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Comparative Epidemiology of Tobacco-related Cancers[1]

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SUMMARY

In a retrospective study, interviews were obtained with 3,716 patients with histologically proven cancer of the lung (Kreyberg types I and II), mouth, larynx, esophagus, or bladder and with over 18,000 controls. For each of these cancers, the relative risk of both male and female present smokers increased with the quantity smoked and the duration of the habit. The strongest increase occurred for cancer of the lung and larynx, and the least increase occurred for cancer of the esophagus and bladder. For exsmokers the risk decreased with years of cessation. The risk for mouth cancer of pipe and cigar smokers who inhaled much less than cigarette smokers was less than that of the latter and increased with the quantity smoked. The risk of mouth, larynx, and esophagus cancer among smokers increased with the quantity of alcohol consumed. Greater smoking habits and lesser cessation rates were noted among lower socioeconomic groups, suggesting that these groups will bear an ever increasing proportion of the burden of tobacco-related cancer.

INTRODUCTION

This paper presents the comparative epidemiology for a number of tobacco-related cancer sites, with reference to the influences of age, sex, socioeconomic status, tobacco usage, and other epidemiological variables. The sites studied have been grouped into 6 categories treated independently (the eighth revision of International Classification of Diseases numbers follow in parentheses): lung cancer Kreyberg type I, Kreyberg type II (162), oral cavity (140 to 149), larynx (161), esophagus (150), and bladder (188).

MATERIALS AND METHODS

For several years we have been obtaining epidemiological information about the smoking habits of patients in 20 hospitals in 8 American cities. Approximately one-third of all patients were interviewed at Memorial Hospital in New York, N. Y., and decreasingly smaller numbers were interviewed in various hospitals in Houston, Texas, Los Angeles, Calif., New York, N. Y., Birmingham, Ala., Miami, Fla., and New Orleans, La. Interviews begun recently in Philadelphia, Pa., and Chicago, Ill., will be summarized in a future report.

Primary data were collected by use of a standard questionnaire (copies are available from the authors on request) administered by interviewers who underwent a rigorous and uniform training period at our Institute. No interview was accepted as final without pathological confirmation of diagnosis.

Each interview elicited details concerning the patient's smoking history, such as quantity and years of usage of the 4 most recent cigarette brands (by name) and the total number of years of filter and nonfilter usage. Histories of pipe, cigar, chewing tobacco, and snuff usage were also taken.

The material available consisted of interviews with 22,101 patients during the years 1969 to 1975. Of these interviews, 3716 (17%) were of patients diagnosed with cancer of 1 of the 6 categories described above, and most of the remainder formed a pool of controls used as a base line for comparison and relative-risk calculations.

Controls were selected on the basis of absence of a history of tobacco-related disease. Tobacco-related disease was defined as a cancer of any of the above study sites and cancer of the pancreas, liver, or kidney; myocardial infarction; stroke; peripheral vascular disease; abdominal aortic aneurysm; chronic bronchitis or chronic obstructive pulmonary disease; gastric ulcer; cirrhosis of the liver. Thus, potential controls with a history of any of the above diseases were eliminated from further study. The diagnoses for persons ultimately included in our control pool were distributed approximately as follows (the numbers in parentheses are the percentages for males and females, respectively): cancer of the stomach (2; 2), colon or rectum (7; 5), prostate (6; 0), breast (0; 13), cervix (0; 10), and skin (including melanoma) (6; 4); leukemia, lymphoma, and Hodgkin's disease (7; 4); other cancers such as cancer of the male genitals or female reproductive organs (9; 11); benign neoplastic diseases (11; 11); fractures (8; 6); other nonneoplastic diseases such as burns, infections, duodenal ulcers, etc. (44; 34).

Method of Analysis. The data in this study are put to 2 distinct uses: evaluation of relative risks for each cancer and comparison of quantitative differences in study factors among the various tobacco-related cancer sites. The index of response to a carcinogenic substance is the relative risk, *i.e.*, the ratio of disease incidence in the exposed population to that in the unexposed population, as estimated by the odds ratio (20). Since we wished to compare relative risks for different types of cancer in reference to a very large group of controls, the choice of those controls and method of risk calculation were critical issues, especially because of the fact that, since data originated from

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20 hospitals in 6 cities, each institution possessed a possibly unique patient profile.

We are well aware of the potential biases that could result from attempts to estimate relative risks from study and control groups in which distributions of possibly confounding variables are widely divergent. Fortunately, we are dealing here with a biological phenomenon, tobacco carcinogenesis, whose gross biological parameters have been largely determined through epidemiological and experimental studies and for which it is therefore possible to anticipate and control effects of confounding variables.

Relative risks were computed by the Mantel-Haenszel method (20), stratified by age (4 levels: 20 to 49, 50 to 59, 60 to 69, and 70 to 89), race and, initially, city. Because of the very small numbers of other races, only data on whites and blacks are presented here. All relative risks presented in this paper are based on this procedure. Results for males and females are reported separately.

Because of the amount of computing time involved and the complexity of calculations, we investigated the possibility of combining cities into a single stratum. Results are given in the "Appendix" and show that no significant errors in odds ratios were introduced by collapsing on this variable. Thus, all reported relative risks have been adjusted for age and race.

In addition to relative risks, the contrasts among the distributions of various factors, such as education and filter usage, are of interest because they provide profiles of patients with different cancers but cancers with a common underlying cause, tobacco carcinogenesis, and furnish insight into the future trends of those diseases through observation of tobacco usage patterns among various social strata. Although it was desirable to include in these comparisons a control group without tobacco-related diseases, it was not immediately obvious how to choose this group. Clearly, our entire sample of controls was not appropriate as a group because its age-race distributions did not match any given cancer site, nor could a general population control be used since admissions at our study hospitals were disproportionately biased with Jewish middle-class patients. It might have been possible to provide a matched set of controls for each of the diagnostic categories, but this would have unnecessarily complicated the tables without much improvement.

As a compromise we obtained a single set of controls "pool-matched" by computer randomization to our entire set of cases. This subset of the control pool has a joint distribution of age, race, sex, and city identical to the one that would have been obtained had the interviewers selected 1 matched control for every case, regardless of specific case diagnosis. This set of controls has a number of useful properties, which will be explored more fully in a future report. In brief, relative risks nearly identical to the Mantel-Haenszel estimates could be computed with these controls, in a small fraction of the computer time required for the latter method.

The reader is cautioned that the data presented in Tables 3 to 6 and 8 are not strictly comparable in a statistical sense, either among cancer sites or between cases and matched controls, because the underlying age distribution is not identical. However, we feel justified in presenting the unadjusted distributions because they provide interesting information about the sites in general, they permit comparison with other published studies of these cancer sites and, in view of the similarity of age distributions given in Table 2, adjustment either to the entire control pool or a matched subset of it did not appreciably alter these distributions.

RESULTS AND DISCUSSION

Background Variables

There are 2 useful reasons to begin by examining distributions of background demographic variables among cases and controls. First, these statistics often furnish clues about special populations in which to search for new etiological leads. Secondly and especially applicable here, this information supplements our knowledge of basic tobacco-related factors and, by noting which factors are interrelated, we can predict disease patterns of the future; we may hence identify high-risk groups most susceptible to preventive intervention.

Sex and Age Distribution

Table 1 presents the numbers of white and black cancer patients interviewed, by diagnosis, and Table 2 gives the age distributions. In the 20-to-49 age group, approximately 3% of the cases are under age 30. The average age at diagnosis is given for each site and sex in Table 2.

The observed sex ratios for lung I cancer, cancer of the oral cavity, and larynx cancer decreased during the 6-year study period (1969 to 1975), and the average age of diagnosis of lung I cancer in females increased by about 4 years and that of lung II cancer by 3 years over the course of the study (not statistically significant). The average lung cancer age for males remained stable at 60 years. An opposite trend was seen among the relatively smaller number of cases of larynx cancer in females.

Our observations reflect recent trends in the mortality rates and smoking habits of women. The United States incidence of lung cancer is about 6 times as great for men as it is for women (8), chiefly due to the lower proportion of female smokers among cohorts of the lung cancer age. We previously predicted that the male/female incidence ratio would diminish, reflecting an increase in cigarette consumption by women, but that concomitant decreasing "tar" content would prevent the female lung cancer mortal-

Table 1

Number of cancer patients (white and black) interviewed during 1969 to 1975, by diagnosis and sex

Diagnosis	No. diagnosed			Males/females
	Males	Females	Total	
Lung I	728	164	892	4.4
Lung II	323	150	473	2.2
Oral cavity	593	280	873	2.1
Larynx	387	80	467	4.8
Esophagus	183	81	264	2.3
Bladder	589	158	747	3.7
Total	2803	913	3716	3.1

ity rate from reaching the present male rate (34). We may observe the early stages of this equalization process.

Demographic Variables

Data on demographic variables are displayed in Tables 3 (males) and 4 (females). Except for racial distributions (only data on whites are shown), there was a virtual absence of blacks from Jewish and higher socioeconomic strata.

Race. Distributions for whites and blacks are given in Tables 3A and 4A. The highest proportion of white males is seen for bladder cancer and the highest proportion of black males for esophageal cancer. Racial distributions for the 4 other cancer sites are similar to each other. Racial distributions of cancers among women are similar, except for esophageal cancer, which has a white to black ratio of 2.1, compared to a ratio of 4.5 or more for other sites. It must be stressed that variations in admission patterns among participating hospitals may account for some differences. At present, there is no adequate explanation for the high rate of cancer of the esophagus among blacks as found in this and other studies (8).

Religion. Table 3 shows that, among whites, Jewish males are underrepresented in all disease categories except bladder cancer. Jews comprise 10% of lung I and 21% of lung II cancer cases (reflecting in part possible differences in etiology of Kreyberg I and II lung cancer) compared with 27% of bladder cancer cases. The percentage of Jews among male cases of oral cavity, larynx, and esophagus cancer ranged from 6 to 9%. The distribution by religion among bladder cancer patients is distinctly different from the other sites, more nearly resembling the distribution of controls than do the other cases. The influence of religion is less important for females, (Table 4); there were slightly fewer Jewish women with Kreyberg I, slightly more with Kreyberg II, and about an equal proportion of Jewish women with bladder cancer compared with controls. There are substantially fewer Jewish female cases than there are

Table 2

Age distributions for male and female cancer patients, 1969 to 1975

Diagnosis	% males 20–49[a]	50–59	60–69	70–89	Av. age at diagnosis for males	% females 20–49	50–59	60–69	70–89	Av. age at diagnosis for females
Lung I	16	34	37	14	60	24	37	24	15	52
Lung II	19	37	28	16	58	27	39	27	7	56
Oral cavity	16	36	32	17	60	22	31	28	20	60
Larynx	18	36	30	15	59	24	36	34	6	56
Esophagus	15	33	36	16	60	11	36	32	21	61
Bladder	11	28	41	20	61	12	25	32	31	63

[a] Age range at diagnosis.

Table 3

Selected demographic characteristics of white male cancer and matched control patients, 1969 to 1975

	Lung I		Lung II		Oral cavity		Larynx		Esophagus		Bladder		Matched controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Religion[a]														
Protestant	317	57	114	50	255	53	168	56	48	47	216	42	990	49
Catholic	186	33	65	29	197	41	111	37	46	45	156	31	534	27
Jewish	53	10	48	21	32	7	19	6	9	9	138	27	490	24
Occupation														
Professional	71	12	34	14	51	10	32	10	15	14	110	21	452	22
Skilled or clerical	270	46	114	46	236	47	138	45	47	45	285	53	1015	48
Semiskilled and unskilled	244	42	97	40	213	43	139	45	42	40	138	26	636	30
Education														
Grade school	307	52	118	48	242	48	168	54	52	49	232	43	822	38
High school	144	24	56	23	126	25	72	23	23	21	103	19	502	23
Some college or trade school	72	12	35	14	68	13	41	13	8	7	87	16	308	14
College graduate and beyond	71	12	36	15	68	13	32	10	24	22	117	22	510	24

[a] Percentages are based on Protestants, Catholics, and Jews only.

Table 3A

Racial distribution of male cancer matched control patients, 1969 to 1975

	Lung I		Lung II		Oral cavity		Larynx		Esophagus		Bladder		Matched controls	
Racial distribution	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
White	596	82	248	77	505	85	313	81	108	59	542	92	2097	83
Black	132	18	76	23	88	15	74	19	76	41	47	8	422	17

Table 4

Selected demographic characteristics of white female cancer and matched controls, 1969 to 1975

	Lung I		Lung II		Oral cavity		Larynx		Esophagus		Bladder		Matched controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Religion"														
Protestant	67	53	56	48	149	63	36	58	28	56	63	49	344	51
Catholic	40	32	31	27	64	27	21	34	13	26	37	29	187	28
Jewish	19	15	29	25	23	10	5	8	9	18	29	23	143	21
Occupation														
Professional	3	2	8	6	9	4	5	8	4	8	6	5	65	9
Skilled or clerical	45	35	39	32	58	24	15	24	8	15	37	28	201	29
Semiskilled and unskilled	17	13	12	10	34	14	17	27	7	13	15	11	85	12
Housewife	65	50	64	52	139	58	25	40	34	64	73	56	347	50
Education														
Grade school	57	42	44	36	102	42	30	45	52	49	47	36	265	37
High school	49	36	36	29	80	33	22	33	23	21	47	36	198	28
Some college or trade school	19	14	27	22	44	18	11	17	8	8	29	22	147	21
College graduate and beyond	10	7	16	13	19	8	3	5	24	22	9	7	101	14

" Percentages are based on Protestants, Catholics, and Jews only.

Table 4A

Racial distribution of female cancer and matched control patients, 1969 to 1975

	Lung I		Lung II		Oral cavity		Larynx		Esophagus		Bladder		Matched controls	
Racial distribution	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
White	135	82	123	82	245	88	66	83	55	68	134	85	705	85
Black	29	18	27	18	35	12	14	17	26	32	24	15	126	15

controls among those with mouth, larynx, and esophagus cancer (8 to 18%).

Ten years ago we reported that the lower incidence of lung cancer in Jewish males compared to Catholics and Protestants was consistent with their reduced smoking experience (43), an observation also noted by Greenwald *et al.* (11). The lower rate of cancer of the upper alimentary tract among Jews is consistent with their lower consumption of alcohol, as also shown by Seidman (26) and reviewed by Greenwald *et al.* (11).

Occupation. In Tables 3 and 4, occupation is broken down into the following categories: professionals, skilled and trade, semiskilled and unskilled and, for women, housewife. There are significantly fewer professional males among lung I cancer cases compared with controls. The same can be said for all other sites except the bladder. Bladder cancer on the other hand seems to affect more skilled professionals than do the other cancers.

An occupational component is known to exist for bladder cancer (6, 7, 17), although the confinement of the risk to certain occupational groups makes our data insufficient for establishing this. It must also be considered that, since bladder cancer is difficult to treat, its distribution in hospital studies will be affected by the specialization of study hospitals. A more detailed analysis of the epidemiology of bladder cancer has been presented separately (37). The occupational groupings among women show little variation among sites or between sites and controls.

Education. A better indicator of socioeconomic status than occupation is education. The 4 categories in Tables 3 and 4 are grammar school (sixth grade or less), some high school, high school graduate through some college, and college graduate and postgraduate. For white males, 76% of lung I cancer cases are in the 2 lowest educational categories compared to 61% of the controls. Comparable figures for women are 78% lung I cancer *versus* 65% for controls. Among black males (not shown), the 2 lower educational strata contained 95% of lung I cancer cases compared to 90% among controls. For black females the corresponding numbers were 89% lung I cancer cases compared to 92% for controls.

The highest degree of both educational and occupational achievement is exhibited by bladder cancer patients, among whom 38% of the white males have had at least a year of college compared with only 24% of lung I cancer patients. For females the percentage of college or trade school attendees is 29% for bladder cancer *versus* 21% for lung I cancer.

Residence. Each patient was asked place of residence during 3 periods of life: childhood, adolescence, and adulthood. Residences were recorded as urban (population, 2500 or more), rural, or mixed. By and large, males and females with the same cancer site did not differ in their responses. These data of course reflect the urban orientation of our study hospitals. It has been suggested that long-term urban residence may be associated with exposure to carcinogens in airborne particulate matter (22, 24). If so, one would expect to see a clear excess of urban residents among lung cancer patients. In fact, the largest adult urban percentage for cases or controls occurred for females with lung I cancer but was the lowest for corresponding males. It further needs to be considered that

Table 5

Smoking habits of male cancer cases and matched controls interviewed during 1969 to 1975

	Nonsmokers		Exsmokers		Present smokers (≥10 yr)								
					STF[a]		LTF		NF		PC		
Diagnosis	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	Total
Lung I	8	1	207	29	114	16	164	23	200	28	18	3	711
Lung II	11	3	81	26	51	16	88	28	73	23	11	3	315
Oral cavity	22	4	113	20	71	12	117	20	179	31	76	13	578
Larynx	10	3	92	24	68	18	74	20	118	31	16	4	378
Esophagus	15	9	35	20	16	9	36	21	58	33	15	9	175
Bladder	70	12	158	27	76	13	131	23	107	18	40	7	582
Matched controls	509	20	723	29	215	9	414	16	398	16	260	10	2519

[a] STF, smokers whose present brand is filtered, with <10 years of lifetime filter use; PC, pipe and cigar smokers.

Table 6

Smoking habits of female cancer cases and matched controls interviewed during 1969 to 1975

	Nonsmokers		Exsmokers		Present smokers (≥10 yr)						
					STF[a]		LTF		NF		
Diagnosis	No.	%	No.	%	No.	%	No.	%	No.	%	Total
Lung I	24	15	32	20	22	14	62	39	21	13	161
Lung II	35	24	32	22	22	15	46	31	13	9	148
Oral cavity	84	31	30	11	28	10	95	35	33	12	270[b]
Larynx	10	13	7	9	14	18	27	35	20	26	78
Esophagus	22	29	9	12	15	20	21	28	9	12	76[b]
Bladder	67	45	23	15	12	8	34	23	14	9	150
Matched controls	483	58	117	14	43	5	157	19	30	4	830

[a] STF, smokers whose present brand is filtered, with ≤10 years of lifetime filter use.
[b] Additionally, 3 pipe and cigar users were observed.

smoking habits and selected industrial exposures are greater in cities than they are in rural areas (13).

When residence is broken down by smoking status, it is observed that the greatest percentage of respondents indicating urban adult residence occurred among exsmokers and long-term filter smokers. Conversely, the lowest proportion of urbanites was found among nonfilter smokers. This observation is consistent with the higher level of education among urban residents compared to rural dwellers and reflects the reduction in smoking habits among more educated people (35).

Tobacco Usage

The Effect of Smoking Cigarettes. All persons were assigned to one of the following mutually exclusive smoking status categories: nonsmokers; exsmokers (those who have formerly smoked cigarettes but do not now smoke and have given up smoking for at least 1 year); pipe and cigar smokers with no history of cigarette use; current cigarette smokers (including those who quit less than 1 year prior to the interview) who have smoked for at least 10 years, broken down into (*a*) short-term filter (STF) smokers (lifetime cigarette usage of 10 years or more and filter cigarette usage of 1 to 9 years), (*b*) LTF[2] smokers, and (*c*) NF smokers. Persons in the latter category have smoked few if any filter cigarettes. Persons with both cigarette and pipe and/or cigar usage are classified according to their cigarette usage.

Tables 5 and 6 show the number and percentage of cases and controls in each category, for males and females, respectively. Distributions of smoking status differ considerably among diagnosis categories and in comparisons of males to females for each diagnosis. This, of course, is due to the widely divergent smoking experiences of the 2 sexes over the past 5 decades and implies that all analysis of tobacco-related variables must be done separately by sex. As an example of this disparity, we see that 58% of the matched female controls, more than one-half, have never smoked compared to 20% for males.

The smallest proportion of nonsmokers was found among male lung cancer types I and II (1 and 3% *versus* 20% for controls), and the largest proportion was found among male bladder cancer cases (12%). Proportions of nonsmokers for other sites range from 3 to 9%. Exsmokers appear to account for roughly equal proportions of cases and controls but, as will be shown below, the distributions of number of years of cessation differ greatly and are of etiological importance.

Present smokers constitute about two-thirds of all male cases, except for bladder cancer cases, which are only 54%. Among male cases who currently smoke cigarettes, the highest proportion of NF was found among esophageal cancer patients (53%), and the lowest was found among bladder cancer and lung II cancer patients (34%). The greatest proportion of LTF occurred among lung II cancer patients (42% of present smokers), and the smallest proportion occurred among larynx cancer patients (28%).

[2] The abbreviations used are: LTF, long-term filter cigarette users (10 years or more); NF, nonfilter cigarette users presently.

As fewer women than men have smoked, we observe a much larger proportion of female nonsmokers in all disease categories (Table 6). On the other hand, among persons who have ever smoked, larger numbers of men than women have given up smoking; 34% of female matched controls were ex-cigarette smokers compared to 41% for male matched controls. Women also exhibited a much higher rate of filter usage than did men; 68% of present smokers were LTF for female controls (28% more than males, based on all persons who have ever smoked), and the same percentages were found for lung I cancer cases as well. By contrast, NF is far lower for women than for men for each cancer site, as it also is for controls, ranging from 9% of controls who have ever smoked to 29% of larynx cancer cases (compare the range of male NF smokers: 23% of controls who had ever smoked to 40% of esophageal cancer cases).

Cigar and Pipe Usage. A significant dose-response relation between both cigar and pipe usage and oral cavity cancer is observed and displayed in Chart 1. The adjusted relative risk for oral cavity cancer relative to a nonsmoker is considerable (between 4 and 6), even for relatively small usage (1 to 5 cigars or pipe bowls/day). In determination of such risk, 1 pipe bowl is roughly equivalent to 1 cigar (19 of the 85 persons in Chart 1 gave histories of both pipe and cigar use and were included in each risk calculation).

Compared to 13% of male oral cavity cancer cases and 10% of male controls who smoked only cigars and pipes, less than 7% of male lung, larynx, and bladder cancer cases were cigar or pipe smokers. Our previous study showed an increased risk for lung cancer among heavier smokers of cigars and pipes (41), but the small numbers here are only suggestive of such an effect.

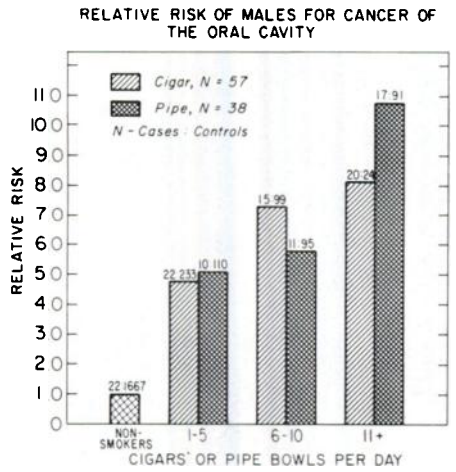

Chart 1. Relative risk of male cigar and pipe smokers for cancer of the oral cavity, by quantity smoked.

Inhalation. Patients were asked to describe their inhalation practices for cigarettes, cigars, and pipes in terms of 5 possible responses ranging from "deeply into chest" to "do not inhale." Results for controls are shown in Table 7, in which the column labeled cigarettes is for current smokers (10 years +); and the cigar and pipe column is for those who smoked these products exclusively. Although the reliability of these data may be questioned due to its subjective nature, it may be broadly concluded that most cigarette smokers inhale (at least beyond the throat), whereas most cigar and pipe smokers inhale little if at all. Only 7% of male control cigarette smokers claimed not to inhale. This high percentage of inhalers (93%) among cigarette smokers is similar to that reported elsewhere (29, 41). Cigar and pipe smokers closely resemble each other in inhalation practice ($\chi^2_{(4)} = 5.2$; $p > 0.05$). Only 3% of male lung II cancer cases who were cigarette smokers and 8% of females said that they did not inhale. Inhalation among cases generally exceeded that of controls, and within each group men inhaled more than did women. This observation largely explains the lower risk for lung cancer of cigar and pipe smokers compared to cigarette smokers.

Chewing Tobacco and Snuff. The use of chewing tobacco and snuff, 2 tobacco products that are not smoked, was investigated in the same manner as smoking among cases and controls. Those products are used much less frequently than are cigarettes: 9.0% of the male controls had used chewing tobacco and 2.7% had used snuff at some time in their lives. Female usage of chewing tobacco was virtually nil (less than 0.5%), and less than 1% of females had ever used snuff.

In Table 8 we present the number and percentage of male users of chewing tobacco and snuff among cases and controls. All relative risks computed from this table included 1.0 within 99% confidence limits. The smoking habits of users of chewing tobacco (broken down into nonsmokers, exsmokers, present smokers of 1 to 20, 21 to 40, and over 40 cigarettes, and pipe and cigar smokers) did not differ significantly from nonusers of chewing tobacco in any cancer diagnosis category.

Relative risk among snuff users ranged from 0.5 (lung II cancer) to 1.7 (esophagus), with 99% confidence intervals

Table 7

Reported inhalation practices of male matched controls, 1969 to 1975

	Cigarette smokers[a]		Cigar smokers[b]		Pipe smokers[b]	
Inhalation	No.	%	No.	%	No.	%
"Deeply into chest"	446	58	6	3	2	2
"Partly into chest"	174	23	21	11	15	13
"Back to throat"	39	5	12	6	2	2
"Inhale, don't know how deeply"	49	6	9	5	3	3
"Do not inhale"	57	7	140	74	91	80
Total	765	99	188	99	113	100

[a] Current smokers for 10 years or more.
[b] No history of cigarette use.

that included 1.0. Our data contain insufficient cases to demonstrate an increased risk due to chewing tobacco and snuff usage alone. These results are similar to those reported by us earlier (33) but differ considerably from data from India, in which a high rate of mouth cancer is strongly associated with chewing a betel leaf tobacco product (18, 21).

Effect of Smoking Cessation. The possible recovery from some of the tumorigenic effects of tobacco smoking after smoking has ceased depends, as expected, on the duration and level of exposure and the nature of the disease process. Quantitative evidence for this phenomenon for males is given in Table 9 and Chart 2. Relative risk has been calculated as a function of the number of years since quitting. For males the decline in risk for cancer of the lung, mouth, and larynx is the greatest, approaching but not usually attaining that of nonsmokers. For esophagus and bladder cancers, the effect of cessation is much less but, because of the lesser association of tobacco with these 2 cancers, the risk has less distance to drop. The same trends occur for females (Table 10), but small numbers of historical long-term quitters impose longer error bounds on the tabulated risks for women than for man.

We also note an actual increase in risk for those who have only quit within the 3 years preceding diagnosis. A similar effect was previously observed by Hammond (12) who noticed an elevated death rate among recent exsmokers in his prospective study. He explained this phenomenon by the fact that many persons are induced to quit by the onset of a serious illness. We would add that other persons quit because of existing severe chronic cough.

Dose-Response Analysis. To confer consistency of our data with the causal hypothesis, we thought it essential to quantify our results in terms of dose-response curves in which tumorigenesis is developed as a mathematical function of dosage factors, such as quantity of tobacco consumed, years of consumption, and tar levels of cigarettes. Although experimental studies with animals have previously yielded dose-response curves for smoke condensate (38), it is obviously impossible to perform the analogous experiments on humans in a controlled, clinical setting. However, it is not necessary to contemplate such experiments; in a sense, they have already been performed by man himself. It only remains for us to extract the appropriate information from our data base, controlling wherever possible those variables that would have been controlled in a clinical setting. The following analysis deals mostly with dosage parameters established previously as significant in the etiology of these cancers, such as the quantity smoked per day and duration of the habit.

The index of response is the relative risk as previously described, which shows the risk of developing cancer of a particular site, in relation to some standard characteristic such as absence of tobacco usage (10). The relative severity beteeen 2 sites may be assessed by comparing the rate (slope) at which relative risk increases with smoking for each site. However, no absolute severity may be inferred.

Response to Daily Quantity Consumed. Charts 3 and 4

Table 8

Number and percentage of male chewing tobacco and snuff users, by diagnosis, 1969 to 1975

	Ever chewed tobacco					Ever used snuff				
	Yes		No			Yes		No		
Diagnosis	No.	%	No.	%	Total	No.	%	No.	%	Total
Lung I	91	12.5	637	87.5	728	29	4.0	698	96.0	727
Lung II	26	8.1	294	91.9	320	6	1.9	314	98.1	320
Oral cavity	61	10.3	530	89.7	591	10	1.7	581	98.3	591
Larynx	46	11.9	341	88.1	387	15	3.9	372	96.1	387
Esophagus	20	10.9	163	89.1	183	8	4.4	175	95.6	183
Bladder	47	8.0	539	92.0	586	11	1.9	576	98.1	587
Matched controls	233	9.0	2327	91.0	2560	69	2.7	2491	97.3	2560

Table 9

Relative risk of cancer for male exsmokers by diagnosis and years of cessation

	Years since quitting												
	0[a]		1-3		4-6		7-10		11-15		16+		
Diagnosis	No.	RR[b]	No.	RR	No.	RR	No.	RR	No.	RR	No.	RR	Nonsmokers
Lung I	478	*32.3*[c]	80	*53.8*	44	*24.9*	36	*17.2*	22	*13.7*	19	5.0	8
Lung II	212	*10.7*	29	*14.2*	14	*5.9*	18	*6.6*	11	*5.4*	6	1.2	11
Oral cavity	366	*8.9*	41	*9.0*	18	*3.5*	18	*3.2*	15	*3.4*	17	1.6	22
Larynx	260	*14.3*	36	*17.9*	20	*8.5*	10	*4.0*	7	3.4[d]	13	2.5	10
Esophagus	110	*3.6*	13	*4.8*[d]	5	*1.5*	5	1.4	4	1.3	7	1.0	15
Bladder	314	*2.7*	39	*2.9*	31	*1.9*	25	1.4	25	1.6	37	1.1	70
Controls	3110		307		321		340		259		530		1667

[a] Present smokers who have smoked for at least 10 years.
[b] RR, relative risk, relative to nonsmokers (= 1.0) adjusted for age and race.
[c] Numbers in *italics*, significant at $p < 0.01$.
[d] Significant at $p < 0.05$.

show the relative risk for cancer of each site, as a function of quantity (number of cigarettes per day) for men and women who are current smokers and have smoked cigarettes for at least 10 years.

For all cancer sites, relative risk increases with dosage and for several sites this increase appears to be approximately linear. Therefore, it seemed appropriate to fit the relative risk to a straight line by linear least squares. Table 11 gives the results of this calculation, with *abscissa* values of 0, 10, 20, 30, 40, and 50 for the risks in Chart 3 and 0, 10, 20, 30, and 40 for Chart 4. By definition an *ordinate* of 1 corresponds to 0 cigarettes/day. Slopes for all sites except female larynx, esophagus, and bladder cancer give evidence of a very strong dose-response relation.

Although this does not necessarily demonstrate that the dose-response relationship is strictly linear, it does show that the strongest observed response to quantity for men is for lung I cancer, in which the risk for males increases by 1.6 units/cigarette. The site showing the next strongest response to quantity is the larynx, with a slope of 0.59 risk units/cigarette. Lung II and oral cavity cancer have slopes that are lower and of approximately equal magnitude; and slopes for esophagus and bladder are about equal and relatively small, although there is no question that a response exists, considering that 95% confidence limits on

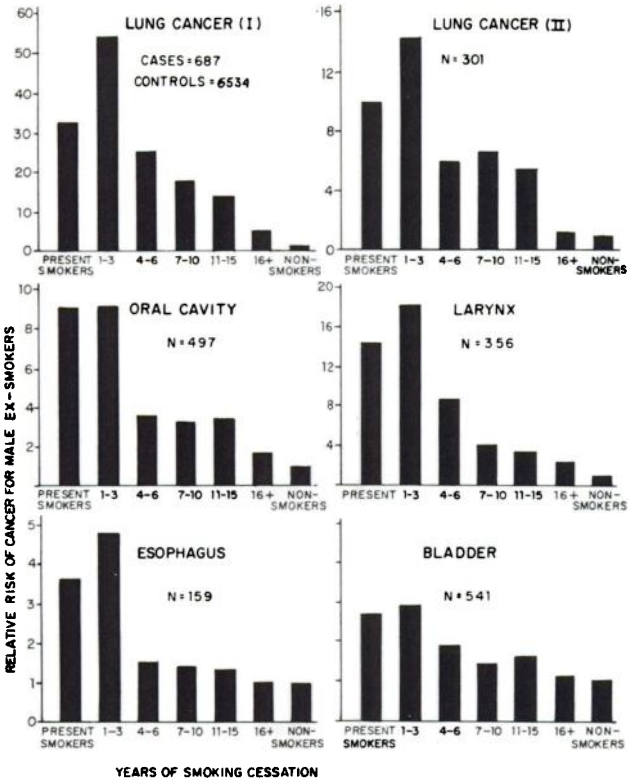

Chart 2. Relative risk of male exsmokers for cancer, by years since quitting smoking.

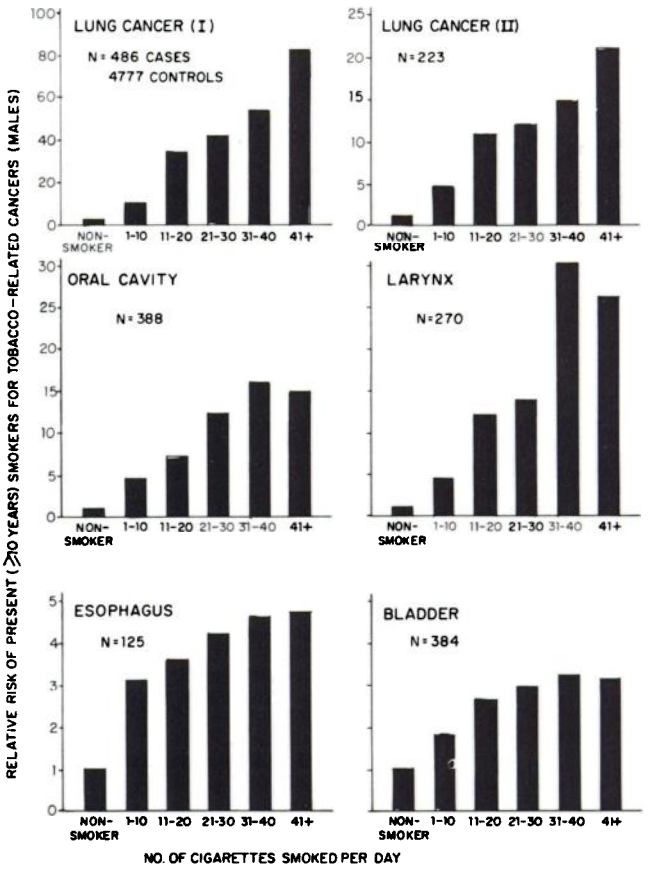

Chart 3. Relative risk of present (≥10 years) male smokers for tobacco-related cancers, by quantity smoked.

Table 10

Relative risk of cancer for female exsmokers by site and years of cessation

	Years since quitting												
	0[a]		1-3		4-6		7-10		11-15		16+		
Diagnosis	No.	RR[b]	No.	RR	No.	RR	No.	RR	No.	RR	No.	RR	Non-smokers
Lung I	105	*10.5*[c]	17	*13.6*	5	*6.2*	4	*5.1*	4	*8.8*	0	(0)	24
Lung II	81	*4.4*	13	*6.7*	5	*3.6*	6	*4.1*	5	*5.6*	2	0.9	35
Oral cavity	156	*4.4*	16	*3.8*	6	2.2	4	1.4	1	0.6	3	0.8	84
Larynx	61	*11.6*	4	*6.9*	1	2.6	0	(0)	2	8.8[d]	0	(0)	10
Esophagus	45	*5.3*	3	3.0	2	3.1	0	(0)	1	2.2	2	1.8	23
Bladder	60	*2.4*	10	3.1[d]	3	1.5	0	(0)	2	1.5	8	2.4[d]	67
Controls	2129		231		147		132		79		171		3633

[a] Present smokers who have smoked for at least 10 years.
[b] RR, relative risk, relative to nonsmokers (= 1.0) adjusted for age and race.
[c] Numbers in *italics*, significant at $p < 0.01$.
[d] Significant at $p < 0.05$.

the slope do not include 0. For women, lung I cancer is also highly sensitive to quantity, although it is considerably less so than that for men.

Response to Changing Tar Levels. The dose-response curves derived in the preceding section are consistent with the concept that the tar yield of a cigarette is the determining factor for the carcinogenic activity of the smoke. If this concept is correct, when total daily cigarette consumption is adjusted for differential tar delivery due to use of filters, the observed response should also reflect this difference. Previous studies have already suggested a decreased risk for lung cancer among LTF smokers (5, 28, 31, 42) compared to NF smokers. Table 12 shows the average number of cigarettes consumed daily as reported collectively by lung I cancer patients and controls who were current smokers and who have been smoking cigarettes for 10 years or more. Averages are further broken down by filter usage (NF or LTF). Among both filter types there is a clear trend toward greater cigarette consumption for younger cohorts among cases but not for controls. Filter cigarettes have only achieved widespread popularity and a major share of the United States market within the past 15 years (39). Consequently, one would generally expect filter smokers to be younger than nonfilter smokers. Among white lung I cancer cases, the average age of NF exceeds LTF by 3.6 years. Therefore, each younger age group has been exposed to a market in which the average tar content is lower than it was previously, necessitating our consideration of the age factor. We emphasize that the shift from a nonfilter to a filter market predominance has been a gradual one, as has been the continuing decline in tar yields for both cigarette types. Younger cancer patients, who have on the average been exposed to cigarettes of lower carcinogenic potency, have had to smoke a greater quantity of cigarettes to develop tobacco-related cancers than their older counterparts.

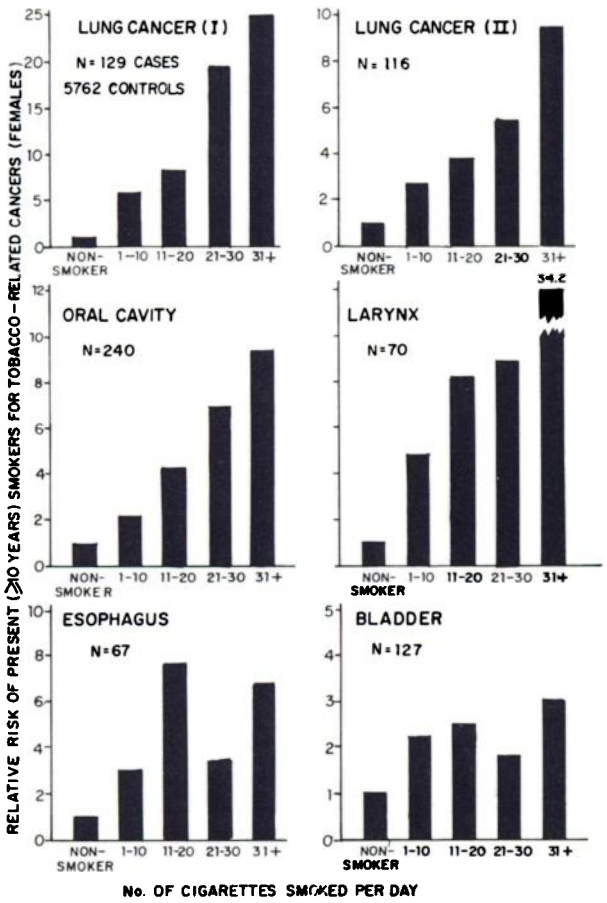

Chart 4. Relative risk of present (≥10 years) female smokers for tobacco-related cancers, by quantity smoked.

Duration of Smoking. In Table 13 we have listed the average number of years for which people have smoked all cigarettes, filter and nonfilter, and the age at which smoking began, broken down by age at diagnosis for lung I cancer and controls. On the average, lung cancer patients started smoking more than 1 to 2 years earlier in life than did controls and smoked cigarettes for up to 3 years longer.

The joint effect of duration and dosage was studied by calculating the risk of developing lung I cancer, relative to a risk of 1 for a smoker of 1 to 20 cigarettes/day who had smoked 21 to 40 years, for males in 3 dosage categories and 2 duration spans. These results are given in Table 14 and Chart 5. Because of the strong correlation between age and duration, age standardization in this table was done with only 2 age strata (20 to 59 and 60+). We emphasize that the variable, duration, has a rather narrow observed range since people began to smoke at ages 15 to 20 and developed cancer at ages 55 to 65. We have insufficient observations on smokers who began smoking later in life to permit drawing analogies to the animal experiments involving duration (23). The general trend for each cancer type is that the relative risk increases with quantity at either duration level and that a steeper rate of increase is generally associated with the longer duration. The actual magnitude of the risk is a function of quantity and duration and varies markedly by site and sex.

Table 11

Relative risk as a linear function of cigarette quantity, by site and sex

	Males			Females		
Diagnosis	Slope	Intercept	95% confidence limits for slope	Slope	Intercept	95% confidence limits for slope
Lung I	1.55	−2.14	1.19–1.91	0.61	−0.40	0.36–0.86
Lung II	0.37	1.18	0.28–0.46	0.20	0.51	0.10–0.30
Oral cavity	0.31	1.52	0.20–0.42	0.21	0.44	0.16–0.26
Larynx	0.59	0.01	0.30–0.88	0.70	−2.67	−0.10–1.50
Esophagus	0.07	1.82	0.03–0.11	0.12	1.99	−0.12–0.36
Bladder	0.04	1.36	0.02–0.07	0.04	1.36	−0.02–0.10

Table 12

Average number of cigarettes per day smoked by male lung I cancer patients and matched controls who are presently smokers and have smoked cigarettes for at least 10 years (by race and type of cigarette), 1969 to 1975

	NF				LTF			
	Whites		Blacks		Whites		Blacks	
Age	Qty[a]	N[b]	Qty[a]	N[b]	Qty[a]	N[b]	Qty[a]	N[b]
				Lung I				
20–49	37.8	17	22.3	15	37.4	29	27.3	6
50–59	32.6	45	27.8	20	35.2	59	21.4	7
60–69	31.8	69	27.8	11	30.1	41	26.0	5
70–89	27.4	20	21.7	3	23.3	15	10.0	1
				Matched controls				
20–49	28.5	37	20.5	27	25.5	61	19.4	17
50–59	27.4	104	19.9	52	28.7	157	18.9	24
60–69	29.3	100	16.9	30	25.3	110	19.6	14
70–89	19.6	41	15.7	7	22.2	25	13.0	5

[a] Qty, quantity (average number) of cigarettes smoked per day.
[b] *N*, number of smokers.

Table 13

Average duration of lifelong cigarette smokers[a] habits for male lung I cancer patients and matched controls, 1969 to 1975

	Combined use		Filter use		Nonfilter use		Age began smoking	
Age	N[b]	Av. yr	N[b]	Av. yr	N[b]	Av. yr	N[b]	Av. yr
				Lung I				
20–49	88	28.5	58	11.7	81	22.5	88	15.8
50–59	178	38.6	114	10.8	177	31.9	178	16.4
60–69	164	47.5	85	10.7	164	42.1	164	16.5
70–89	48	55.0	26	13.2	47	48.7	48	18.4
				Matched controls				
20–49	188	28.9	126	12.3	180	21.6	188	16.5
50–59	424	37.2	273	12.0	419	29.7	424	17.6
60–69	316	44.8	188	12.1	315	38.0	316	18.5
70–89	99	53.8	51	11.1	97	48.5	99	20.1

[a] All subjects were current smokers with at least 10 years of smoking history.
[b] *N*, number of smokers.

Alcohol

Consumption of alcohol has been shown in previous studies to be associated with development of cancer of the mouth (25, 33), larynx (36), and esophagus (30). Evidence has been adduced from these studies for a possible cocarcinogenic effect of alcohol. The precise influence of alcohol on human cancer has been difficult to measure since there is a substantial correlation between smoking and drinking.

The index of alcohol consumption was taken to be oz of alcohol per day. As in previous studies an equivalence among beer, wine, and liquor quantities has been constructed, although use of such equivalence may lack the accuracy of some other study variables. Consequently, we report here daily alcohol consumption broken down into 3 categories: none or occasional usage; 1 to 6 oz daily; 7 or more oz daily.

A simple calculation was carried out to obtain percentages of liquor consumption and relative risks for these 3 alcohol-related cancers for males and females, regardless of tobacco usage. It was found that the risk for each type of cancer increases with the quantity of liquor consumed, and larger proportions of heavy drinkers (and lower proportions of nondrinkers) occur for cancers of the mouth, larynx, and esophagus than do for lung or bladder cancer.

Alcohol-tobacco correlation can be most clearly seen among controls, as Chart 6 shows. The percentage of the pool matched controls reporting none or occasional liquor usage decreases as cigarette usage increases from 91% of nonsmokers to 61% of heavy smokers, but the percentage of controls reporting 7 or more alcohol units/day increases as cigarette usage increases from 2% of nonsmokers to 23% of heavy smokers. Among cases the highest proportion of heavy alcohol usage in each tobacco use category

Table 14

Relative risk[a] of present smokers (>20 years) by quantity, duration, sex, and diagnosis

Diagnosis	Duration (yrs.)	Sex: Male 1-20[b]	Male 21-40[b]	Male 41+[b]	Female 1-20[b]	Female 21-40[b]	Female 41+[b]
Lung I (N_M[c], 480; N_F, 98)	21-40	1.0	*1.8*[d]	*3.8*	1.0	*2.7*	2.8
	41+	1.6[e]	*4.4*	*5.5*	1.3	*4.8*	2.2
Lung II (N_M, 211; N_F, 73)	21-40	1.0	1.4	1.5	1.0	1.7	1.2
	41+	1.6	1.9	*3.7*	1.6	*7.1*	*8.7*
Oral cavity (N_M, 371; N_F, 140)	21-40	1.0	*2.0*	1.6	1.0	1.6[e]	0.6
	41+	1.5	*2.2*	*2.8*	1.7	*6.5*	5.7[e]
Larynx (N_M, 261; N_F, 58)	21-40	1.0	1.7[e]	*3.6*	1.0	*3.9*	*11.5*
	41+	2.0[e]	*4.2*	2.9[e]	1.2	3.4[e]	9.0
Esophagus (N_M, 113; N_F, 45)	21-40	1.0	1.5	1.8	1.0	0.8	
	41+	1.8	1.7	1.8	2.7	3.0	
Bladder (N_M, 309; N_F, 58)	21-40	1.0	0.8	1.1	1.0	0.5	
	41+	0.9	1.4	1.3	3.2	4.7[e]	

[a] Relative to a smoker of 1 to 20 cigarettes/day, who has smoked 21 to 40 years, adjusted for race and age.

[b] Number of cigarettes/day.

[c] N_M, number of males; N_F, number of females.

[d] Numbers in *italics*, $p < 0.01$.

[e] $p < 0.05$.

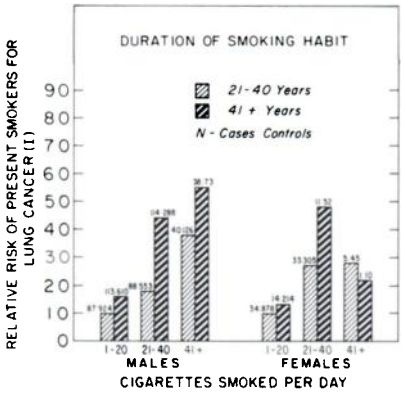

Chart 5. Relative risk of male and female present smokers for lung cancer I, by quantity and duration of habit.

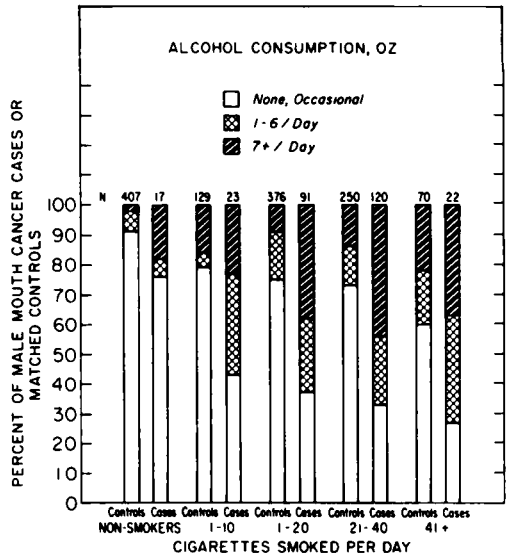

Chart 6. Correlation of alcohol and tobacco consumption among male mouth cancer cases and controls.

occurs for mouth, larynx, and esophagus cancer. For example, among smokers of more than 2 packs/day, 35% of mouth cancer cases and 29% of larynx cases reported heavy liquor intake compared to 23% of controls. Even among light smokers (1 to 10 cigarettes/day), 30% of esophagus cancer cases were heavy drinkers *versus* 16% of controls in this smoking category. These generalizations are readily apparent in Chart 6, in which the percentages of nondrinkers and heavy drinkers are plotted against cigarette consumption for mouth cancer cases and controls.

To test for separate effects of alcohol and tobacco, we cross-classified the number of present cigarette smokers (10 years or more) according to cigarette quantity (1 to 10, 11 to 20, 21 to 40, and 41+ cigarettes/day) and alcohol consumption (none or occasional, 1 to 6, and 7+ units/day). The relative risks for males for these 3 cancer sites are given in Table 15; in this table the referent is nondrinkers within each tobacco category. This simplifies some comparisons and avoids the use of some of the smallest and least stable cells of the table (nonsmoker/nondrinker) as referents.

Reading down Table 15 we may examine the dose-response relation for liquor at constant tobacco usage within the given categories. Within each class of tobacco usage, daily consumption of alcohol generally increases the risk of these cancers. The effect of tobacco and alcohol on oral cavity, larynx, and esophagus cancer can be seen clearly in Chart 7. The relative risks shown in Chart 7 are adjusted

Table 15

Relative risk[a] among male nonsmokers and present smokers (10 years +) by cigarette consumption and liquor consumption

Nondrinker = 1.0.

Diagnosis	Liquor (oz/day)	N[b]	Cigarettes/day None	1-10	11-20	21-40	41+	Combined
Oral cavity	None or occasionally	273	1.0	1.0	1.0	1.0	1.0	1.0
	1-6		0.46	2.4	1.5	1.3	2.5	1.5[c]
	7+		4.1	4.2[c]	*3.4*[d]	*3.5*	2.4	*3.4*
Larynx	None or occasionally	205	1.0	1.0	1.0	1.0	1.0	1.0
	1-6		0.77	0.77	1.6	1.9	6.6[c]	*1.8*
	7+		4.4	1.2	*3.4*	*3.1*	3.4	*3.1*
Esophagus	None or occasionally	89	1.0	1.0	1.0	1.0	1.0	1.0
	1-6		1.5	1.2	1.9	0.56	2.2	1.2
	7+		6.4	1.8	*4.9*	2.1	1.4	2.8

[a] Relative to nondrinkers and adjusted for age and race.
[b] Number of patients at each cancer site.
[c] $P < 0.05$.
[d] Numbers in *italics*, $p < 0.01$.

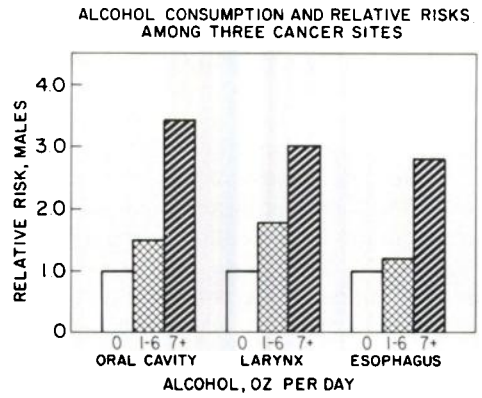

Chart 7. Relative risk of males for cancer of the mouth, larynx, and esophagus, adjusted for age, race, and smoking variables.

for age, race, and cigarette quantity within each alcohol consumption category. Among nonsmokers considered alone, a significant increase in risk with alcohol consumption was not observed.

Epidemiological Considerations

Although the number of cases and controls and their distribution through various parts of the United States makes the analysis of the data quite meaningful, there are nevertheless some problems that need to be considered. One potential problem is possible interviewee bias. Although an interview with a patient with tobacco-related cancer would probably not have aroused a "guilt" complex in the patient 25 years ago, the current public knowledge about the carcinogenic potential of cigarette smoke is quite widespread.

As many as three-fourths of the public believe in the causative association between smoking and lung cancer (1). With this kind of background, it is likely, although it remains to be proved, that there exists a tendency for patients with a tobacco-related cancer, especially lung, mouth, and larynx cancer, to underestimate their smoking history as well as their alcohol history. We are currently investigating this issue in a parallel study of biased reporting in spouse pairs. Underestimation of cigarette consumption by cases would mean that differences between study and control groups would actually be larger than has been reported. It could also mean that the actual dose of cigarette smoke required to elicit lung cancer would be larger than that apparent from the present set of data.

Another issue that deserves further study involves histological classification of lung cancer type II. We have previously shown that glandular lung cancer is related to cigarette smoking to a lesser degree than are squamous and oat cell cancers, whereas the relationship of smoking to terminal bronchiolar cancer is weak. Some of the inconsistencies of lung II cancer data may in part relate to a mixture of lesions, those containing both squamous and glandular cancer and terminal bronchiolar lesions. To unravel possible etiological differences would require special histological studies of all of the cases. It should also be considered that false primary lesions of the lung (metastatic lesions) that originated at other sites yielding adenocarcinomas are more likely to occur than are those derived from squamous cancers. From an etiological point of view, therefore, the particular care given to clinical and histological verification of cancer of the lung is a major feature of this study.

The observed sex ratio of tobacco-related cancers is consistent with long-term smoking habits of men and women. Notable exceptions are cancers of the tongue, buccal mucosa, supraglottic larynx, and esophagus. Cancers at these sites appear to occur more commonly in nonsmoking women than in nonsmoking men (33). This greater female susceptibility may be related to a subclinical type of Plummer-Vinson disease, a condition more common in women because of their inherent greater risk for iron deficiency (19, 40).

Cancer of the larynx and upper alimentary tract is affected by heavy alcohol intake, as was clearly shown once more by the present study. Alcohol, whose effects interact with cigarette smoke, may be regarded as a promoter of tobacco carcinogenesis. We have previously suggested that the effect of alcohol in this setting may be related to nutritional deficiencies associated with alcoholism (27, 32). Whatever the mechanism, in the absence of alcohol consumption the rate of cancer of the larynx and upper alimentary tract among smokers would be greatly reduced.

The epidemiology of cancer of the bladder cannot be fully explained on the basis of smoking and occupational exposure alone. The particularly low rate among Japanese suggests additional etiological agents, possibly of dietary origin. We have computed a correlation coefficient of 0.57 between the age-adjusted mortality rate of males and per capita dietary fat consumption for 15 countries, a finding similar to that presented by Armstrong and Doll (2). This means that up to 32% of the variability of bladder cancer mortality could be explained by dietary fat components (37).

Although some occupational exposures increase the risk of both lung cancer and bladder cancer, the size of the populations at risk are relatively small compared to the number of smokers in the general population (15). A recent study by Hoover *et al.* (16) has found a relatively high incidence of bladder cancer in the counties of the United States in which chemical and other heavy industries are concentrated. Cole *et al.* (7) has suggested that in northeast Massachusetts, 8% of male and 6% of female bladder cancers have an occupational basis.

The National Academy of Sciences has summarized evidence suggesting that general air pollution enhances the risk of lung cancer (22). Blot and Fraumeni (4) have attempted to link geographical variations with industralization centers, whereas Henderson *et al.* (14), evaluating this issue in Los Angeles, suggested that at least some of the observed examples of lung cancer are due to air pollution. Hammond (13), however, in a detailed review of this issue has stressed that, if one standardizes the data for smoking habits and occupational exposures, general air pollution does not appear to be of the same quantitative importance as smoking in the etiology of lung cancer. Even the limited computation of "Appendix" is consistent with this hypothesis.

A strong relationship between socioeconomic status and tobacco-related cancer is reflected by the smoking habits of different groups. In this study the ratio of present male nonfilter to filter cigarette users among whites is about 1.0 for both cases and controls, but it is 2.4 among black cases and controls. The median education level is several years of high school for LTF smokers and grammar school for NF users, regardless of disease status. The distribution of education levels is the same among both cases and controls for LTF and among cases and controls for NF, but it is different between LTF and NF, regardless of disease category. The proportion of exsmokers is also higher among persons of higher educational achievement. These are points that we have previously reported in more detail (35). The conclusion to be drawn is that tobacco-related cancer, particularly lung and larynx cancers, will increasingly afflict the lower socioeconomic groups of males because of their lower cessation rate and their lesser preference for low-tar cigarettes, compared to more educated groups. Similarly, those groups of smokers among whom heavy alcohol intake is most common and among whom associated nutritional deficiencies are likely to be most prevalent will have the highest rates of cancer of the oral cavity, larynx, and esophagus. At the core of these risk factors lie, as has so often been stated before, the preventive opportunities for cancers of the respiratory and upper alimentary tract.

CONCLUSION

The present retrospective study has investigated the epidemiology of several tobacco-related cancers, based on 3,716 cases of histologically proven cancers and a subset of age-, sex-, race-, and city-matched controls drawn from a pool of more than 18,000 patients. Tobacco smoke, especially cigarette smoke, continues to be a major causative factor of cancers of the respiratory tract, oral cavity and, to a lesser extent, of the esophagus and bladder. The effect of dose on tobacco-related cancer appears to be somewhat stronger than that of duration and both variables have an important influence for those cancers.

Cigar and pipe smokers have a risk similar to cigarette smokers for cancer of the oral cavity. They carry a lower risk for lung and larynx cancers, attributable probably to lower levels of inhalation of cigar and pipe smoke.

For lung cancer the etiological importance of cigarette smoking is greater for squamous and oat cell cancers (type I) than it is for the glandular lung cancers (type II), although the risk for both of these is increased by smoking.

The sex ratio especially for lung I cancer is declining, an observation consistent with the stabilizing male rate of lung cancer and its increasing rate among women.

Lung I cancer and cancer of the upper alimentary tract were observed less frequently among Jews, consistent with their lower cigarette consumption. Such a relationship has not been shown for lung II cancer. The reduced incidence of cancer of the upper alimentary tract among Jews is also in line with their lower intake of alcohol.

Our data confirm the observation that United States blacks have a significantly higher rate of esophagus cancer than do whites.

The higher frequency of bladder cancer among Jews and the lower rate among blacks compared to other cases and to controls indicates at least in part a different etiology for bladder cancer than for the other tobacco-related cancers.

The risk of developing tobacco-related cancers decreases with the extent of exsmoking in comparison to persons who continue to smoke, approaching the level of nonsmokers after about 15 years.

As younger age groups have had a relatively shorter exposure to the smoke of high-tar nonfilter cigarettes than the older age groups, we observe that younger smokers have had to smoke more cigarettes than older smokers to reach a similar risk of lung cancer. Thus far, we cannot estimate the risk of tobacco-related cancer for those smoking filter cigarettes exclusively, since today's patients began their smoking habits with the older, nonfilter cigarettes.

Tobacco-related cancers will become increasingly less common among more highly educated individuals, especially males, consistent with their changing smoking habits. The most influential changes are cessation and switching to lower-tar brands. These changes are beginning to have an increasing amelioratory effect on the incidence of all tobacco-related cancers in the general population.

Among smokers, heavy alcohol consumption specifically enhances the risk of cancers of the mouth, larynx, and esophagus. Reduction of excessive alcohol consumption will have an important impact on reducing these types of cancers.

Tobacco smoking continues to be a major although a preventable cause of cancer of the respiratory and upper alimentary tract. Whereas it is projected that male rates, especially among the younger age groups, will continue to decline because of a reduction in tar yields of cigarettes and an increase in the number of exsmokers, rates for females are expected to continue to increase because increasing numbers of female smokers enter the cancer age groups. We need to increase our efforts to discourage younger people from starting to smoke, and we must expand our activities in cost-effective smoking cessation programs. As long as society condones smoking, young people will continue to begin the habit, and many adults will continue to smoke in spite of our best educational efforts. Therefore, we must accelerate our efforts in the development of acceptable less harmful cigarettes, not only in terms of reduction of smoke condensate but in terms of a specific reduction of established carcinogenic and toxic components. Obviously, as long as the rate of tobacco-related cancer remains as high as is currently the case, our task has not been accomplished. A major and properly coordinated effort in all 3 of these areas should help advance the day when the tobacco-related cancers and other tobacco-related diseases, so clearly amenable to preventive approaches, will no longer plague our society.

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Appendix: Influence of City on Smoking and Disease

A log linear model (3) was fit to a subset of our data comprising Caucasian males between ages 50 and 69. Three variables were considered: disease status (lung I; controls), smoking variables, and region (Miami-Birmingham; New York; Los Angeles).

A model containing parameters in all 2-way interactions between each of the 3 variables but with no 3-way effect provided an excellent fit to the observed data with all the controls (9). The hypothesis was tested that the effect of smoking on disease is constant across differing hospital locations. Such an excellent fit shows that with our data the observed increase in risk for lung I cancer as a function of cigarettes smoked per day is identical in each of the 3 environments.

If smoking patterns were exactly the same in all 3 regions, absolutely no distortion between smoking and disease would occur without stratifying on city and collapsing tables on this variable. In a statistical sense the distribution of smoking patterns is not identical across region. However, we are dealing with very large numbers of observations and, as a result, tests of statistical significance are extremely sensitive to very slight fluctuations in smoking patterns. From a practical point of view, in our data we find that smoking patterns are so similar across region and that the relationship between disease and smoking are so overwhelming, compared to the slight fluctuations in smoking patterns, that little if any distortion in odds ratios would occur by ignoring stratification by region. Furthermore, stratifying by location leads to a large number of empty cells in various strata, which produces unstable risk estimates. The following table is presented to show how little the odds ratios change by collapsing on the location variable.

Cigarettes/day	Relative risk of lung I for males	
	Stratified by region	Collapsed on region variable
1-10	8.93	9.43
11-20	25.83	32.81
21-30	43.49	41.57
31-40	52.76	53.90
41+	80.41	81.16

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