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CHAPTER 4

Cancer

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LUNG CANCER

Cigarette smoking has been established as the major cause of lung cancer. The 1971 report, "The Health Consequences of Smoking" (39), in summarizing this association, concluded:

1. Epidemiological evidence derived from a number of prospective and retrospective studies coupled with experimental and pathological evidence confirms the conclusion that cigarette smoking is the main cause of lung cancer in men. These studies reveal that the risk of developing lung cancer increases with the number of cigarettes smoked per day, the duration of smoking, and earlier initiation, and diminishes with cessation of smoking.
2. Cigarette smoking is a cause of lung cancer in women but accounts for a smaller proportion of the cases than in men. The mortality rates for women who smoke, although significantly higher than for female nonsmokers, are lower than for men who smoke. This difference may be at least partially attributed to difference in exposure: the use of fewer cigarettes per day, the use of filtered and low "tar" cigarettes, and lower levels of inhalation. Nevertheless, even when women are compared with men who apparently have similar levels of exposure to cigarette smoke, the mortality ratios appear to be lower in women.
3. The risk of developing lung cancer among pipe and/or cigar smokers is higher than for nonsmokers but significantly lower than for cigarette smokers.
4. The risk of developing lung cancer appears to be higher among smokers who smoke high "tar" cigarettes or smoke in such a manner as to produce higher levels of "tar" in the inhaled smoke.
5. Ex-cigarette smokers have significantly lower death rates for lung cancer than continuing smokers. There is evidence to support the view that cessation of smoking by large numbers of cigarette smokers would be followed by lower lung cancer death rates.

6. Increased death rates from lung cancer have been observed among urban populations when compared with populations from rural environments. The evidence concerning the role of air pollution in the etiology of lung cancer is presently inconclusive. Factors such as occupational and smoking habit differences may also contribute to the urban-rural difference observed. Detailed epidemiologic surveys have shown that the urban factor exerts a small influence compared to the overriding effect of cigarette smoking in the development of lung cancer.
7. Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with these exposures in the pathogenesis of lung cancer so as to produce very much higher lung cancer death rates in those cigarette smokers who are also exposed to such substances.
8. Experimental studies on animals utilizing skin painting, tracheal instillation or implantation, and inhalation of cigarette smoke or its component compounds, have confirmed the presence of complete carcinogens as well as tumor initiators and promoters in tobacco smoke. Lung cancer has been found in dogs exposed to the inhalation of cigarette smoke over a period of more than two years.

In the interim, additional epidemiological, pathological, and experimental studies have added to our understanding of these relationships.

EPIDEMIOLOGICAL STUDIES

The major prospective epidemiological studies to date, demonstrating associations between cigarette smoking and specific diseases, were conducted primarily in the United States, Canada, and Great Britain in Caucasian populations. A large, prospective study currently in progress in Japan adds to the weight of evidence supporting a causal relationship between cigarette smoking and lung cancer. It is the first large-scale prospective study to be conducted in a population characterized by genetic, dietary, behavioral, and cultural influences distinctively different from those in previously examined Western populations. The 3-year preliminary prospective data for lung cancer from this population of 265,118 adults in Japan (10) demonstrate overall effects and dose-response relationships similar to those observed in previous studies (figure 1).

The mortality ratio for male smokers of 1 to 9 cigarettes a day was 2.7 and rose to 24.8 for smokers of more than 2 packs a day. The mortality ratio was 6.9 for ex-smokers. Of the 122,261 men in the study, 74.3 percent were daily smokers, 3.4 percent were ex-smokers, and 19.1 percent nonsmokers. The percentage of males who were daily smokers decreased with advancing age.

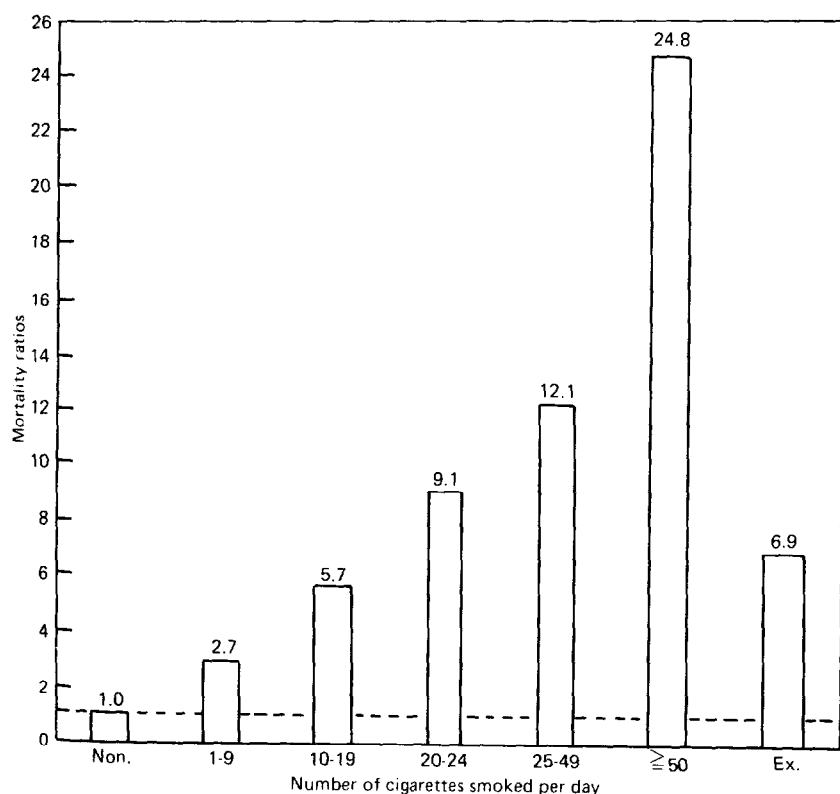


FIGURE 1.—Lung cancer mortality ratios of Japanese males by amount smoked.

SOURCE: Hirayama, T. (10).

In a prospective study of 12,322 Czechoslovakian males, Kubik, et al. (19) analyzed various factors associated with the development of lung cancer. During the 3½-year follow-up period, 61 cases of lung cancer were discovered. The incidence of lung cancer among males aged 40 to 64 was 460/100,000 among heavy cigarette smokers (more than 200,000 lifetime cigarettes), 90/100,000 for light cigarette smokers (less than 200,000 lifetime cigarettes), and 10/100,000 for nonsmokers. There were no cases of lung cancer among the 222 smokers of pipes and cigars.

In the past 50 years Poland has experienced a rise in cigarette consumption and, more recently, a sharp rise in the incidence of and mortality from lung cancer (16, 34). In the 5-year period between 1963 and 1967, the mortality rate from lung cancer for men rose from 33.0 to 49.1 per 100,000. This increase was more pronounced in urban areas. Lung cancer has been the leading cause of death from malignant neoplasms in Polish men since 1959.

Additional studies conducted in Germany (26), Lebanon (1), Scotland (6), and Sweden (37) have demonstrated a strong association between cigarette smoking and lung cancer.

Rimington (28) examined the smoking habits and sputum production of 21,579 British males aged 40 and older who were screened for lung cancer by X-ray examination. During the follow-up period of 36 to 56 months, 64 new cases of lung cancer were identified. Because chronic bronchitis and lung cancer are both associated with cigarette smoking, the data were standardized by cigarette consumption categories. An increase in both lung cancer and chronic bronchitis was demonstrated with increasing consumption, but for each level of smoking there was a higher incidence of lung cancer among the individuals with chronic bronchitis than among those without this condition. Standardization with respect to age showed that the differences in lung cancer incidence between those with and without chronic bronchitis could not be accounted for by the increase seen in these diseases with advancing age. It was concluded that persons who smoke run a higher risk of chronic bronchitis than nonsmokers and those smokers who develop chronic bronchitis run a higher risk of developing lung cancer than smokers without chronic bronchitis. The relationship between lung cancer and chronic bronchitis was not demonstrated for pipe smokers.

Graham and Levin (7) examined the effect of cessation of cigarette smoking on the risk of developing lung cancer in a retrospective study of 700 lung cancer patients. The risk of developing lung cancer in ex-smokers declined sharply after cessation (figure 2). The decline occurred both in those who smoked for less than 31 years and those who had smoked 31 years or more (figure 3). Those who had smoked for less than 31 years had a lower risk of lung cancer following cessation than those with the longer smoking history in each category of time following cessation. Although there was an appearance of a somewhat more rapid rate of decline in risk with time following cessation for those who smoked for the shorter period, the difference was not statistically significant. The relative risk for the development of lung cancer for pipe and cigar smokers was 2.6. The reduction in risk following cessation of these forms of smoking was not examined.

The relationship of smoking to lung cancer in women has recently been examined by several authors. The smoking patterns of 142,857

Japanese women were described by Hirayama (10). Only 10.9 percent were daily smokers of cigarettes. Women started smoking at an older age than men and, in contrast to Western populations, there was a higher percentage of smokers in the older age groups than among younger women. The mortality rates were lower for women than for men, but a dose-response relationship was demonstrated. The lung cancer mortality ratio for women smokers of 1 to 9 cigarettes a day was 2.65 and rose to 3.14 for smokers of 20 to 24 cigarettes a day compared to nonsmokers.

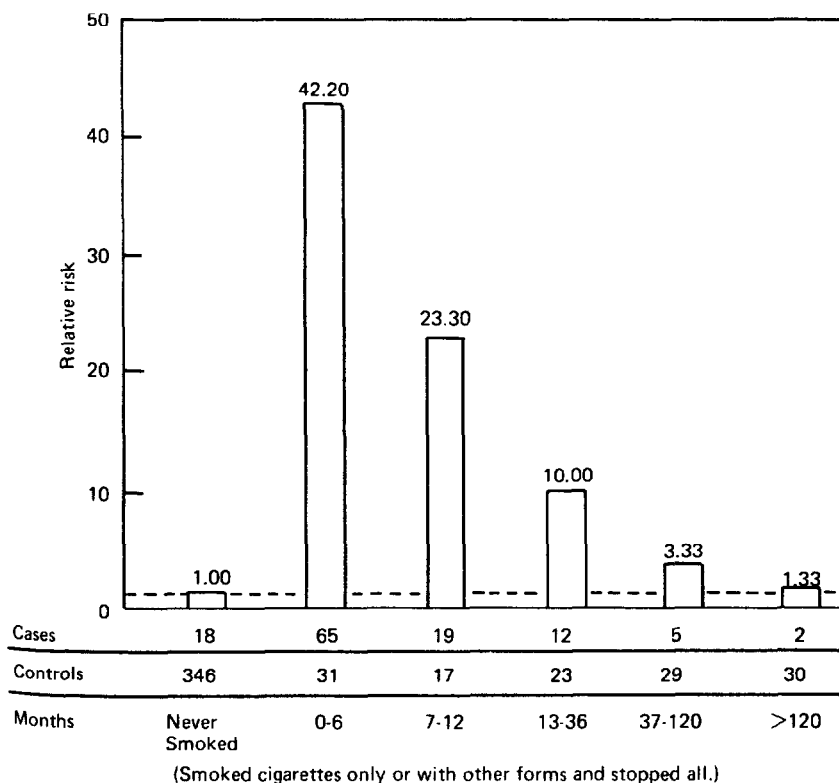


FIGURE 2.—Relative risk of lung cancer in ex-smokers of cigarettes by length of cessation before diagnosis.

SOURCE: Graham, S., Levin, M. L. (7).

In two recent investigations (9, 13), both similar in design, the authors described higher rates of lung cancer among Jewish women in Pittsburgh and Montreal than among Catholic and Protestant controls. The proportion of epidermoid and anaplastic carcinomas was found to be lower for the 87 Jewish women with lung cancer in these studies than for the non-Jewish women. A survey of smoking

habits in the two cities suggested that the increased incidence of lung cancer in Jewish women could not be entirely attributed to variations in smoking patterns. A low incidence of lung cancer was found among Jewish males, and this was correlated with their low cigarette consumption.

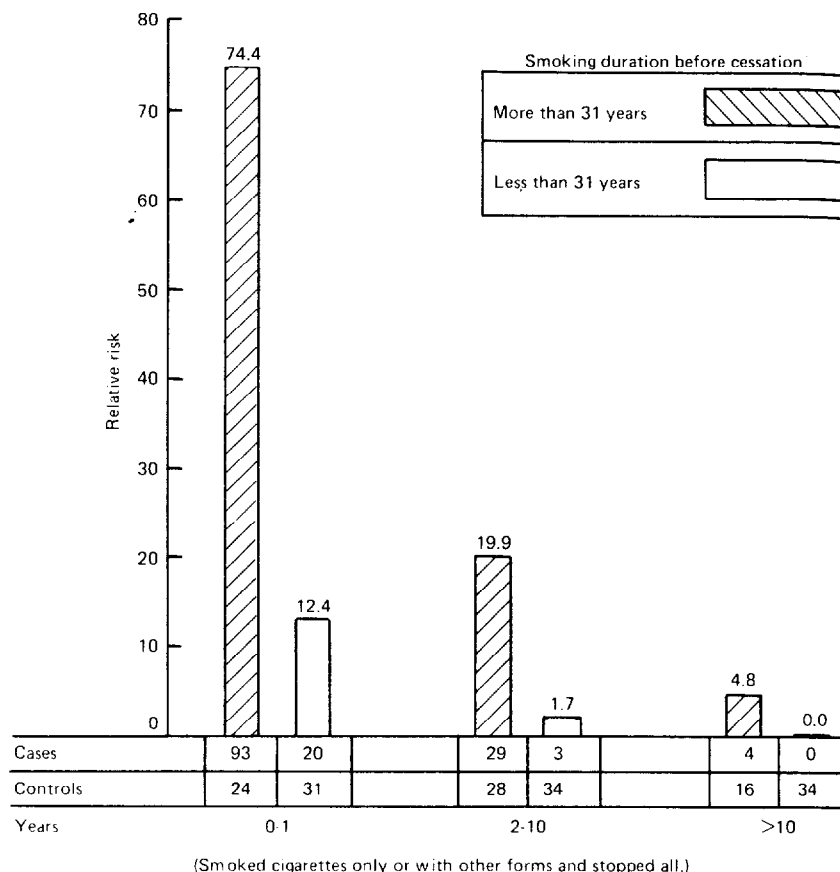


FIGURE 3.—Relative risk of lung cancer in ex-smokers of cigarettes by length of cessation and previous duration of smoking.

SOURCE: Graham, S., Levin, M. L. (7).

The increased risk for the development of lung cancer among uranium miners is well established. The 1971 report, "The Health Consequences of Smoking" (39), summarized the recent investigations in this area. The histologic types of 121 cases of lung cancer in American uranium miners were studied by Saccomanno, et al. (30) using the WHO classification of lung tumors. A marked increase was noted in the small cell undifferentiated types with in-

creasing radiation exposure. The author examined the role of tobacco in the etiology of these tumors stating, "... among uranium miners, cigarette smoking is a potent co-carcinogen in the cause of lung cancer, but exerts little, if any, influence on the cell type of lung cancer. . . ."

EXPERIMENTAL ASPECTS

Chemicals present in the particulate phase of tobacco smoke have been tested for their carcinogenic potential in experimental animals and/or tissue and organ cultures and have been grouped according to the type of activity observed. On mouse skin, certain chemicals induce tumor formation and are called *complete carcinogens*; others appear to act only in conjunction with additional treatment, and are referred to as *incomplete carcinogens*. They include *tumor initiators* and *tumor promoters*. *Tumor initiators* induce an irreversible change in epidermal cells which causes them to respond to subsequent applications of *tumor promoters* with the development of skin tumors. This two-stage mechanism of carcinogenesis, well known for mouse skin, has not been demonstrated in other animal species or tissues under comparable conditions.

Hoffmann and Wynder (11, 44) discussed the major initiators and promoters found in cigarette smoke and described an additional property of *acceleration* possessed by N-alkylated carbazoles, N-alkylated indoles, and Trans-4, 4'-dichlorostribene (DCS) which is a pyrolysis product of the insecticides DDT and DDD. These compounds are inactive as complete carcinogens, initiators, or promoters but accelerate the initiator-promoter activity of polynuclear aromatic hydrocarbons (PAH).

The initiating activity of polycyclic aromatic hydrocarbons in two-stage carcinogenesis was investigated and reviewed by Van Duuren, et al. (41). Several compounds previously thought to be of little or no significance in tobacco carcinogenesis have been found by Van Duuren and other independent investigators to be tumor *initiators*. Table 1 lists a number of these compounds. Tumor *promoting* agents probably allow these weak carcinogens to express their tumorigenic potential. Dibenz(a, c)anthracene which was reported by Van Duuren, et al. (41) to be an *initiating agent* was found by Lijinsky, et al. (22) to also act as a *complete carcinogen* in mouse skin experiments.

In another investigation, Van Duuren, et al. (42) confirmed that tobacco smoke condensate is primarily a tumor-promoting agent with weak carcinogenic activity. They also found that benzo(a)-pyrene, a carcinogen in cigarette "tar," acts as a tumor promoter when applied to mouse skin in low doses over a long time period

TABLE 1.—Some initiating agents in two-stage carcinogenesis.

Compound
† Dibenz (a,c) anthracene
† Chrysene
† Benz (a) anthracene
† 6-Methylanthanthrene
Chloromethyl methyl ether
Urethan
Triethylenemelamine
1,4-Dimethanesulfonyl-2-butyne

† Those found in cigarette smoke.

SOURCE: Van Duuren, et al. (41).

after the application of an initiating agent. This supports the observation that the tumor-promoting activity of cigarette "tar" may represent the summation of carcinogenic activities of the several carcinogenic aromatic hydrocarbons present in cigarette "tar."

In tobacco carcinogenesis research the choice of bioassay is of major importance. Mouse and rabbit skin models have been an important source of experimental data concerning tobacco carcinogenesis (44). Several relatively rapid screening bioassays have been recently suggested. Major (24) examined the effects of tumor promoters and initiators on mouse skin, measuring cell numbers, cell size, mitotic index, and epidermal thickness. Changes found during the first five days were characteristic for different agents.

The effects of polycyclic aromatic hydrocarbons on the nonspecific esterase activity in sebaceous glands of mice were examined by Healey, et al. (8). The changes observed were not entirely specific for carcinogenic activity and were probably related more to the toxicity of the painted substances to the sebaceous gland cells. This suggests that further improvement is needed in this system before it can be a practical screening bioassay for potential carcinogenic compounds.

Shabad (33) reviewed experimental studies from Russia and elsewhere relating tobacco with tumor formation, and concluded, "... it is indicated that cigarette smoke can actually induce lung cancer in animals."

Leuchtenberger and Leuchtenberger (21) have described adenomas and adenocarcinomas in the lungs of mice chronically exposed to cigarette smoke.

Takayama (36) found that subcutaneous injections of cigarette "tar" in newborn mice produced benign and malignant tumors of the liver, lung, and lymphoid tissue.

The compound 7H-Dibenz(c,g)carbazole (7H-DBC), a component of cigarette smoke, was tested for its carcinogenic potential on the respiratory tract of Syrian golden hamsters using 15 or 30 intratracheal injections per week. Sellakumar and Shubik (32) found a high percentage of squamous tumors of the trachea and bronchi in the tested animals and observed that 7H-DBC appeared to be a potent carcinogen for the respiratory system of hamsters.

Krasnyanskaya (18) has examined the effects of chronic exposure to cigarette smoke on the respiratory tract of 95 rabbits. One group was pretreated with an intratracheal injection of benz(a)-pyrene. Although premalignant changes were found in treated animals, no malignancies were observed after four years of exposure.

OTHER CANCERS

The relationships between tobacco smoking in its various forms and cancers of the oral cavity, larynx, esophagus, kidney, urinary bladder, and pancreas were summarized in the 1971 report, "The Health Consequences of Smoking" (39).

1. *Cancer of the Larynx*

- a. Epidemiological, experimental, and pathological studies support the conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx.
- b. The risk of developing laryngeal cancer among cigarette smokers as well as pipe and/or cigar smokers is significantly higher than among nonsmokers.
- c. The magnitude of the risk for pipe and cigar smokers is about the same order as that for cigarette smokers, or possibly slightly lower.
- d. Experimental exposure to the passive inhalation of cigarette smoke has been observed to produce premalignant and malignant changes in the larynx of hamsters.

2. *Cancer of the Oral Cavity*

- a. Epidemiological and experimental studies contribute to the conclusion that smoking is a significant factor in the development of cancer of the oral cavity and that pipe smoking, alone or in conjunction with other forms of tobacco use, is causally related to cancer of the lip.
- b. Experimental studies suggest that tobacco extracts and tobacco smoke contain initiators and promoters of cancerous changes in the oral cavity.

3. *Cancer of the Esophagus*

- a. Epidemiological studies have demonstrated that cigarette smoking is associated with the development of cancer of the esophagus.
- b. The risk of developing esophageal cancer among pipe and/or cigar smokers is greater than that for nonsmokers and of about the same order of magnitude as for cigarette smokers, or perhaps slightly lower.
- c. Epidemiological studies have also indicated an association between esophageal cancer and alcohol consumption and that alcohol consumption may interact with cigarette smoking. This combination of exposures is associated with especially high rates of cancer of the esophagus.

4. *Cancer of the Urinary Bladder*

- a. Epidemiological studies have demonstrated an association of cigarette smoking with cancer of the urinary bladder among men.
- b. The association of tobacco usage and cancer of the kidney is less clear-cut.
- c. Clinical and pathological studies have suggested that tobacco smoking may be related to alterations in the metabolism of tryptophan and may in this way contribute to the development of urinary tract cancer.

5. *Cancer of the Pancreas*

Epidemiological studies have suggested an association between cigarette smoking and cancer of the pancreas. The significance of the relationship is not clear at this time.

Additional relevant epidemiological, pathological, and experimental data have been reported.

CANCER OF THE LARYNX

McNelis and Esparza (23) reported 14 cases of carcinoma *in situ* of the larynx found among 387 vocal cord biopsies. Thirteen patients were men and with one exception all smoked cigarettes.

Lavelle (20) described 11 patients with carcinoma of the larynx which occurred as a second primary cancer at least one year after the successful treatment of an initial primary cancer of the bronchus. "Although it was not possible to ascertain with certainty the smoking habit of all these patients there were no definite non-smokers among them."

ORAL CANCER

Leukoplakia of the oral mucosa represents a keratinization of surfaces normally unkeratinized. Over a 23-year period, Sugar and Banoczy (35) observed 535 patients with leukoplakia. Of the 324 patients examined in the latest survey, 96 (30 percent) had leukoplakia for more than 10 years. Two hundred sixty-nine patients (83 percent) were smokers. Treatment was ineffective in those patients who continued to smoke. Oral cancer eventually developed in 13 of 48 patients (27 percent) who had severe leukoplakia.

The initial changes in the mouth caused by smoking may not be the hyperkeratotic lesions of leukoplakia. Meyer, Rubinstein, and colleagues (25, 29) examined the effects of smoking on the surface cytology of clinically normal oral mucosa and, in general, found that smoking produced changes in cytoplasm characterized by less mature cell configurations. These changes were most pronounced on those surfaces most directly exposed to the stream of cigarette smoke.

Etiological aspects of squamous cancers of the head and neck were reviewed by Wynder (43). There was an increased likelihood of a second primary tumor forming at the site of the first cancer if a patient had been a heavy smoker, or if he continued to smoke, after surgical removal of the first primary. From a preventive point of view it was observed that squamous cell cancers of the head and neck would be comparatively rare in the absence of tobacco and excessive alcohol consumption.

Jussawalla and Deshpande (15) examined various types of smoking and chewing habits in a retrospective investigation of 2,005 patients in Bombay, India, who had histologically established cancers of the oral cavity, pharynx, larynx, and esophagus. Smokers used either a manufactured cigarette or the Indian "bidi" which contains a small quantity of shredded tobacco rolled in a dried leaf, usually of the Temburni tree (*Dispyros Melanoxyton*). Chewers used "pan" made with betel leaf, lime, and spices. A small quantity of tobacco was, on occasion, added to this mixture as an optional ingredient. Smoking and chewing both resulted in an increased risk of cancer at each site examined with a striking increase in risk observed in patients who had the combined habits of chewing and smoking (figure 4). The independent contribution of tobacco to the increased risk of cancer at each site could not be clearly isolated as there was no control for chewing when smoking characteristics were examined and vice versa.

Intra-oral smoking with the lighted end of a cigar or cigarette inside the mouth is a custom found in parts of the Caribbean, South America, India, and the Island of Sardinia. Morrow and Suarez

(27) examined 79 intra-oral smokers, most of whom had sought medical attention for reasons other than symptoms associated with smoking-related diseases. All but one patient demonstrated "nicotinic stomatitis" characterized by hyperplasia, acanthosis, hyperkeratosis, and parakeratosis. Sixteen cases of squamous cell carcinoma were found. These were located predominantly at the base of the tongue, tonsillar fauces, and adjacent pharyngeal mucosa.

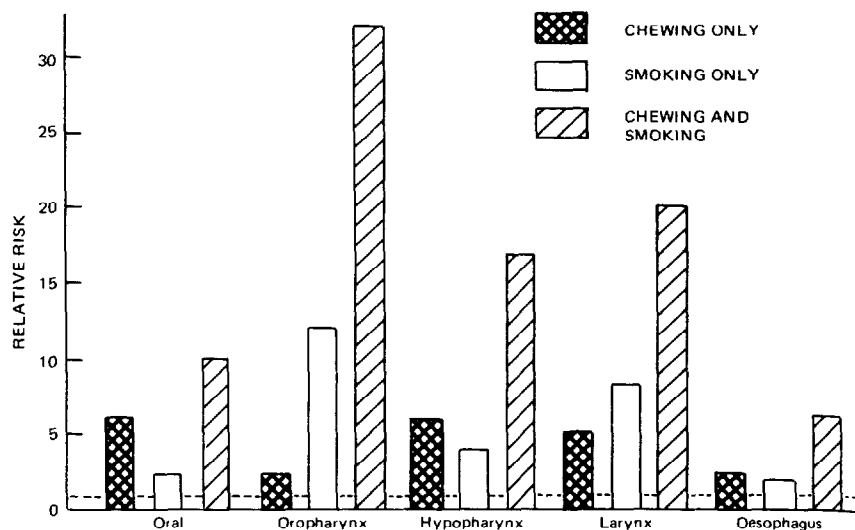


FIGURE 4.—Relative risk of cancer of the oral cavity, pharynx, larynx, and esophagus associated with smoking and chewing in various forms.

SOURCE: Jussawalla, D. J., Deshpande, V. A. (15).

The oral mucosa of many experimental animals appears to be resistant to the induction of cancers. Cohen, et al. (4) failed to produce any distinctive cancerous or precancerous changes in the mucosal lining of surgically created buccal pouches of monkeys filled with chewing tobacco for varying lengths of time. Homburger (12) exposed the oral mucosa of Syrian golden hamsters to snuff and 7,12-Dimethylbenz(a)anthracene (DMBA) using a bit inserted in the mouth. Snuff alone failed to produce any changes that were not also seen in the control animals who had a plain cotton plug inserted in the mouth. Benzo(a)pyrene and DMBA caused a few carcinomas of the oral mucosa, but they produced a much higher number of cancers outside the mouth where the carcinogenic agents had spilled onto the perioral skin. The authors observed that "... skin-painting experiments are more sensitive indicators of carcinogenicity for the oral mucosa than applications to the mucosa itself."

CANCER OF THE ESOPHAGUS

Cancer of the esophagus is associated with both tobacco and alcohol consumption.

In the prospective study from Japan, Hirayama (10) found no significant association between the use of cigarettes or alcohol alone and cancer of the esophagus, but there were high rates of esophageal cancer among individuals using both cigarettes and alcohol (figure 5).

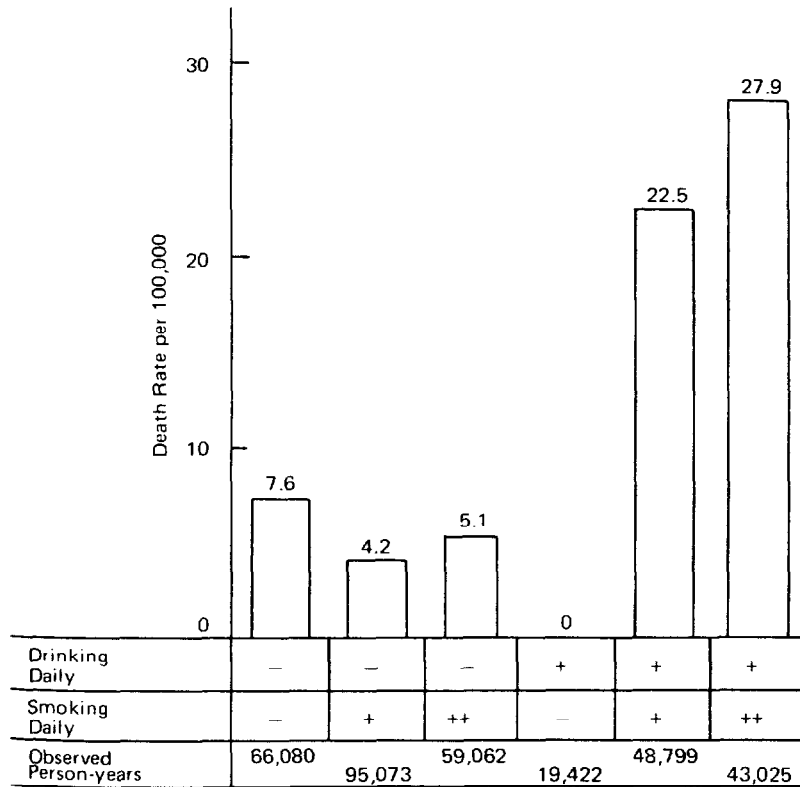


FIGURE 5.—Death rates for cancer of the esophagus in Japanese males by smoking and drinking characteristics.

SOURCE: HIRAYAMA, T. (10).

Schoenberg, et al. (31), using cohort analysis, examined mortality from esophageal cancer in the United States. Substantial ethnic, geographic, and temporal variations were observed. On a state-by-state basis, mortality from esophageal cancer was correlated about equally with urbanization, per capita cigarette sales, and per capita

alcohol sales. The correlation with urbanization was partially explained by increased sales of tobacco and alcohol in urban areas.

CANCER OF THE URINARY BLADDER

In a retrospective study of 470 confirmed cases of transitional cell or squamous cell cancers of the bladder, Cole, et al. (5) found a consistent positive relationship between cigarette smoking and bladder cancer. The relative risk and standard error for the development of bladder cancer were 1.89 ± 0.22 for male smokers and 2.00 ± 0.33 for female smokers. A dose-response relationship was demonstrated for both the number of cigarettes smoked per day (figures 6 and 7) and various degrees of inhalation. Bladder cancer has been shown to be associated with certain occupational categories such as dye workers, certain textile workers, tailors, and nurses (2, 14). Cole standardized the data with respect to occupation and found that the risk demonstrated could not be explained by any indirect association with industrial exposure. Cole concluded: "The

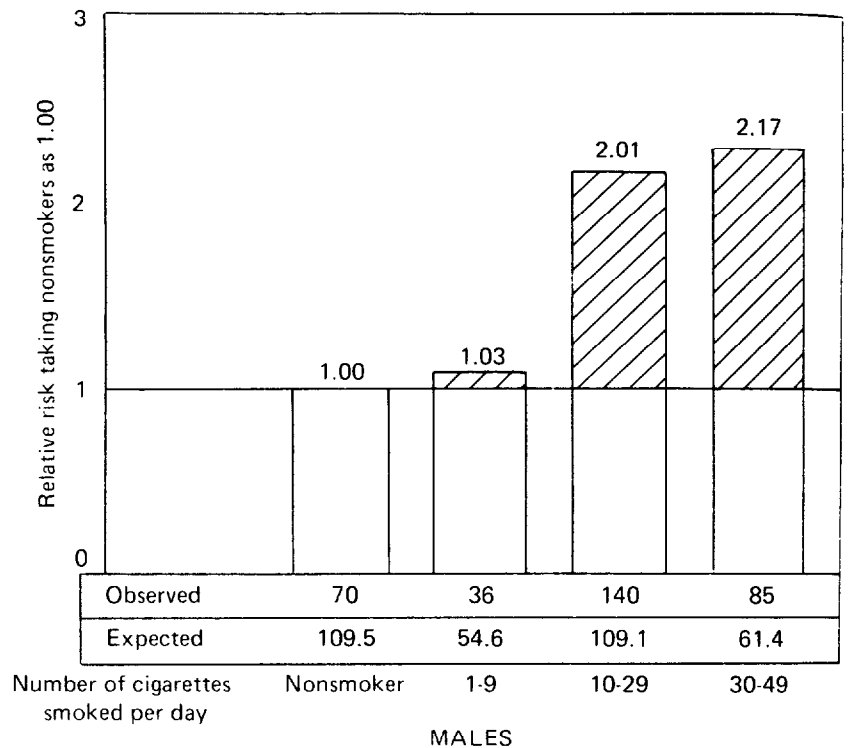


FIGURE 6.—Relative risk of urinary bladder cancer for males by amount smoked.

SOURCE: Cole, P., et al. (5).

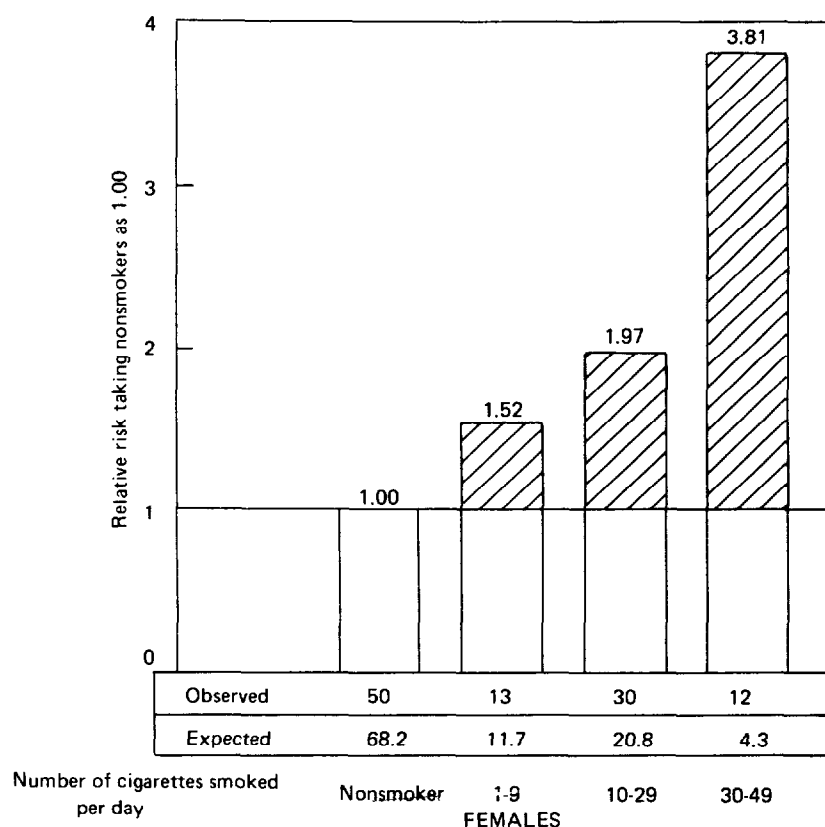


FIGURE 7.—Relative risk of urinary bladder cancer for females by amount smoked.

SOURCE: Cole, P., et al. (5).

present findings indicate that about 35 percent of cases of cancer of the lower urinary tract in the study population are associated with cigarette smoking. If this association is accepted as causal, and if it is generalized to the entire population of the United States, smoking is associated with about 3,100 deaths per year from cancer of the lower urinary tract." No significant association was found between pipe or cigar smoking and bladder cancer.

Tyrrell, et al. (38) examined several factors including smoking history and occupation in a group of 250 patients treated for urinary bladder cancer in Ireland. No significant association between occupation and bladder cancer was found. This may have been due to the low concentration of high-risk industries for this cancer in Ireland. A significant ($P < 0.005$) association was found in males between cigarette smoking and cancer of the urinary bladder, but

no significant association was found for the 50 cases of bladder cancer in females.

In an extensive review of cancer of the urinary tract, Clayson and Cooper (3) included data that demonstrated an association between cigarette smoking and excessive mortality from bladder cancer.

CANCER OF THE PANCREAS

Cancer of the pancreas was responsible for 9,696 deaths among men and 7,190 deaths among women in the United States in 1967 (40). The United States age-adjusted mortality rate for carcinoma of the pancreas has risen from 2.9 to 8.2 per 100,000 from 1920 to 1965 (17).

In the prospective Japanese study by Hirayama (10), the preliminary data showed a pancreatic cancer mortality ratio of 2.7 for male smokers and a mortality ratio of 3.0 for female smokers.

In an epidemiologic appraisal of cancer of the pancreas, Krain (17) found that cigarette smoking and industrial exposure were more strongly associated with this disease than either air pollution or genetic factors.

HIGHLIGHTS OF CURRENT CANCER INFORMATION

In addition to the comprehensive summary from the 1971 report, "The Health Consequences of Smoking" (39), cited earlier in this chapter, the following statements are made to emphasize the most recent developments in the field:

1. Preliminary results from a major prospective epidemiological study in Japan demonstrate a strong association between cigarette smoking and lung cancer. A dose-response relationship was demonstrated for the number of cigarettes smoked. These findings in an Asian population with distinct genetic and cultural characteristics confirm the major importance of cigarette smoking in the causation of lung cancer, a conclusion which up to now has been based largely on studies of Caucasian populations in the United States, Canada, and Europe.
2. Ex-smokers have significantly lower death rates for lung cancer than continuing smokers. The decline in risk following cessation appears to be rapid both for those who have smoked for long periods of time and for those with a shorter smoking

history, with the sharpest reductions taking place after the first two years of cessation.

3. The risk of developing lung cancer appears to be higher for smokers who have chronic bronchitis. Though both conditions are directly related to the amount and duration of smoking, an additional risk for lung cancer appears to exist for cigarette smokers with chronic bronchitis which is independent of age and number of cigarettes consumed.
4. Experimental studies on animals have demonstrated that the particulate phase of tobacco smoke contains certain chemical compounds which can act as complete carcinogens, tumor initiators, or tumor promoters. Recently, other compounds have been described that have no independent activity in two-stage carcinogenesis but *accelerate* the carcinogenic effects of polynuclear aromatic hydrocarbons in the initiator-promoter system.
5. Additional epidemiological evidence confirms a significant association between the combined use of cigarettes and alcohol, and cancer of the esophagus.
6. Epidemiological studies have demonstrated a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the risk of developing bladder cancer increases with inhalation and the number of cigarettes smoked.
7. Epidemiological evidence demonstrates a significant association between cigarette smoking and cancer of the pancreas.

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