td>
</tr>
<tr>
<td>100: Carcinoma in situ</td>
<td>0</td>
<td>....</td>
<td>0</td>
<td>....</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>0</td>
<td>....</td>
<td>6</td>
<td>....</td>
</tr>
</tbody>
</table>

Source: Auerbach, O., et al. (I).

The 116 ex-smokers had laryngeal histology similar to that of the nonsmokers, as far as atypical nuclei were concerned. However, disintegrating nuclei were found in 40.5 percent of the ex-cigarette smokers and in only 0.4 percent of the remaining cases. Only one of the 94 cigar and/or pipe smokers had no atypical cells. Three had carcinoma in situ and one case had a section showing early invasive primary carcinoma. The highest percentage of atypical cells was found among the cigarette smokers. The proportion of cases with a high degree of cellular change increased with increased daily smoking. None of the pack-or-more-a-day smokers was free of atypical nuclei. Of those who smoked two or more packs per day, 85 percent had lesions with 60 percent or more atypical cells as compared to 4 percent of the nonsmokers. Between 10 and 18 percent of the cigarette smokers had areas of carcinoma in situ, and four of the 644 cases showed early microscopic invasion. The thickness of the basal level of the true vocal cord was also directly related to the amount smoked (table 3).
Table 3.—Number and percent distribution, by highest number of cell rows in the basal layer of the true vocal cord, of men classified by smoking category

<table>
<thead>
<tr>
<th>Number of cell rows</th>
<th>Never smoked regularly</th>
<th>Ex-cigarette smokers</th>
<th>Cigar/pipe smokers</th>
<th>Current cigarette smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>100.0</td>
<td>116</td>
<td>100.0</td>
</tr>
<tr>
<td>Less than 6 cell rows</td>
<td>30</td>
<td>34.1</td>
<td>7</td>
<td>6.0</td>
</tr>
<tr>
<td>6 cell rows</td>
<td>29</td>
<td>33.0</td>
<td>27</td>
<td>23.3</td>
</tr>
<tr>
<td>7 cell rows</td>
<td>6</td>
<td>6.8</td>
<td>12</td>
<td>10.3</td>
</tr>
<tr>
<td>8 cell rows</td>
<td>8</td>
<td>9.1</td>
<td>14</td>
<td>12.1</td>
</tr>
<tr>
<td>9 cell rows</td>
<td>1</td>
<td>1.1</td>
<td>7</td>
<td>6.0</td>
</tr>
<tr>
<td>10 or more cell rows</td>
<td>6</td>
<td>6.8</td>
<td>34</td>
<td>29.4</td>
</tr>
</tbody>
</table>

Source: Auerbach, O., et al. (1).

Cancer of the Urinary Bladder and Kidney

Several studies have dealt with the relationship of smoking to cancer of the bladder and kidney. James, et al. (23) demonstrated that an association existed for cancer of the bladder. The study by Fraumeni (17) also showed epidemiological evidence for such a relationship for bladder and kidney cancers. Bennington, et al. (3, 4) indicated an association between all kinds of tobacco usage and adenocarcinoma of the kidney as well as adenoma of the kidney. However, on the basis of this study alone, the relationship between “all kinds of tobacco” and cancer of the kidney cannot be considered as established in view of the small number of cases involved. In a preliminary report of a study on the epidemiology of cancer of the kidney, Wynder, et al. (68) have shown a strong association between excessive cigarette smoking and adenocarcinoma of the kidney, and although the disease is not uncommon in non-smokers, they considered excessive cigarette smoking to be a contributory factor. This study found no relationship to pipe smoking, and only a very weak relationship to cigar smoking. A significant association was found between cigarette smoking and epidermoid cancer of the kidney, a relatively uncommon type of cancer. Further research on the strength and mechanisms of the association between smoking and cancers of the urinary tract is needed.

Cancer of the Pancreas

The previously suggested association between cigarette smoking and cancer of the pancreas was again noted in a Japanese study by Ishii, et
al. (22), in which the authors reported a higher relative risk for pancreatic cancer among smokers than among nonsmokers.

**General Aspects of Carcinogenicity**

The majority of the tumorigenic agents in tobacco smoke are found in the particulate matter “tar.” The well established carcinogenicity of tobacco “tar” in a variety of animal species and tissues (66) was reconfirmed recently (11, 35, 40, 52, 56). A small portion of the smoke particulates (0.03 percent) is made up of polynuclear aromatic hydrocarbons (PAH) with two or more rings. A concentrate containing polynuclear aromatic hydrocarbons and amounting to 0.6 percent of the whole “tar” was found to be the most carcinogenic fraction of tobacco smoke (66). Another preparation of a PAH concentrate induced significant cytologic changes in mouse trachea and human fetal lung when grown in organ culture (28, 29). Other applications of concentrations of selected polynuclear aromatic hydrocarbons have produced similar results (27).

Of the identified PAH, at least 12 are known tumor initiators. These particular compounds have been shown to be carcinogenic, even when applied in doses of a few micrograms (63, 66). Tumor initiators induce changes in the target cells, especially in DNA (9, 14). Tumor promoters are agents which promote the neoplastic transformation of initiated cells. Although the structures of most of these tumor promoters are still unknown, there appear to be several different types in tobacco smoke (6, 41, 59, 66). Recently, Bock, et al. (6) published data which confirmed earlier findings that whole cigarette tar, the neutral fraction, two neutral subfractions and the weak acidic (phenolic) fraction contain tumor promoters. One recent study indicated that “tar” obtained from tobacco stems only had essentially no tumor promoting activity (65).

During the last year, several studies have reconfirmed the finding that selection of tobacco and the use of tobacco sheets and filters can lead to a significant reduction of “tar” and PAH in cigarette smoke, as well as to a reduction of the tumorigenicity of tobacco “tars.” Similar results have also been reported for commercial cigarettes (21, 34). Experimental studies demonstrated that with tobacco additives one can reduce “tar,” nicotine, PAH and tumorigenicity of cigarette smoke (12, 21). In terms of selective reduction of tobacco smoke components, these investigations may be of practical value, as well as of academic interest (57).

**Tobacco Alkaloids**

Present evidence does not indicate that tobacco alkaloids are carcinogenic. A possible exception may be cotinine, which was reported to induce malignant tumors in rats [principally leukemias (58)] and
adenomas of the bladder in mice (7). Boyland recently suggested that one or more of the three possible nicotine-N-oxides may be present in tobacco smoke and may be carcinogenic (7).

Tobacco alkaloids could theoretically contribute to the overall carcinogenicity of tobacco smoke, based on the possibility that in tobacco smoke nornicotine and other secondary amines may react with nitrogen oxides to form the N-nitrosamines, of which several are known carcinogens, especially N-nitrosonornicotine and N-nitrosoanabasine (36). So far, however, N-nitrosamines of nornicotine and other alkaloid N-nitrosamines have not been detected in tobacco smoke (36).

Nickel

The relationship of nickel compounds to the development of cancer has been discussed in a recent review by Sunderman (55), who suggests that there is a possibility that nickel carbonyl may be present in cigarette smoke and may act as a cocarcinogen by inhibiting the induction of pulmonary benzopyrene hydroxylase, an enzyme which converts 3,4-benzpyrene to noncarcinogenic hydroxylated derivatives.

Experimental Aspects of Carcinogenesis

Retention of Smoke Constituents

Studies on human smokers by Dalhamn, et al. (15) demonstrated that about 60 percent of the volatile, water soluble compounds of cigarette smoke, 20 percent of the volatile, nonwater soluble compounds, and 16 percent of the particulate matter of cigarette smoke can be retained in the mouth when the smoke is held in the mouth for up to 2 seconds. Under conditions in which the smoke is immediately deeply inhaled, between 91 and 99 percent of the components of cigarette smoke investigated (particulate matter, toluene, acetonitrile, acetone, isoprene, acetaldehyde) were retained, with the exception of carbon monoxide, of which 50 to 60 percent was retained (16).

Changes in Cell Cultures Induced by Cigarette Smoke

Leuchtenberger, et al. (30) have reported that passing cigarette smoke through a charcoal filter prevented the damage caused by either whole smoke, or the isolated gas phase of cigarette smoke, to cultures of mouse kidney cells. In the same paper, they reported that the single exposure of tissue cultures to puffs of charcoal-filtered smoke produced a significant increase in the mitotic index of the kidney cells. In another study, Leuchtenberger, et al. (31) reported that single exposure to nine puffs of the gas phase from charcoal-filtered cigarette smoke quickly stimulated the synthesis of DNA and RNA by cultures of mouse fibroblasts. Repeated exposure of the cultures to the filtered gas phase resulted in morphological and cytochemical changes indicative
of abnormal proliferation. Since the same alterations were found to be present, to a much lesser extent, in some control cultures, the authors considered that the filtered gas phase enhanced characteristics already possessed by the cells. They concluded that the gas phase of unfiltered cigarette smoke contains not only substances which inhibit cellular metabolism, but also factors which stimulate cellular metabolism. These latter factors may be unmasked by passing the gas phase through a charcoal filter. The identities of the specific gases removed by the charcoal filter and the extent to which each was removed were not reported by the authors. Investigation of the relationship between the changes observed in the tissue cultures and \textit{in vivo} metabolism is necessary for the interpretation of the results of these experiments.

\textit{Experimental Studies of Bronchogenic Carcinoma in Animals}

Because of the technical problems involved in inhalation experiments in small animals \((59, 61)\), various animal models have been developed which do not employ the inhalation of smoke. These models have been used to study the role played by carcinogenic substances found in tobacco smoke in the induction of bronchogenic carcinoma.

Saffiotti \((43)\) in a recent review of experimental respiratory tract carcinogenesis described the development of experimental models for the induction of pulmonary tumors and discussed a method of inducing bronchogenic carcinomas in Syrian golden hamsters by intratracheal instillation of a finely particulated crystalline carcinogen (e.g., benzo(a)pyrene) attached to a suspension of fine particles of a carrier dust (e.g., ferric oxide). This method reproduces some of the conditions of human exposure to inhaled carcinogens and has resulted in incidences of up to 100 percent of respiratory tumors, mostly squamous cell and anaplastic carcinomas of the larger bronchi. These tumors have been found to be invasive, metastasizing, and transplantable. Saffiotti reported that the carrier dust particles play an essential role in transporting the carcinogens through the bronchiolar and alveolar wall into the lung tissues where they are phagocytized. The carcinogens are then eluted by the plasma and diffused into the lung tissue, reaching up to the mucosa of the larger bronchi \((42, 44, 45, 46)\). Variations in particle size and distribution in the suspended particulate matter affect the retention rates of benzpyrene in the lungs \((47)\). The development of this experimental model has led to the undertaking of new research in many laboratories attempting to define the factors responsible for carcinogenesis in the respiratory tract.

Two other techniques used to produce squamous cell carcinoma in small laboratory animals are the passage of threads impregnated with carcinogenic hydrocarbons into the lung and the implantation of wire
mesh pellets in the bronchus. The latter technique gives a dose-response relationship between carcinogenic hydrocarbons and squamous cell carcinoma of the lung in rats (27). In order to overcome the traumatic effects of the surgery involved in these procedures, two additional techniques have been utilized. In one method, the carcinogen is suspended in Freund’s adjuvant and upon tracheal instillation can lead to bronchial cancer (69). In this experiment, even more cancers were found when the rats were pretreated with tubercle bacilli. Pretreatment of the animals with tubercle bacilli produced infarcts, as well as scarring of the lung. This finding is of interest because earlier studies showed that scarring of rat lung by the halogenated hydrocarbon hexachlorotetrafluorobutane increases their susceptibility to the development of squamous carcinoma when exposed to carcinogenic hydrocarbons (54). That scarring of the lung may increase the susceptibility of the lung to carcinogens is in line with some recent observations on humans by Bennett, et al. (28) who showed the frequent occurrence of pulmonary scars in males with adenocarcinoma of the lung.

**Experimental Aspects of Cancer of the Bladder and Kidney**

Tobacco smoke appears to contain traces of several aromatic amines which are established bladder carcinogens. Of these, however, only Betanaphthylamine has thus far been identified in tobacco smoke with \(2.2 \times 10^{-8} \text{ g. per cigarette (20)}\). At concentrations such as this, it appears unlikely that such aromatic amines can account for the increased risk among cigarette smokers of developing kidney and bladder cancer. A more likely correlation may exist between these types of cancers in smokers and their elevated urinary excretion rate of carcinogenic metabolites of tryptophan, and their oxidation products (49, 60).

Recently, the tobacco alkaloid cotinine was reported to induce adenomas in the bladder of mice [16 percent (7)]. This observation needs further testing. Cotinine is one metabolic product of nicotine and is found in tobacco, cigarette smoke (26) and the urine of smokers (33).

A study by Schlegel, et al. (51) indicates an elevated concentration of certain o-aminophenols plus their phenoxazon-oxidation products in the urine of certain types of bladder cancer patients and cigarette smokers, when compared to the urine of nonsmokers. Further studies are needed on this problem.
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CHAPTER 4

Effects of Smoking on Pregnancy

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