

TABLE 16.—*Summary of methods used in retrospective studies of smoking and cancer of the stomach*

Investigator, year, and reference	Country	Sex	Cases		Controls		Collection of data
			No.	Method of selection	No.	Method of selection	
Dunham & Brunshwig 1946 (94).	U.S.A.	M&F	40	Not clear. Patients in Dept. of Surgery, Univ. of Chicago.	40	Not clear. Patients without gastric tumor.	Not specified
Kraus et al., 1957 (193).	U.S.A.	M	56	Admissions to Roswell Park Memorial Inst., 11/48-9/51, 25-74 years of age.	677	Patients admitted to Roswell Park during same time period in following 4 diagnostic groups: (1) Digestive cancer other than esophagus or stomach. (2) Cancer—other than digestive—respiratory, urinary, skin, hemat. (3) Non-tumor diag. of digestive system other than esophagus or stomach. (4) Non-tumor diag. other than digestive—respiratory, urinary, skin, hemat. Each control group matched to cancer group by age and population size of place of residence.	Questioned by trained interviewers
Staszewski 1960 (327).	Poland	M	136	Patients admitted to Oncological Institute during 1957-59.	912	See TABLE 11	See TABLE 11. Two-thirds of cancer of stomach diagnoses were histologically confirmed.
Schwartz et al., 1961 (315).	France	M	263	See TABLE 11	263	Patients hospitalized from 1954-1956 with gastric cancer in Paris and other large cities.	See TABLE 11

TABLE 17.—*Summary of results of retrospective studies of smoking and cancer of the stomach*

Investigator, reference, and year	Percent non-smokers		Percent heavy smokers		Percent inhalers among smokers		Relative risk: ratio to non-smokers	
	Cases	Controls	Cases	Controls	Cases	Controls	All Smokers	Heavy Smokers
Dunham and Brunschwig 1946 (94).....	47.5	47.5					0	
Kraus et al. 1957 (193).....	19.2	24.2					1.3	
Staszewski 1960 (325).....	12.5	18	75.6	59	88.2	80	1.5	2.1
Schwartz et al. 1961 (315).....	16	17	Total cigarettes smoked daily 14.6      15.3		37	34	1.0	

cancer. The other two studies, to date, suggested an association but these were not statistically significant (193, 325). Two of the studies did not approach the smoking variable specifically but as part of attempts to examine several possible etiological factors (94, 193); the other two were specifically directed to the role of smoking (315, 325). The relative risks as calculated are not significantly different from unity.

#### PROSPECTIVE STUDIES

The seven prospective studies brought up-to-date (except for the original Hammond and Horn study) have yielded a total of 413 deaths from gastric cancer. The mean gastric cancer mortality ratio for the seven studies is calculated to be 1.4. This is obviously lower than for any of the sites described earlier. The individual studies, however, with fairly adequate numbers for stability, show a range of mortality ratios from 0.8 in the Dunn, Linden, Breslow occupational study (96) to 2.3 in the Hammond and Horn study (163) (Table 1 of this chapter). The Hammond and Horn ratio is not statistically significant ( $p=0.12$ ) (163).

Two of the earlier reports (84, 88) provide information on mortality rates or mortality ratios for the several cigarette smoking classes by amount smoked. In neither of these is any gradient apparent.

For cigar and pipe smokers the combined studies provide a mean gastric cancer mortality ratio of 1.1 (Table 24, Chapter 8).

#### *Carcinogenesis*

Squamous cell carcinoma has been produced in the forestomach of mice by the oral administration of various polycyclic aromatic hydrocarbons (8, 19, 59, 113a, 223, 276, 308, 334, 364, 368) including benzo(a)pyrene (19, 59, 276, 364). It should be noted that the forestomach of mice and rats is covered with squamous epithelium extending down from the esophagus. The incidence of such cancers in mice varies with the strain used. Stewart and Lorenz (333) produced the same type of cancer in the forestomach by injecting 20-methylcholanthrene intramurally.

Rats also develop squamous cell tumors in the forestomach after prolonged oral administration of carcinogens (249).

Adenocarcinoma has been produced in the glandular stomach of mice and rats by the intramural injection of carcinogenic hydrocarbons (17, 19, 187, 339) or by inserting a silk thread impregnated with 2-methylcholanthrene into the glandular stomach wall between the serosa and mucosa (332, 333).

Attempts at production of cancer of the stomach with tobacco tars or condensates have not been successful (294).

#### *Evaluation of the Evidence*

Squamous and adeno-carcinomas have been produced experimentally in mice with benzo(a)pyrene and dibenz(a,h)anthracene injected directly into the fore- or glandular stomach. None of the retrospective studies shows an association between gastric cancer and smoking. Nor do the prospective studies yield gastric cancer mortality ratios significantly higher than the total

mortality ratio. In fact, the mean gastric cancer mortality ratio for cigarette smokers is below the mean total mortality ratio, and for cigar and pipe smokers it is approximately the same. Even a gradient by amount smoked is lacking in at least two of the prospective studies.

### *Conclusion*

No relationship has been established between tobacco use and stomach cancer.

## SUMMARIES AND CONCLUSIONS

Cancer deaths per year increased seven-fold (in the United States death registration area of 1900) between 1900 and 1960—from 10,000 in 1900 to 80,000 in 1960. Less than half of this increase was due to aging and growth of the population. A large part of the increase was due to lung cancer.

### LUNG CANCER

While part of the rising trend for lung cancer is attributable to improvements in diagnosis, the continuing experience of the State registers and the autopsy series of large general hospitals leave little doubt that a true increase in the lung cancer death rate has taken place. About 5,700 women and 33,200 men died of lung cancer in the United States in 1961; as recently as 1955, the corresponding totals were 4,100 women and 22,700 men. This extraordinary rise has not been recorded for cancer of any other site.

When any separate cohort (a group of persons born during the same ten-year period) is scrutinized over successive decades, its lung cancer mortality rates vary directly with the recency of the birth of the group: the more recent the cohort, the higher the risk of lung cancer throughout life. Within each cohort, lung cancer mortality apparently increases unabated to the end of the life span. The pattern would suggest that the mortality differences may be due to differences in exposure to one or more factors or to a progressive change in population composition among the several cohorts.

A considerable amount of experimental work in many species of animals has demonstrated that certain polycyclic aromatic hydrocarbons identified in cigarette smoke can produce cancer. Other substances in tobacco and smoke, though not carcinogenic themselves, promote cancer production or lower the threshold to a known carcinogen. The amount of known carcinogens in cigarette smoke appears to be too small to account for their carcinogenic activity.

There is abundant evidence, however, that cancer of the skin can be induced in man by industrial exposure to soots, coal tar, pitch and mineral oils; all of these contain various polycyclic aromatic hydrocarbons known to be carcinogenic in many species of animals. Some of these compounds are also present in tobacco smoke. Although it is noted that the few attempts to produce bronchogenic carcinoma directly with tobacco extracts, smoke, or

condensates applied to the lung or the tracheobronchial tree of experimental animals have not been successful, the administration of polycyclic aromatic hydrocarbons, certain metals, radioactive substances, and certain viruses have been shown to produce such cancers. The characteristics of the tumors produced are similar to those observed in man. Since the response of most human tissues to carcinogenic substances is qualitatively similar to that observed in experimental animals, it is highly probable that the tissues of man are susceptible to the carcinogenic action of some of the same polycyclic aromatic hydrocarbons that produce cancer in experimental animals. Neither the available epidemiological nor the experimental data is adequate to fix a safe dose of chemical carcinogens for men.

The systematic evidence for the association between smoking and lung cancer comes primarily from 29 retrospective studies of groups of persons with lung cancer and appropriate "controls" without lung cancer and from 7 prospective studies (described in Chapter 8). The 29 retrospective studies of the association between tobacco smoking and lung cancer (summarized in Tables 2 and 3 of Chapter 9) varied considerably in design and method. Despite these variations, every one of the retrospective studies showed an association between smoking and lung cancer. All showed that proportionately more heavy smokers are found among the lung cancer patients than in the control populations and proportionately fewer non-smokers among the cases than among the controls.

The differences are statistically significant in all the studies. Thirteen of the studies, combining all forms of tobacco consumption, found a significant association between smoking of any type and lung cancer; 16 studies yielded an even stronger association with cigarettes alone. The degree of association between smoking and lung cancer increased as the amounts of smoking increased. Ex-smokers generally showed a lower risk than current smokers but greater than non-smokers. Relatively few of the retrospective studies have dealt with "age started smoking," but all except one of these studies found that male lung cancer patients began to smoke at a significantly younger age than the controls. Except at the highest cigarette consumption levels, the relationship of inhalation to lung cancer was significant for those smoking cigarettes alone.

Several investigators have utilized mathematical techniques to calculate, from retrospective studies, the relative risks of lung cancer for smokers as compared with non-smokers. All of the 9 studies in which relative risk ratios were derived showed a significantly greater risk among smokers, ranging from as low as 2.4-to-1 for light smokers to as much as 34.1-to-1 for heavy smokers, with most of the ratios between these two extremes.

All seven of the prospective studies show a remarkable consistency in the higher mortality of smokers, particularly from lung cancer. Of special interest is that the size of the association between cigarette smoking and total lung cancer death rates has increased with the ongoing progress of the studies. Depending on the kind of population studied, the relative risks of lung cancer for current cigarette smokers in America compared with non-smokers range from 4.9 in one study to 15.9 in another. A study among British doctors showed a ratio of 20.2. For the studies as a whole, cigarette smokers have a risk of developing lung cancer 10.8 times greater than non-

smokers. The mortality ratios increase progressively with amount of smoking; the pivot level appears to be 20 cigarettes a day. For those who smoke pipes and/or cigars (to the exclusion of cigarettes), the lung cancer ratios are lower than for any of the cigarette smoking classes including combinations of cigarettes with pipe and/or cigars.

In extensive and controlled blind studies of the tracheobronchial tree of 402 male patients, it was observed that several kinds of changes of the epithelium were much more common in the trachea and bronchi of cigarette smokers and subjects with lung cancer than in non-smokers and patients without lung cancer. The epithelial changes observed are (1) loss of ciliated cells, (2) basal cell hyperplasia (more than two layers of basal cells), and (3) presence of atypical cells. Each of the three kinds of epithelial changes was found to increase with the number of cigarettes smoked. Extensive atypical changes were seen most frequently in men who smoked two or more packs of cigarettes a day. Men who smoke pipes or cigarettes have more epithelial changes than non-smokers but have fewer changes than cigarette smokers consuming approximately the same amount of tobacco. It may be concluded, on the basis of human and experimental evidence, that some of the advanced epithelial lesions with many atypical cells, as seen in the bronchi of cigarette smokers, are probably pre-malignant.

Other pathologic studies show that squamous and oval-cell carcinomas are the predominant types associated with the increase of lung cancer in the male population, and that a significant relationship exists between smoking and the epidermoid and anaplastic types. In several studies, adenocarcinomas have also shown a definite increase, although to a lesser extent. Various studies have suggested that adenocarcinomas have little or less relationship to smoking.

In general, the association between smoking and lung cancer may be measured by certain crude indirect indicators as well as by the direct measures (retrospective and prospective studies) described earlier. Indirect measures include: a parallel increase in lung cancer mortality rates and in per capita consumption of tobacco; disparities between male and female lung cancer rates and the corresponding differences between smoking habits of men and women by amounts smoked and duration of smoking.

The retrospective and prospective studies directly measure the occurrence and relationship of smoking and lung cancer in the same kinds of population. Careful analysis of these studies demonstrates that neither diagnostic errors nor classification errors in terms of amount smoked are of sufficient size to invalidate the results. Possible bias due to selection of subjects is diminished by the fact that in the continuing studies, lung cancer death rate differentials increase with the passage of time. Thus, it would appear that an association between cigarette smoking and lung cancer does indeed exist.

No single criterion is sufficient to evaluate the causal significance of this association, but a number of different kinds of criteria, considered together, provide an adequate test: the association is *consistent*; no prospective study and no reasonably designed retrospective study has found results to the contrary. In the nine retrospective studies for which relative risks for smokers and non-smokers were calculated, and in the seven prospective studies, the relative risk ratios for lung cancer were uniformly high and remarkably

close in magnitude, attesting to the *strength* of the association. Moreover a dose-effect phenomenon is apparent in that the relative risk ratio increases with the amount of tobacco consumed or of cigarettes smoked. From the prospective studies, it is estimated that in comparison with non-smokers, average smokers of cigarettes have approximately a 9- to 10-fold risk of developing lung cancer and heavy smokers at least a 20-fold risk.

An important criterion for the appraisal of causal significance of an association is its *coherence* with known facts of the natural history and biology of the disease. Careful examination of the natural history of smoking and of lung cancer shows the relationship to be coherent in every aspect that could be investigated. The probability that genetic influences might underlie both the tendency toward lung cancer and the tendency to smoke were also examined. The great rise in lung cancer recorded in man, that has occurred in recent decades, points to the introduction of new determinants without which genetic influences would have had little or no potency. The genetic factors in man were evidently not strong enough to cause the development of lung cancer in large numbers of people under environmental conditions that existed half a century ago. The assumption that the genetic constitution of man could have changed gradually, simultaneously, and identically in many countries during this century is most unlikely. Moreover, the risk of developing lung cancer diminishes when smoking is discontinued, although the genetic constitution must be assumed to have remained the same.

It has been recognized that a causal relationship between cigarette smoking and lung cancer does not exclude other factors. Approximately 10 percent of lung cancer cases occur among non-smokers. The available evidence on occupational hazards, urbanization or industrialization and air pollution, and previous illness was considered for possible etiologic factors.

A significant excess of lung cancer deaths was found among workers in certain industries—notably chromate, nickel processing, coal gas, and asbestos—but the population exposed to industrial carcinogens is relatively small; these agents cannot account for the increasing lung cancer risk in the general population. The urban-rural differences in lung cancer mortality risk, though small and accounted for in part by differences in smoking habits, imply that intensity of urbanization or industrialization and air pollution may have a residual influence on lung cancer mortality. Observations on previous respiratory illness are too few in number to place any degree of assurance on relationship with lung cancer.

### *Conclusions*

1. Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction.
2. The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking.

3. The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers, and pipe and cigar smokers is greater than in non-smokers, but much less than for cigarette smokers. The data are insufficient to warrant a conclusion for each group individually.

## ORAL CANCER

The suspicion of an association between use of tobacco and oral cancer dates back to the early 18th century when cancer of the lip was first noted among users of tobacco. In modern times, 20 retrospective studies have shown a significant association of oral cancer with smoking or chewing of tobacco or use of snuff. Associations between oral cancer and smoking of cigarettes, cigars, and pipes were noted in nearly all of these studies, but in many of them pipes and cigars seemed to exert a stronger influence.

In a study in which the sample size was large and controls adequate, it was possible to establish gradients for lip cancer by number of pipefuls smoked a day, for tongue cancer by amount of tobacco in pipes and cigars, and oral cancers by number of pipefuls. No gradient by amount smoked was noted for cigarettes.

The seven prospective studies show that cigarette smokers have proportionately 4.1 times as much mortality from oral cancer as non-smokers. This is the third highest mortality ratio of cigarette smokers to non-smokers among the several specific types of cancer deaths and the fourth highest among all causes of death associated with cigarette smoking. For cigar and pipe smokers compared with non-smokers, oral cancer has the highest mortality ratio, 3.3, of all causes of death, exceeding cancer of the esophagus, larynx, and lung.

Cancer of the oral cavity has not been produced experimentally by the exposure of animals to tobacco smoke or to carcinogenic aromatic polycyclic hydrocarbons except in the special case of benzo(a)pyrene and other hydrocarbons on the cheek pouch of the hamster. Leukoplakia was reported to have been induced by the injection of tobacco smoke condensates into the gingiva of rabbits. A strong clinical impression links the occurrence of leukoplakia of the mouth with the use of tobacco in its various forms.

## *Conclusions*

1. The causal relation of the smoking of pipes to the development of cancer of the lip appears to be established.

2. Although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications cannot at present be stated.

## LARYNX

Retrospective studies with adequate sample size all designate cigarette smoking as the most significant class associated with cancer of the larynx.



In each of the seven prospective studies, laryngeal cancer has been observed among smokers in frequencies in excess of the expected. A summation yields a mean mortality ratio of 5.3 for cigarette smokers.

Recently calculated material from six prospective studies shows a gradient of risk ratios from 5.3 for smokers of one pack or less of cigarettes per day to 7.5 for smokers of more than a pack per day. Laryngeal cancer cases were also associated with cigar and pipe smoking, but the number of cases is not yet large enough for judgment.

The relative strength of the association, as measured by the specific mortality ratio (as an average of combined experiences), is not as high as that noted for lung cancer, but two of the three major studies with adequate case loads indicate that the real value of the relative risk may approach that for lung cancer. As with lung cancer, a dose-effect of smoking is also demonstrable. The majority of the retrospective studies have shown a greater association with heavy smoking. So far as known, no attempts to induce carcinoma of the larynx by tobacco smoke or smoke condensates have been reported.

### *Conclusion*

Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male.

## ESOPHAGUS

Both the retrospective and prospective studies show an association between esophageal cancer and tobacco consumption. In the seven prospective studies, smokers have died of esophageal cancer 3-4 times as frequently as non-smokers; the mortality ratio for pipe and cigar smokers (compared to non-smokers) is 3.2, second only to that for oral cancer. Recent data from six of the prospective studies show a gradient of risk ratios from 3.0 for smokers of one pack or less of cigarettes per day to 4.9 for smokers of more than a pack per day.

So far as known, no attempts to induce carcinoma of the esophagus by tobacco smoke or smoke condensates have been reported.

### *Conclusion*

The evidence on the tobacco-esophageal cancer relationship supports the belief that an association exists. However, the data are not adequate to decide whether the relationship is causal.

## URINARY BLADDER

In 1955, when the lips and oral mucosa of mice were painted with tobacco tars for five months, 10 percent of the animals developed carcinoma of the urinary bladder. This experimental work led to four retrospective studies, all of which found a significant association between cigarette smoking and

urinary bladder cancer in males. Two of the studies also found significant associations with pipe or cigarette smoking. Compared with non-smokers, the relative risk of smokers developing cancer of the urinary bladder varied from 2.0 to 2.9.

The mean mortality ratio—cigarette smokers to non-smokers—for all seven prospective studies is 1.9. Among smokers of one pack or less per day the mortality from urinary bladder cancer is 1.4 times that of non-smokers; for smokers of more than a daily pack, it is 3.1.

### *Conclusion*

Available data suggest an association between cigarette smoking and urinary bladder cancer in the male but are not sufficient to support judgment on the causal significance of this association.

## STOMACH

None of the retrospective studies shows an association between gastric cancer and smoking. The prospective studies show that cigarette smokers die of gastric cancer 1.4 times more often than non-smokers, but this is below the total mortality ratio. No gradient of risk by amount smoked is apparent.

Attempts to produce cancer of the stomach in experimental animals with tobacco tars have not been successful.

### *Conclusion*

No relationship has been established between tobacco use and stomach cancer.

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