GENERAL CHEMICAL AND EXPERIMENTAL DATA ON CARCINOGENESIS AND TOBACCO SMOKE

Polynuclear Aromatic Hydrocarbons

As criteria for the presence of polynuclear aromatic hydrocarbons in tobacco smoke, the list of J. W. Cook (*20*) has been widely accepted by tobacco chemists.

The Surgeon General's 1964 Report and Cook's paper are in agreement with respect to the presence of benzo(a)pyrene (3:4-benzopyrene), dibenz(a,h)-anthracene (1,2:5,6-dibenzanthracene),[1] benzo(c)phenanthrene (3:4-benzophenanthrene), and dibenzo(a,i)pyrene (3,4:9,10-dibenzopyrene), all having carcinogenic activity.

Cook considers, furthermore, as identified: Benz(a)anthracene (1,2-benzanthracene) marginal carcinogenic activity; chrysene, benzo(e)pyrene (1,2-benzopyrene), questionable carcinogenic activity; benzo(g,h,i)-perylene (1,12-benzoperylene),[2] benzo(b)fluoranthene (3,4-benzofluoranthene) carcinogenic (*59*, *106*), and benzo(j)fluoranthene (10,11-benzofluoranthene) carcinogenic (*106*).

Indeno (1.2.3-cd)pyrene (2,3-phenylenepyrene) has since been isolated from tobacco smoke (*45*). This polynuclear aromatic hydrocarbon was found to be carcinogenic (*44*, *59*). The following carcinogens, or questionable carcinogens, were isolated by Kiryu and Kuratsune (*55*) in the smoke of cigarettes smoked by human volunteers: benz(a)anthracene, chrysene, benzo(a)pyrene, benzo(e)pyrene, benzo(b)fluoranthene and benzo(k)fluoranthene. The carcinogenic polynuclear aromatic hydrocarbons are regarded as the major initiating carcinogens in tobacco smoke.

N-Heterocyclic Aromatic Hydrocarbons

The Surgeon General's 1964 Report lists as carcinogenic compounds three N-heterocyclics, dibenz(a,j)acridine, dibenz(a,h)acridine and 7 H-dibenzo-(c,g)carbazole. An independent investigation has confirmed the presence of the first named compound in cigarette smoke (*107*).

N-Nitrosamines

N-nitrosamines are among the most powerful known animal carcinogens. Since tobacco smoke contains secondary amines (*57*, *71*)

[1] Dibenzo (a,h)anthracene in the Surgeon General's 1964 Report should be replaced by dibenz(a,h)anthracene (*24*).

[2] Benzo(g,h,i)perylene was not tested for carcinogenicity until 1966 and then was found to be inactive (*44*).

and most tobaccos, certainly Burley and Maryland varieties, contain nitrates (*64*), tobacco smoke can be considered as a potential environment for the formation of N-nitrosamines. The major nitrates in tobacco are alkaline nitrates.

Neurath, et al., isolated three aliphatic N-nitrosamines from the smoke of a cigarette rich in volatile basic components and high in nitrate content. One of them tentatively has been identified as methy-n-butyl-nitrosamine (*73*).

When the particulate matter, "tar," was collected from cigarettes not enriched with basic components or when the smoke particulate matter was collected without aging and not in cold traps, N-nitrosamines could not be isolated from cigarette smoke (*72*). Since the only other publication concerned with the isolation of nitrosamines in cigarette smoke was based on cold trap collection of "tar," the positive finding of three N-nitrosamines appears questionable (*86*).

In summary, tobacco smoke can be regarded as a potential environment for the formation of N-nitrosamines. However, additional information is needed to substantiate their presence in tobacco smoke.

Polonium 210

Several investigators (*33*, *35*, *50*, *76*, *92*, *93*, *112*) have found trace amounts of Po^{210} in tobacco leaf and cigarette smoke. The concentration of Po^{210} in lung tissue is relatively high (*33*, *67*) as compared to other body tissues and is higher in smokers than in nonsmokers (*33*, *43*, *65*, *66*).

Lung tumors have been induced experimentally by intratracheal implantation of various radioactive substances. These radioactive substances must, however, be present in the respiratory environment above a certain threshold level and must be in contact with the target organ long enough to be effective (*68*, *77*, *88*, *107*). Because Po^{210} emits alpha particles, it has been implicated as a lung cancer initiator (*43*, *68*, *76*, *77*). More research is needed before definitive conclusions can be made. Until such time, however, Po^{210} should be considered as a potential tumor initiator in tobacco smoke.

Selenium

Selenium has been mentioned as possibly being important in the pathogenesis of human lung cancer (*100*). Preliminary reports suggest that selenium may be present in some cigarette papers. Because earlier reports (*17*, *34*, *97*) indicated the ingestion of selenium caused cancer of the liver in mice, a recent investigation (*101*) by the National Cancer Institute was conducted, with negative results. So far the earlier reports of the carcinogenicity of selenium have not been substantiated. Additional information is needed on the possible carcinogenicity of selenium and its presence in cigarette smoke before selenium can be indicted as an agent in human cancer.

Phenols

Tobacco smoke contains a large number of phenols (*107*). Several of them are known to be tumor promoting agents when applied in high concentrations to mouse skin previously treated with a tumor initiator (*14*).

In Vitro Cellular Changes by Tobacco Smoke

Lasnitzki (*60*) extended her studies with tobacco smoke condensate on cultured human fetal lung tissue to include a "highly purified fraction of hydrocarbons" isolated from cigarette smoke condensate. In 33 out of 50 treated lung tissue explants, the epithelium of the bronchi was hyperplastic and sometimes showed squamous changes. These changes were not observed with the untreated controls. Although a hydrocarbon-free fraction was weakly active by producing some squamous metaplasia in these explants, these tissue culture tests point strongly to carcinogenic hydrocarbons as the active group in the smoke. The findings with purified carcinogenic hydrocarbons in organ culture (*21*) support the finding that polynuclear aromatic hydrocarbons are one group of active smoke constituents. Carcinogenic hydrocarbons are also the only group of chemical components that have been demonstrated *in vitro* to induce malignant conversion of single cells (*7*, *13*).

In summary, tobacco smoke has been demonstrated *in vitro* to induce pathological changes in tissue explants. Although such changes may be induced by different smoke constituents, as yet the carcinogenic hydrocarbons are the only agents identified in tobacco smoke which have been shown to induce malignant changes in tissue cultures.

In Vivo Tumor Formation by Tobacco Smoke

Passive inhalation experiments with tobacco smoke have not yet led to fully established squamous carcinoma in mice (*109*). This method of application has resulted only in papillomatous growth in the tracheobronchial mucosa of a few hamsters. None of the tumors, however, was found to be invasive (*30*, *111*). It appears that passive inhalation may not lead to the induction of squamous cell bronchogenic cancer in experimental animals. This conclusion can also be applied to passive inhalation studies in which the animals are infected by a virus before long-term smoke exposure (*62*, *110*). The pathological changes seen in the mice were reversible whether or not the animals were previously infected with a virus. The hyperplasia and metaplasia seen in mice and rats after passive inhalation appears, at least in part, to be secondary to viral or bacterial infection that is enhanced by exposure to tobacco smoke. The relatively negative findings with pas-

sive inhalation experiments probably relate to the relatively small amounts of smoke aerosols that bypass the nasal passages. The defensive nature of the upper respiratory tract against airborne irritants has to be fully appreciated in the evaluation of any passive inhalation study.

Active inhalation studies with tracheostomized dogs, as carried out by Rockey, (*79*, *80*) and Auerbach (*2*), suggest that this approach may lead to the induction of bronchogenic carcinoma. The change in the bronchial epithelium after 1 year of active smoking indicates early pathological changes that may, upon continued smoke exposure, lead to tumors in the bronchi.

So far, neither passive nor active inhalation studies have contributed to our knowledge about the nature of the tobacco smoke carcinogens. Studies with the particulate matter, tar, of cigarette, pipe, and cigar smoke, however, have clearly demonstrated that at the site of application tumors can be induced. Tumors have been induced on the skin of mice and rabbits, the ears of rabbits, the subcutaneous tissue and hilum of rats and the cervices of mice (*9*, *11*, *22*, *31*, *32*, *46*, *48*, *61*, *74*, *82*, *83*, *84*, *107*, *108*).

Only relatively few investigators have been concerned with the nature of chemical carcinogens in tobacco smoke (*47*, *84*, *107*). Although the acidic and nicotine-free basic portions of tobacco tar had been found to have weak tumorigenic activity, the only fraction shown to have induced significant numbers of tumors is fraction B of the neutral portion (2 percent of the whole condensate) (*107*). This B fraction was further fractionated into three subfractions from which only B_1 was shown to have tumorigenic activity (*47*). The B_1 fraction equals 0.6 percent of the tar and combines all aromatic hydrocarbons with three to seven rings including the carcinogenic ones. This can be considered as evidence that in *in vivo* studies, the polynuclear aromatic hydrocarbons are the major carcinogens in tobacco smoke. Although these compounds alone can account for only a small portion of the tumorigenic activity of tobacco tar, they are, nevertheless, the only identified carcinogens and tumor initiators in tobacco smoke shown by experimentation to be biologically active. Their tumorigenic effect is enhanced by the presence of tumor-promoting agents in the smoke.

Tumor-Promoting Agents in Tobacco Products

In the experimental setting, the tumorigenicity of tobacco smoke condensate cannot be solely explained by the presence of known carcinogens. In assays on mouse skin and rat subcutaneous tissue, the known carcinogens must be enhanced by other components such as tumor-promoting agents. In fact, it has been demonstrated that to-

bacco extract and tobacco smoke condensate can act as promoters to mouse skin previously treated with tumor-initiating carcinogenic polycyclic aromatic hydrocarbons (*10*, *12*, *96*, *107*). Although some tumor-promoting activity of tobacco "tar" can be explained by some phenols and carboxylic acids, additional tumor promoters in tobacco products remain to be isolated and identified.

It is important, however, that a significant decrease of the polynuclear aromatic hydrocarbons in tobacco "tar" leads to a significant decrease of the overall activity of the "tar" on mouse skin (*9*, *46*, *108*, *109*).

In summary, experimental studies have demonstrated that the particulate matter of tobacco smoke, "tar," is tumorigenic. Some polynuclear aromatic hydrocarbon-carcinogens have been identified as contributing significantly to the overall tumorigenic activity of tobacco smoke condensates in the experimental setting.

LUNG CANCER

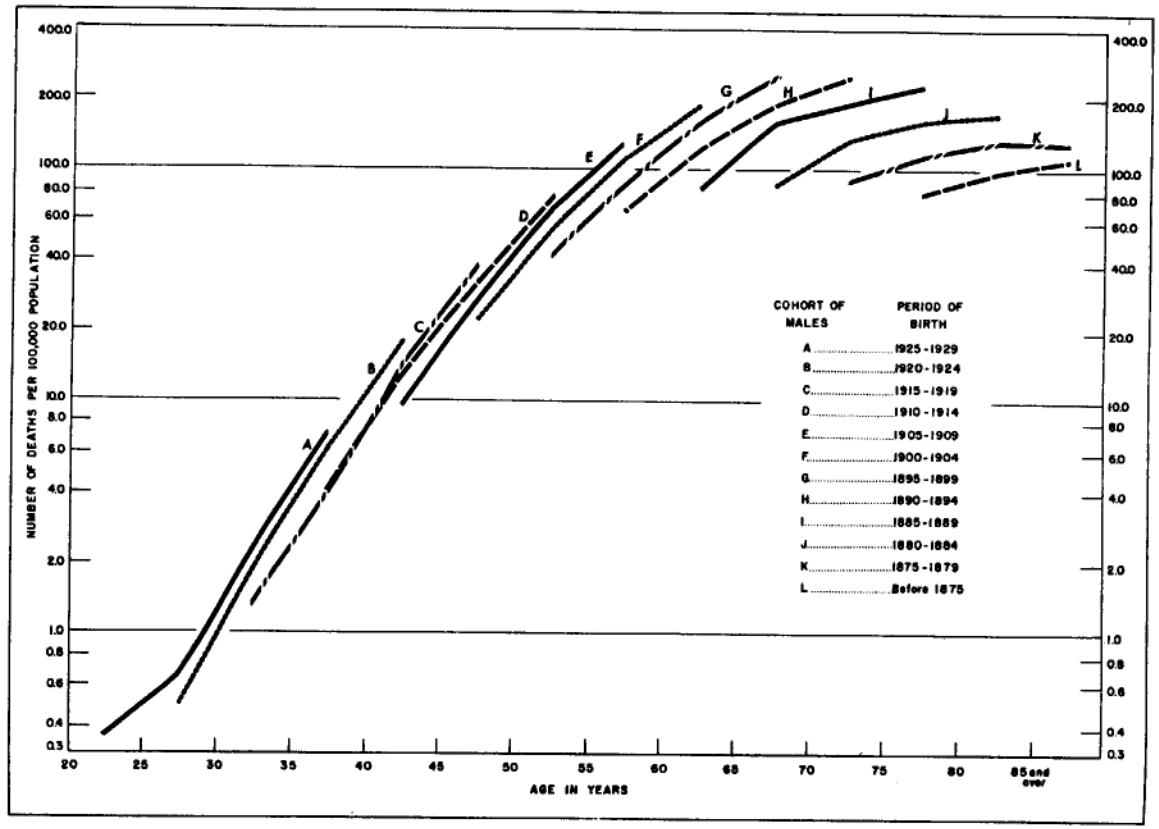
Mortality Data [1]

The annual number of deaths in the United States from cancer of the lung (International Classification of Diseases, Codes 162, 163) rose from 18,313 deaths in 1950 to 45,838 in 1964 (*94*). In this 15-year period, deaths from lung cancer totaled 467,442. During this same time period the death rate for cancer of the lung almost doubled, a rise from 12.2 deaths per 100,000 population in 1950 to 24 deaths per 100,000 population in 1964. (The corresponding age-adjusted rate has also nearly doubled, therefore the increase in the death rate cannot be attributed to the changing age composition of the population.) The lung cancer mortality in the male population increased from 19.9 deaths per 100,000 population in 1950 to 41.4 in 1964, while in the female population the deaths increased from 4.5 to 7.1 per 100,000 population over the same time period.

The mortality experience of the individual male cohorts during 1949–64 (fig. 1) shows that at any given age the risk of dying from lung cancer was almost always higher for the more recently born cohort. Within each cohort, the death rate for lung cancer increased steadily to the end of the life span.

Figure 2 shows the death rate for women by cohort groups and age at death. One can see the increasing death rate slope for each more recently-born cohort, starting with cohort F—those women who were 26–30 years old in 1930. This corresponds to the time when smoking became increasingly popular among women.

[1] All death rates throughout this chapter are per 100,000 population unless otherwise indicated.



Source: National Center for Health Statistics (*94*).

FIGURE 1.—Cancer of the lung among men, by birth cohort and age at death: 1949, 1954, 1959, and 1964.

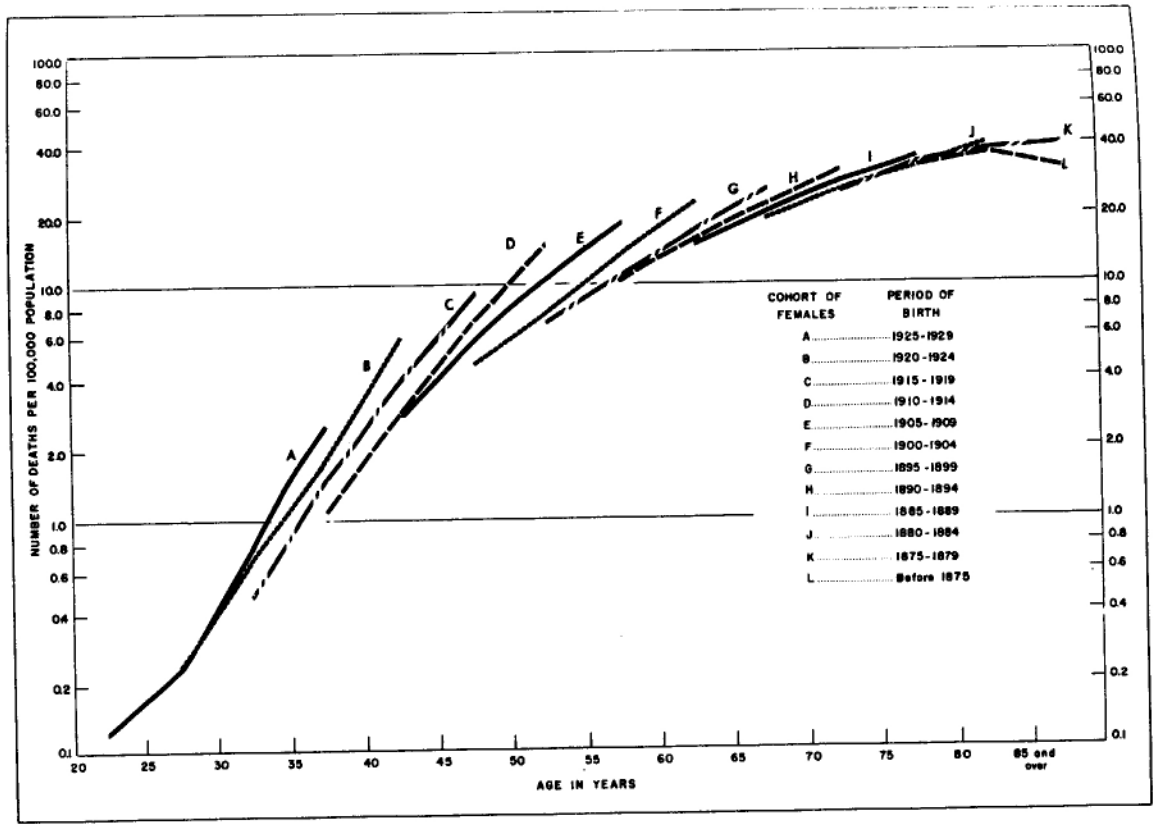


FIGURE 2.—Cancer of the lung among women, by birth cohort and age at death: 1949, 1954, 1959, and 1964.

Source: National Center for Health Statistics (94).

In the female population the greatest percentage increase (116 percent) over the 15-year period, 1949–64, occurred in the 35–44 year age group. The next highest percentage increase was noted in the age group 45–54 years. The death rate from lung cancer among women, 25 years and over, rose steadily with advance in age for each year during 1950–64, and the cohort experience shows that these death rates continued to increase for each cohort to the end of the life span.

Hammond's (*40*) prospective study provides extensive information about the lung cancer mortality experience of both men and women in relation to cigarette-smoking history as presented by mortality ratio [1] and by death rates per 100,000 person-years. (Table 1).

TABLE 1.—*Lung cancer mortality ratios and death rates* * *of smokers by sex and specific age groups*

	45–64 years		65–79 years	
	Females	Males	Females	Males
Mortality ratios	2. 17	7. 84	[1] 1. 76	11. 59
Death rates	[2] (7)15	[2] (*11*)87	[2] (*17*)30	[2] (*23*)262

[1] Computed from app. table 19.
[2] Numbers in parentheses indicate death rate for nonsmokers.

SOURCE: Hammond, E. C. [tables 24 and 26, app. table 19 (*40*)].

Tables 2 and 3 below show the relationships of number of cigarettes smoked per day, degree of inhalation, and age smoking began, to lung cancer mortality ratios and death rates for males and females, respectively. Generally, mortality ratios and death rates increase with increasing amount of cigarettes smoked and degree of inhalation, and with a longer lifetime history of smoking. Table 3 shows the relatively lower lung cancer mortality among women as contrasted to men, but reveals, for the most part, the same relationship to amount smoked, degree of inhalation, and age when smoking began.

Table 4 illustrates the fact that cessation of cigarette smoking is associated with a decline in lung cancer death rates.

* The mortality ratio is the ratio of the death rate of smokers to that of nonsmokers—the mortality ratio of nonsmokers always being *one*, by definition.

TABLE 2.—*Lung cancer (men). Number of deaths, and age-standardized death rates and mortality ratios, by current number of cigarettes smoked per day, degree of inhalation, and age began smoking, by age at start of study* [1]

Number of cigarettes a day, degree of inhalation, and age began smoking	Age 35–54		Age 55–69		Age 70–84		All ages, 35–84	
	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate
Current number of cigarettes a day:								
1 to 9	9	38	12	68	5	134	26	56
10 to 19	15	24	57	168	10	243	82	90
20 to 39	138	58	216	264	27	446	381	159
40 plus	26	47	50	334	6	754	82	201
Degree of inhalation:								
None or slight	19	29	87	203	14	193	120	102
Moderate	114	52	177	224	20	401	311	138
Deep	55	55	73	266	13	638	141	173
Age began cigarette smoking:								
25 or older	5	17	12	65	3	85	20	39
20 to 24	31	36	72	212	7	306	110	118
15 to 19	112	54	176	250	27	490	315	155
Less than 15	35	79	57	302	9	424	101	183
Never smoked regularly	11	6	27	19	11	25	49	12
	Lung cancer mortality ratios (men)							
Current number of cigarettes a day:								
1 to 9	--------	6.17	--------	3.53	--------	5.32	--------	4.60
10 to 19	--------	3.90	--------	8.77	--------	9.62	--------	7.48
20 to 39	--------	9.37	--------	13.82	--------	17.62	--------	13.14
40 plus	--------	7.67	--------	17.47	--------	29.84	--------	16.61
Degree of inhalation:								
None or slight	--------	4.75	--------	10.60	--------	7.65	--------	8.42
Moderate	--------	8.48	--------	11.72	--------	15.88	--------	11.45
Deep	--------	9.00	--------	13.93	--------	25.26	--------	14.31
Age began cigarette smoking:								
25 or older	--------	2.77	--------	3.39	--------	3.38	--------	3.21
20 to 24	--------	5.83	--------	11.11	--------	12.11	--------	9.72
15 to 19	--------	8.71	--------	13.06	--------	19.37	--------	12.81
Less than 15	--------	12.80	--------	15.81	--------	16.76	--------	15.10

[1] Mortality ratios are based on death rates carried out to 1 more significant figure than shown.

SOURCE: Hammond, E. C. [table 20 (*40*)].

TABLE 3.—*Lung cancer (women). Number of deaths, age-standardized death rates, and mortality ratios, by type of smoking (lifetime history), current number of cigarettes smoked per day, degree of inhalation, and age began smoking, by age at start of study* [1]

Type of smoking (lifetime history)	Age 40–54		Age 55–74		All ages, 40–74	
	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate
Never smoked regularly	25	4	77	12	102	7
History of cigarette smoking	48	11	33	23	81	16
	Current regular cigarette smoking					
Current number of cigarettes a day:						
1 to 19	15	8	5	7	20	8
20 plus	28	17	22	50	50	35
Degree of inhalation:						
None or slight	16	13	9	13	25	13
Moderate or deep	27	11	18	48	45	27
Age began smoking:						
25 or older	7	6	16	21	23	12
Less than 25	35	14	11	43	46	27
	Lung cancer mortality ratios (women)					
Never smoked regularly	----------	1.00	----------	1.00	----------	1.00
History of cigarette smoking	----------	2.82	----------	1.93	----------	2.20
	Current regular cigarette smoking					
Current number of cigarettes a day:						
1 to 19	----------	2.08	----------	0.62	----------	1.06
20 plus	----------	4.43	----------	4.91	----------	4.76
Degree of inhalation:						
None or slight	----------	3.33	----------	1.12	----------	1.78
Moderate or deep	----------	2.90	----------	4.04	----------	3.70
Age began smoking:						
25 or older	----------	1.55	----------	1.76	----------	1.70
Less than 25	----------	3.78	----------	3.60	----------	3.65

[1] Mortality ratios are based on death rates carried out to 1 more significant figure than shown.

SOURCE: Hammond, E. C. [table 23 (*40*)].

TABLE 4.—*Lung cancer (men). Age-standardized death rates and mortality ratios for ex-cigarette smokers with a history of cigarette smoking only, by former number of cigarettes smoked per day, and years since last cigarette smoking. Death rates for current cigarette smokers with a history of cigarette smoking only. Men who never smoked regularly are shown for comparison. Men aged 50–69.*

Ex-cigarette smokers (years since last cigarette smoking)	Smoked 1–19 cigarettes a day			Smoked 20+ cigarettes a day			Mortality ratio, smoked—	
	Number of men	Number of deaths	Death rate	Number of men	Number of deaths	Death rate	1–19	20+
Under 1 year	746	3	108	2,244	33	437	------	------
1 to 4 years	1,844	5	69	5,435	33	180	------	------
5 to 9 years	1,770	1	15	5,803	22	108	------	------
10 plus years	4,209	1	6	8,142	5	16	------	------
Total ex-smokers	9,569	10	30	21,624	93	119	[1]2.0	7.9
Current cigarette smokers	22,808	80	97	56,886	351	205	6.5	13.7
Never smoked regularly	55,728	32	15	55,728	32	15	------	------

[1] Computed from source.

SOURCE: Hammond, E. C. [table 21 (*40*)].

The Dorn study (*49*) of U.S. veterans provides additional information on the relationship of dosage to mortality ratios and death rates for males who smoked cigarettes only (table 5).

TABLE 5.—*Lung cancer mortality ratios and death rates for U.S. veterans by age, type, and amount of smoking*

	Number of cigarettes/day									
	0		1–9		10–20		21–39		40+	
	DR[1]	MR[1]	DR	MR	DR	MR	DR	MR	DR	MR
Current cigarette smokers only:										
Age 45 to 54	------	------	------	------	24	------	52	------	72	------
Age 55 to 64	10	1.00	70	7.00	123	12.30	205	20.50	338	33.80
Age 65 to 74	30	1.00	135	4.50	265	8.83	432	14.40	696	23.20
Age 75 plus	46	1.00	------	------	------	------	------	------	------	------
Total	------	1.00	------	5.49	------	9.91	------	17.41	------	23.93
Ex-cigarette smokers only	------	------	------	.95	------	3.48	------	9.33	------	8.24

[1] DR, Death rate; MR, Mortality ratio.

SOURCE: U.S. veterans study [app. table A (*49*)].

The mortality ratios of the Dorn (*49*) study can be compared with those of the Canadian veterans study, in table 6:

TABLE 6.—*Lung cancer mortality ratios for Canadian veterans by age, type, and amount of smoking*

	Number of cigarettes/day			
	0	1-9	10-20	21+
Current cigarette smokers only:				
Age 30 to 49	1. 00	2. 47	4. 15	4. 08
Age 50 to 69	1. 00	10. 71	26. 92	26. 83
Age 70 plus	1. 00	12. 15	9. 43	24. 53
Total	1. 00	10. 00	16. 41	17. 31
Ex-cigarette smokers only total	6. 06			

SOURCE: Canadian Pensioners study [(8), Table 8.1 and 8.2].

From the data shown in table 2 mortality ratios of 17.47 and 29.84 may be noted for smokers of 40+ cigarettes per day, age 55–69 and 70–84, respectively. The Dorn (*49*) study (see table 5) similarly shows mortality ratios of 33.80 and 23.20 for smokers of 40+ cigarettes per day, age 55–64 and 65–74, respectively. The Canadian study (see table 6) shows mortality ratios of 26.83 and 24.53 for smokers 50–69 and 70 years of age and older respectively who smoked over 20 cigarettes per day. There is rather close agreement among the three large prospective studies for the general range of mortality ratios observed in heavy smokers. From the data supplied by the Doll and Hill survey of British physicians (*28*, *29*) a mortality ratio of 31.86 can be calculated for all smokers of more than 25 cigarettes per day, as compared to a mortality ratio of approximately 8, for smokers of 1–14 cigarettes per day (see table 8).

There is relatively little risk of lung cancer associated with pipe or cigar smoking, probably because smoke from these sources is rarely inhaled. "Mixed smokers," i.e., smokers of cigarettes, pipes, and/or cigars, have less risk than do smokers of cigarettes only, also suggesting that they may smoke fewer cigarettes or inhale less tobacco smoke than do smokers of cigarettes only (see tables 7 and 8).

TABLE 7.—*Lung cancer mortality ratios by type and amount smoked*

Current smokers of cigarettes only					Current pipe and/or cigar only	Ex-smokers of cigarettes only
All amounts per day	1–9	10–20	21–39	40+		
12. 14	5. 49	9. 91	17. 41	23. 93	1. 67	5. 00

SOURCE: U.S. veterans study [app. table A (*49*)].

TABLE 8.—*Lung cancer death rates by type of smoker and amount smoked*

Nonsmokers	All smokers	Cigarette smokers				Given up cigarette smoking	Mixed smokers	Pipe or cigar
		All amounts per day	1–14	15–24	25+			
7	71	120	57	129	223	24	52	43

SOURCE: Study of British physicians [tables 23 and 24 (*28*)].

TABLE 9.—*Lung cancer death rates for ex-smokers of cigarettes by length of time stopped smoking*

Continuing cigarette smokers	Ex-smokers				Nonsmokers
	Less than 5 years	5–9 years	10–19 years	20+ years	
128	67	49	18	19	7

SOURCE: Study of British Physicians [table 25 (*28*)].

The preceding studies show appreciably lower mortality ratios and death rates from lung cancer with the cessation of cigarette smoking (see tables 4, 5, 6, 7, 8, 9). This lower risk is evident irrespective of the quantity of cigarettes formerly smoked.

The Doll and Hill study (*28*) of British physicians is of particular interest in respect to ex-smokers. Over the 10-year period of the study (1951–61) 29 percent of the smokers of cigarettes only, had significantly decreased (one-half pack cigarettes or more) their smoking (including those who stopped) and 5 percent had switched to pipes and/or cigars.

While the overall lung cancer mortality of men over age 25 in England and Wales had increased 22 percent over this 10-year period, that for the physician group decreased 7 percent. Since the total physician group is involved in these figures, we can compare this population group to the entire population of England and Wales where there was no general decrease in amount of smoking. This can be thought of as a controlled cessation experiment and the beneficial

effects of stopping or decreasing the amount of smoking become quite evident.

Wicken (*102*), in a retrospective study of lung cancer mortality in Northern Ireland during the period 1960–62, reported the following results (Table 10):

TABLE 10.—*Lung cancer mortality ratios and death rates, by sex, age 35 and over, by type and amount of smoking, Northern Ireland, 1960–62*

	Non-smokers	Cigarette smokers amount per day			Cigarettes and pipe and cigar	Pipe and cigar only
		1–10	11–22	23+		
Male:						
Mortality ratios	1.00	4.83	9.33	21.2	5.22	2.27
Death rates	18	87	168	383	94	41
Female:						
Mortality ratios	1.00	2.27	6.72	19.0	----	----
Death rates	11	25	74	210	----	----

SOURCE: Wicken, A. J. [(*102*), Table 17].

Wicken also analyzed the proportion of lung cancer deaths which would have occurred if the lung cancer mortality rates of the least susceptible groups had been applied to the whole population of Northern Ireland, and found that males would have had only 18 percent of the lung cancer mortality if none smoked and that if they lived in truly rural areas they would have only 10 percent of the mortality. Thus, the difference—8 percent—may be attributable to the urban or suburban residence factor, possibly air pollution. If no females smoked, they would have had only 65 percent of the total female lung cancer mortality, and 53 percent if they lived in truly rural areas. Thus, for females, the difference of 12 percentage points might be attributed to the urban environment. The magnitude of these differences depends on the prevalence of lung cancer in the various subgroups of the particular population studied.

HISTOPATHOLOGY OF LUNG TUMORS

Classification of lung cancer by histologic type was discussed in the Surgeon General's 1964 Report with the conclusion that the squamous, undifferentiated, and oat-cell carcinomas were far more frequently found in smokers than in nonsmokers, while adenocarcinoma was relatively more frequent in nonsmokers, especially women. Changes in the bronchial mucosa resulting from the inhalation of cigarette smoke included loss of cilia, basal cell hyperplasia, and the appearance of atypical cells with irregular hyperchromatic nuclei. These changes, it was concluded, were related to the premalignant process of the de-

velopment of invasive carcinoma. Auerbach (*5*) has more recently reported on a study of the pathology of the tracheobronchial trees of 339 men who died from causes other than lung cancer and of 63 men who died from lung cancer. Up to 55 cross-sections of the tracheobronchial tissue were studied in each case. The 339 non-lung cancer cases included 65 men who had never smoked cigarettes and 274 men who had smoked in various amount. Figure 3 shows that only 1.3 percent of the slides from those who never smoked regularly have 60 percent or more atypical cells, whereas 76 percent of the slides of those smoking more than two packs a day had 60 percent or more atypical cells. (See figs. 3 and 4).

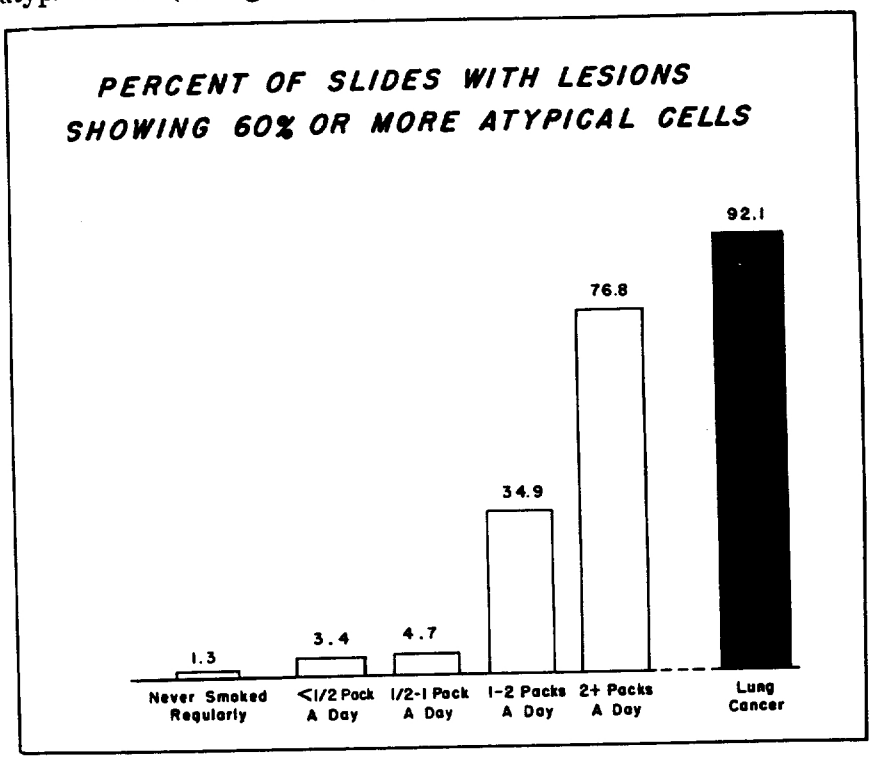


FIGURE 3.—Percent of slides with lesions showing 60 percent or more atypical cells

Source: Auerbach, O., et al. [Table 1(*5*), updated 1967]

Auerbach (*4*) has also studied the bronchopulmonary autopsy material from 255 men and three women who died of lung carcinoma of varying histological types, ranging in the spectrum of the WHO classification (*103*) from the highly differentiated to the undifferentiated squamous cell carcinoma, with others being oat cell, polygonal cell, acinar, and adenocarcinoma. A search for double primaries was made, and by using strict criteria, multiple primary invasive carcinoma was found in 3.5 percent of the autopsies studied. When less

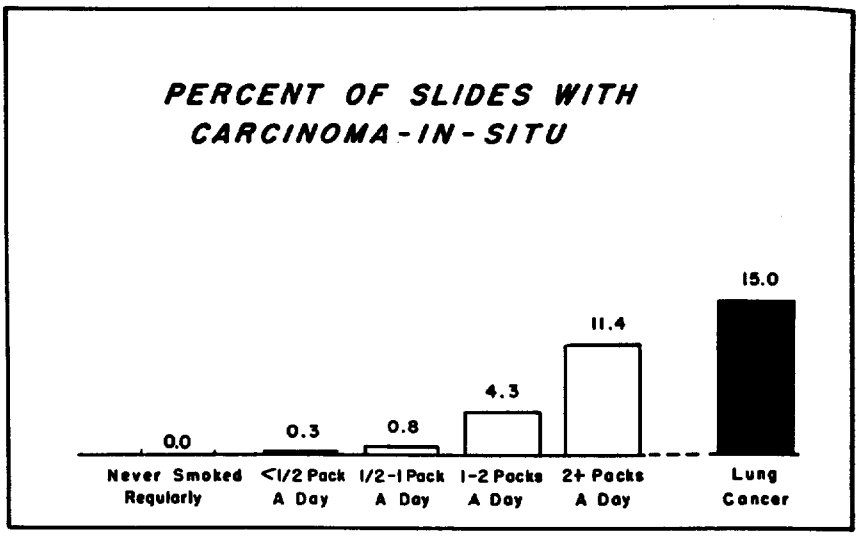


FIGURE 4.—Percent of slides with carcinoma *in situ*.

Source: Auerbach, O., et al. [Table 2(*5*), updated 1967].

strict criteria were used, but very doubtful cases excluded, up to 12.5 percent double primaries were found. This study suggests that multiple primary bronchial carcinomas in the same patient may be more frequent than previously suspected. Further studies are necessary in this area, since therapeutic implications are also involved.

The differentiation of tumor types as related to smoking habits in various groups with clinically diagnosed lung cancer has again been investigated in several recent studies. In one study (*19*), of 417 cases of histologically proven lung cancer, 87 percent were smokers. Among the squamous cell cancer cases 89 percent were smokers; among the undifferentiated cell cancer cases 90 percent were smokers, and among those with adenocarcinomas, 60 percent were smokers. A study (*99*) dealing specifically with alveolar cell cancer of the lung reports that 91 percent of the 180 males in whom this tumor type was diagnosed were smokers and, similarly, that 65 percent of the 85 females with this type tumor were smokers. Another study (*104*) was made of lung cancer cases in nonsmokers, defined as persons smoking not more than one cigarette a day for 10 years. This study group included eight males and 26 females. Of this group, only four patients had epidermoid carcinoma (two males and two females). Both males had a history of occupational exposure to respiratory irritants. Of the two women, one had an unusual history of carcinoma, including multiple basal cell skin cancers and *in situ* carcinoma of the cervix.

A study (*1*) was made of 666 histologically proven cases of lung cancer. A smoking history was recorded on 442 of the men in this

series. The chart below takes into account smoking histories as related to three histologic groups: undifferentiated, squamous, and adenocarcinoma (see table 11).

TABLE 11.—*Distribution of lung cancer deaths by cellular type and type of smoking*

Cellular type	Nonsmoker	Pipe smoker	Cigarette smoker
Undifferentiated	4	14	124
Squamous	6	24	211
Adenocarcinoma	2	1	56

SOURCE: Ashley, D. J. B., et al. [(*1*).Table 4.]

Insufficient information is provided in this study to specify in detail the past smoking histories, but the data suggest that cigarette smoking may be related to adenocarcinoma in some instances.

The preceding studies indicate that squamous, undifferentiated, and oat-cell carcinoma rarely occur in nonsmokers. However, it appears that cigarette smoking may also be associated with alveolar cell carcinoma and glandular carcinoma of the bronchi. This relationship has been previously suspected. In fact as early as 1950 Wynder and Graham (*105*) demonstrated this relationship. This was also shown in the study by Haenszel (*39*). Greater standardization and precision of diagnoses are needed to establish how few cases of undifferentiated or squamous carcinoma occur in nonsmokers who have been established to have never smoked appreciable amounts during their lifetimes. If 100 percent accurate smoking histories were obtainable on every case of lung cancer, it is suspected that very few cases of undifferentiated or squamous cancer would be found in persons who had never smoked.

A report (*98*) on lung cancer in uranium miners noted a frequency of lung cancer, occurring almost entirely in the cigarette-smoking miners, greater than the frequency to be expected in a similar sized cigarette-smoking nonuranium mining population. A recent report (*85*) on bronchogenic carcinoma in asbestos workers also noted an increased frequency of lung cancer, occurring entirely in the cigarette smoking asbestos workers. This frequency was greater than the frequency to be expected for a similar population of cigarette smokers who were not asbestos workers. These reports suggest that cigarette smoking may interact with certain other environmental exposures to increase the frequency of lung cancer occurrence still further.

Analysis of occupation and other environmental exposures must be performed simultaneously to detect which interactions with smoking seem to be especially dangerous.

Experimental attempts to produce lung cancer involve the administration of tobacco smoke condensates and of carcinogens known to be present in tobacco smoke, either *in vitro* to preparations of cells or *in vivo* in experimental animals. Difficulties are encountered with the viability of tissue cultures and experimental animals when subjected to these various substances. Studies of human tissue from lung cancer patients indicate that abnormalities of the tracheobronchial mucosa, such as loss of cilia, basal cell hyperplasia, squamous metaplasia, and cellular atypism are important in the pathogenesis of human lung cancer caused by smoking. These changes have been experimentally produced in dogs exposed to cigarette smoke through a tracheostomy (*2*, *79*, *80*). A large number of dogs is now being studied to determine if lung cancer can be experimentally produced by this technique; if the dogs continue to smoke for a longer time, malignant changes may appear subsequent to the already noted premalignant changes. The squamous metaplasia involved in the premalignant changes may explain why cigarette smoke condensate most readily produces cancer in the squamous epithelium of the skin of laboratory animals.

ADDITIONAL EVIDENCE CONCERNING EXPERIMENTAL CARCINOGENESIS

The inhalation of tobacco smoke by mice was reported to increase the frequency of glandular tumors (*37*, *41*, *63*, *70*). Syrian hamsters exposed to cigarette smoke developed a small number of tumors in the tracheobronchial epithelium (*30*, *110*). Cigarette smoke condensate has been studied in tissue culture preparations (*38*), and implantation of cigarette smoke condensate exposed lung tissue subcutaneously has been reported to cause malignant growths (*26*). Cigarette smoke condensate also causes skin tumors when applied topically (*9*, *11*, *46*, *48*, *61*, *74*, *82*, *107*, *108*). This was confirmed by a large-scale study with about 8,000 mice by the Tobacco Industry Research Council of England (*22*). Repeated injections of cigarette smoke condensate in rats produced sarcomas (*32*, *82*, *83*, *84*). Since 1963 two studies have reported negative results when cigarette smoke condensate was administered intratracheally to rats and Syrian hamsters (*25*, *42*), respectively.

Bronchoscopic painting of cigarette smoke condensate rapidly causes squamous metaplasia in dogs and may accelerate carcinogenesis (*91*). Carcinogens, known to be present in tobacco smoke, have been applied to cells in tissue culture with the observation of malignant changes (*7*) and other effects (*21*), such as differential growth inhibition of normal but not malignant cells (*23*). Inhalation (*53*, *78*, *90*), intratracheal administration (*25*, *36*, *42*, *54*, *81*), subcutaneous, intraperitoneal and intravenous injection, oral administration, and skin painting of carcinogens have all induced pulmonary tumors (*87*).

The search continues for an experimental animal system in which the inhalation of tobacco smoke will produce malignant tissue changes closely approximating those observed in human pulmonary cancer. When dealing with passive inhalation of tobacco smoke, however, a problem of the defensive barrier of the nasal passage is introduced. So far, dogs inhaling cigarette smoke through tracheostomies seem to be the most promising system, but there are problems in keeping the experiments going for the length of time necessary for lung cancer to develop. Additional research is needed using cultured lung tissue together with autograft and homograft studies to determine *in vivo* results. Additional insight may thus be gained into *in vivo* systems. It should be noted, however, that it may not be possible ever to achieve histologic identity in pulmonary cancer production, not only because of difficulties in duplication of man's smoking action for reasons of anatomic and physiologic differences, but also because of inherent species' differences in cellular response.

CANCER OF THE BUCCAL CAVITY AND PHARYNX (LIP, MOUTH, THROAT)

The Surgeon General's 1964 Report concluded that the causal relationship of pipe smoking to the development of cancer of the lip appeared to be established. Although there were suggestions of a relationship between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications could not be stated at that time.

The National Center for Health Statistics (*94*) reports that during 1964, 28 female and 157 male deaths occurred from cancer of the lip. During the period 1950–64, male mortality from this disease declined about 67 percent. This was partially due to changes in the diagnostic classification but was mainly due to increased early diagnosis and therapy. During the period 1958–64 when the seventh revision of the International Classification of Diseases was in use, total mortality from cancer of the lip remained about the same, but when analyzed by age, substantial decreases occurred in this death rate for each 10-year age group from 55–84 years.

As for cancer of the oral cavity, other than the lip, the total death rate showed no marked variation from 1950–64 (3.1 and 3.3 deaths per 100,000 population, respectively). In 1964, the death rate for cancer of these sites in the male population was about three times the corresponding rate in the female population (5.1 and 1.6 deaths per 100,000 population, respectively).

Hammond (*40*) has reported data for males having cancer of the buccal cavity or pharynx, as the underlying cause of death, by mortality ratio and age-standardized death rates (table 12).

TABLE 12.—*Buccal cavity and pharyngeal cancer mortality ratios and death rates for male smokers, by type and specified age groups*

	Cigarettes		Pipe and/or cigars
	Males 45–64 years	Males 65–79 years	Males 55–84 years
Mortality ratio	9. 90	2. 93	4. 94
Death rates	[1] (1) 8	[1] (7) 20	[1] (3) 15

[1] Numbers in parentheses indicate death rates of persons who had never smoked cigarettes regularly.

SOURCE: Hammond, E. C. (*40*).

The Dorn study (*49*) also has provided information with relation to amount and type of smoking on males dying from cancer of the buccal cavity and pharynx (table 13):

TABLE 13.—*Buccal cavity and pharyngeal cancer mortality ratios and death rates for U.S. veterans, by age, type, and amount of smoking*

	Current smokers of cigarettes only					Pipe and/or cigars	Cigars only	Pipe only
	Number of cigarettes per day							
	0	1–9	10–20	21–39	40+			
Buccal Cavity:								
Mortality ratio	1. 00	0. 86	2. 93	7. 34	5. 73	3. 89	4. 11	3. 12
Death rates:								
Age 45 to 54	------	------	------	------	------	28	------	97
Age 55 to 64	2	3	6	12	9	5	3	2
Age 65 to 74	4	------	10	19	9	15	18	11
Age 75 plus	------	------	------	------	------	12	33	------
Pharynx:								
Mortality ratio	1. 00	7. 11	12. 81	14. 59	19. 34	3. 06	------	1. 96
Death rates:								
Age 55 to 64	------	9	8	8	------	2	------	------
Age 65 to 74	1	12	22	10	39	4	------	4

SOURCE: U.S. veterans study [app. table A (*49*)].

The Canadian pensioners study (*8*) has not reported separately on deaths from cancer of the buccal cavity and pharynx.

The Doll and Hill studies (*28*, *29*) of British physicians have reported on cancer of the mouth and pharynx, including cancer of the nose (table 14).

TABLE 14.—*Death rates from cancer of upper respiratory tract and digestive system by site and type of smoker*

Site	Non smokers	All smokers	Cigarette smokers	Mixed smokers	Pipe or cigar smokers
Mouth, pharynx, or nose	0	6	5	10	4
Larynx or trachea	0	6	5	3	10
Esophagus	4	10	6	19	8

SOURCE: Study of British physicians, [table 12 (*25*)].

Data on the relationship between amount of cigarettes smoked and the death rates were also provided (see table 15).

TABLE 15.—*Death rates from cancer of upper respiratory tract and digestive system by site and amount smoked*

Site	Amount of tobacco smoked daily (g.) [1]					
	Non-smoking	All amounts	1-14	15-24	25+	Cessation
Mouth, pharynx, or nose	0	7	4	1	21	6
Larynx or trachea	0	6	2	2	15	5
Esophagus	4	12	8	14	20	2

[1] (g.) = 1 gm. = 1 cigarette per day = ¼ oz. tobacco per week.

SOURCE: Study of British physicians [table 13 (*25*)].

Additional significant information comes from a study (*69*) of 102 cigarette smokers, all of whom were "cured" of a primary mouth or throat cancer and remained asymptomatic for at least 3 years. Of these patients, 37 stopped smoking while 65 continued. Of the 37 who stopped smoking, only two had a second primary cancer develop in a different site in the buccal-pharyngeal area, whereas 14 of those who continued to smoke developed a second cancer in a different site in the buccal-pharyngeal area.

EXPERIMENTAL STUDIES

In one study (*56*), pipe smoke condensate was dissolved in sputum and applied behind the ear of mice. Although no ear lesions were observed, two animals developed scirrhous and planocellular cancer, respectively, of the lower jaw, perhaps as a consequence of licking the ears of other mice. In another experiment (*37*), rats were placed in chambers and exposed to cigarette smoke. Five of 68 surviving rats developed tumors of the buccal mucosa, three of these animals had malignant invasive lesions.

In another setting (*27*), in which the oral area of mice was painted with cigarette smoke condensate for 15 months, no lesions were noted in the oral cavity. However, a significant increase in lung tumors, lymphosarcoma, leukemia, and reticulosarcoma was observed.

Résumé

The Surgeon General's 1964 Report established the causal relationship of pipe smoking with lip cancer, but did not find sufficient evidence for a causal relationship of specific forms of smoking with cancers of other sites in the oral cavity and pharynx. Current information strengthens the association between the various forms of smoking and the general category of cancers of the buccal-pharyngeal area but present information remains inadequate for a judgment of causality. Knowledge of the interaction of smoking and other factors known or suspected as causative agents, when available, could assist in such a judgment.

CANCER OF THE LARYNX

The Surgeon General's 1964 Report concluded: "Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male."

The National Center for Health Statistics reports (*94*) that 2,494 deaths attributed to cancer of the larynx occurred in 1964, as compared with 1,852 deaths in 1950, a 34 percent increase. Almost all these deaths occurred in the male population, with a male-to-female ratio of about 8 to 1. The total death rate in 1964 was 1.3 deaths per 100,000 population, which represented only a slight increase over the death rate of 1.2 noted in 1950. The mortality impact of this disease occurs primarily after middle age, there being a five-fold increase in the death rate for males over 75 years as compared to males under 55 years of age.

The Hammond study (*40*) reports the following information for laryngeal cancer deaths of males with a history of regular cigarette smoking, in terms of mortality ratios and death rates:

TABLE 16.—*Laryngeal cancer mortality ratios and death rates for male cigarette smokers, by specified age groups*

	Cigarette smokers	
	Age 45-64	Age 65-79
Mortality ratios	6. 09	8. 99
Death rates	[1] (1) 4	[1] (2) 14

[1] Numbers in parentheses indicate death rates of persons who had never smoked cigarettes regularly.
SOURCE: Hammond, E. C. [table 24 (*40*)].

The Dorn study (*49*) of U.S. veterans reports the following laryngeal cancer mortality ratios related to amount of cigarettes smoked, and smoking of pipes and cigars, or cigars only.

TABLE 17.—*Laryngeal cancer mortality ratios and death rates for U.S. veterans, by age, type, and amount of smoking*

	Number of cigarettes per day					Pipe and cigar	Cigar only
	0	1-9	10-20	21-39	40+		
Mortality ratio	1	3.27	8.45	13.62	18.85	7.28	10.33
Death rates:							
Age 55 to 64	1	------	4	5	20	4	3
Age 65 to 74	------	7	13	17	--------	12	20
Age 75 to 84	13	------	------	--------	--------	------	------

SOURCE: U.S. Veterans study [app. table A (*49*)].

The Doll and Hill study reported their data in terms of cancer of the larynx or trachea (see tables 14 and 15) for relationships with type and amounts of tobacco smoking.

The Canadian study did not provide separate data on cancer of the larynx. No additional information has become available, since the Surgeon General's 1964 Report, relating the several forms of smoking, i.e., cigarettes, cigars, and/or pipes, to specific laryngeal cancer sites (intrinsic versus extrinsic larynx).

The study previously referred to (*69*) which analyzed the development of second sites of cancer after cure of a primary oral cancer, reports that of 37 smokers who stopped smoking, none developed cancer of the larynx but that four of 65 continuing smokers developed cancer of the larynx. Although small numbers are involved, beneficial aspects of smoking cessation are suggested.

RÉSUMÉ

Additional epidemiological evidence supports the previous conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx.

CANCER OF THE ESOPHAGUS

The Surgeon General's 1964 Report concluded: "The evidence on the tobacco-esophageal cancer relationship supports the belief that an association exists." However, the Committee at that time noted that there was not adequate data on which to base a decision as to whether the relationship was causal.

The National Center for Health Statistics (*94*) reports that from

1950 to 1964 the mortality from cancer of the esophagus rose about 8 percent in the male population and 9 percent in the female population. In 1964, males had a death rate for esophageal cancer that was 3.7 times higher than the female rate. The greatest relative increases were in the age groups under 65 years, especially the age group 35–44 years.

MORTALITY DATA FROM THE LARGE PROSPECTIVE STUDIES: The Hammond (*40*) study reports the following death rates and mortality ratios for males in the age groups 45–64 and 65–79 who have a history of smoking regularly:

TABLE 18.—*Esophageal cancer mortality ratios and death rates for male cigarette smokers, by specific age groups*

	Age 45–64	Age 65–79
Mortality ratios	4.17	1.74
Death rates	[1] (1) 4	[1] (4) 7

[1] Numbers in parentheses indicate death rates of persons who have never smoked regularly.

SOURCE: Hammond, E. C. [table 24 (*40*)].

The Dorn study (*49*) reports the following mortality ratios and death rates in relation to number of cigarettes smoked per day plus other forms of smoking:

TABLE 19.—*Esophageal cancer mortality ratios and death rates for U.S. veterans, by age, type, and amount of smoking*

	Number of cigarettes per day					Pipe and cigar	Cigar only	Pipe
	0	1–9	10–20	21–39	40+			
Mortality ratios	1.00	1.76	4.71	11.50	7.65	4.05	5.33	1.99
Death rates:								
Age 55 to 64	1	2	5	14	9	5	8	------
Age 65 to 74	3	------	16	25	10	20	23	18
Age 75 to 84	45	------	------	------	------	41	------	72

SOURCE: U.S. Veterans study [app. table A (*49*)].

The Canadian veterans study did not give separate information about deaths from esophageal cancer.

Autopsy studies of smokers as compared with nonsmokers, specifically observing the pathological changes in esophageal tissue, have been performed by Auerbach (*3*). A microscopic study was made of 12,598 sections of esophageal autopsy tissue from 1,268 men, who died from causes other than esophageal cancer. The smoking histories were recorded but not known to the person examining the slides. The findings were strikingly similar to the abnormalities generally accepted as