Cigarette Smoking and Large Cell Carcinoma of the Lung[1]

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Abstract

Large cell carcinoma is the fourth most common histological type of lung cancer in the United States. Cigarette smoking causes large cell lung cancer, but it is uncertain whether the effect varies with the amount and duration of smoking. This uncertainty stems from ambiguity in the histopathological classification of large cell cancer, especially before 1971, and the relatively infrequent occurrence of large cell cancer in epidemiological studies. The present case-control investigation demonstrates that the risk of large cell cancer increases with both the frequency and number of years of cigarette smoking. The odds ratio associated with smoking two or more packs/day was 37.0 (95% confidence interval, 16.4–83.2) in men and 72.9 (35.4–150.2) in women. It is concluded that cigarette smoking is the predominant cause of large cell lung cancer.

Introduction

Cigarette smoking has been conclusively established as the major cause of lung cancer. The dose of smoking is strongly related to an increasing risk of epidermoid (squamous) adenocarcinoma and small cell lung cancers (1, 2), which comprise 70% of lung cancers in the SEER[3] program (3; Table 1). The fourth most common lung cancer cell type is large cell carcinoma, comprising about 9% of lung tumors. Although large cell cancer causes approximately 15,000 deaths per year (4) in the United States, the effect of cigarette dose has not been established. In fact, based on the results of an ongoing case-control study conducted by our group, the risk of large cell cancer did not increase with the number of CPD (2). This observation was noted for data analyzed between 1985 and 1990. The lack of a dose-response trend seems inconsistent with the known carcinogenic effects of tobacco smoke. We, therefore, reexamined this relationship using a larger sample size.

Materials and Methods

The study methodology is described in detail elsewhere (2). To summarize, data from an on-going multicenter case-control study of smoking and lung cancer was analyzed for the time period 1980–1995 (see "Acknowledgments"). Hospitalized patients with newly diagnosed bronchogenic cancer were approached and requested to participate in an interview using a structured questionnaire. The histological type of lung cancer was determined by review of the patient's pathology report. Eligible controls were patients admitted to the hospital for conditions unrelated to tobacco exposure. Controls were selected from the daily admission rosters and frequency matched to cases on the basis of sex, age (±5 years), hospital, and year of interview. Among the 2545 male controls, 49.7% had cancer (predominantly colorectal, prostate, stomach, skin, lymphoma, and leukemia); 6% had benign growths including benign prostatic hypertrophy; 37.7% had nonmalignant disease; and 6.6% had fractures or injuries. Among the 1715 female controls, the diagnosis was cancer in 49.7% (predominantly breast, colorectal, and ovarian); 15.4%, benign growths; 11.3%, injuries/fractures; and 23.6%, other nonmalignant conditions. Each participant signed a consent form that had been approved by the hospital's Institutional Review Board.

For the current analysis, we compared the subset of patients with large cell carcinoma to the entire lung cancer control series. For OR calculations, the effects of smoking were adjusted for age at diagnosis (four categories) and years of education (four categories) using nonsmokers as the referent category in logistic regression analyses. Trend tests were calculated for the number of cigarettes smoked per day and the number of years smoking by categorizing these variables and assigning median values to these categories. To determine the effect of the type of cigarette (lifetime filter smoker *versus* lifetime nonfilter smoker *versus* smoker of both types) on large cell cancer risk, the analysis was conducted among ever-smokers with nonfilter smokers serving as the reference group.

Results

There were 228 men and 154 women diagnosed with large cell carcinoma during the study period. These patients were compared to the control series of 2545 men and 1715 women. The ages, educational levels, and races are presented in Table 2. Ninety-three % of cases and 92% of controls were white. The mean years of education were 13.1 in male cases *versus* 13.6 in male controls ($P < 0.01$) and 12.8 in female cases *versus* 13.2 in female controls ($P < 0.01$). Cases began smoking cigarettes earlier than controls. The mean age of smoking onset in men was 16.9 in cases *versus* 17.9 in controls ($P < 0.01$). In women, the mean age of smoking onset was 18.9 in cases *versus* 20.4 in controls ($P < 0.01$).

The risk of large cell cancer increased substantially with the number of cigarettes smoked in current smokers and former smokers (Table 3). The adjusted OR for current smokers of ≥40 CPD was 37.0 (95% CI, 16.4–83.2) in men and 72.9 (95% CI interval, 35.4–150.2) in women. The risk of cancer was also

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[3] The abbreviations used are: SEER, Surveillance Epidemiology and End Results; CPD, cigarettes per day; OR, odds ratio; CI, confidence interval.

Table 1 Distribution of histological types of lung cancer

Histology	SEER, 1983–1987[a]		AHF, 1985–1990[b]	
	Males	Females	Males	Females
Squamous cell	31.2	19.0	32.8	19.5
Small cell	16.6	20.2	10.6	11.7
Large cell	9.3	8.9	10.2	10.4
Adenocarcinoma	22.7	29.7	36.4	45.4
Bronchioalveolar	2.5	4.6	1.9	4.7
Other	16.7	17.6	8.1	8.3

[a] SEER program, 1983–1987 based on 39,653 male lung cancers and 20,867 female lung cancers.
[b] AHF, American Health Foundation case-control data of 1,165 male lung cases and 750 female lung cases.

highly dependent on the number of years of smoking (Table 3). In ex-smokers, the risk decreased with the number of years since quitting (Table 3). Most smokers had smoked both filter and nonfilter cigarettes over their lifetimes. There were too few men and women who smoked exclusively nonfilter or filter cigarettes to examine the effects of cigarette type with precision.

Discussion

It is established that the likelihood of contracting lung cancer increases with the frequency and duration of cigarette smoking. In former cigarette smokers, the risk decreases substantially with the number of years since quitting. The present study demonstrates the same associations between cigarette smoking and large cell lung cancer. No association was found with cigar smoking. When comparing the association between smoking and large cell cancer with the other major histological types of lung cancer in this data during the same study period (1980–1995), the OR for current cigarette smokers (18.0 in men and 20.2 in women; Table 3) was intermediate between the OR for squamous cell carcinoma (56.6 in men and 37.1 in women) and adenocarcinoma (10.2 in men and 12.7 in women).

Several possible biases should be considered when interpreting these findings. In case-control studies, the smoking rates in the hospital control population may exceed that in the community. To address this issue, a randomly selected sample of age-matched neighborhood controls were interviewed in 1980 and 1981 (5). The data showed a slightly greater smoking rate in the community than in the hospital control group that was interviewed during 1980 and 1981, suggesting that the selection of hospital subjects for the control group did not introduce bias. Another concern is that the data collection protocols and procedures varied over the long study interval and that changes in hospital referral patterns may have affected the risk calculations. The study procedures did remain uniform throughout the course of the investigation, and all subjects were interviewed at bedside using the same structured questionnaire. No changes were made in field supervision staff and interviewing instructions and techniques. When the data were analyzed by three separate time periods (1980–1985, 1986–1990, and 1990–1995), there appeared to be relatively little variability in the distribution of smoking habits. For example, the percentage of nonsmoking cases was 2.8, 3.9, and 0% in men and 10, 6.2, and 10% in women, respectively. Similarly, there were no gross differences in smoking patterns of subjects between hospitals.

The causes of large cell lung cancer has not been extensively studied for several reasons. Large cell lung cancer is often a poorly differentiated tumor and was ill-defined in the 1967 WHO classification. Several morphological features of large cell cancer are shared with other lung cell types. Campobasso *et al.* (6) calculated an interobserver reliability kappa value of 0.71 for large cell lung carcinoma in an archived series of slides using the 1967 classification. When using the 1981 WHO classification that uses stricter classification criteria, the number of discrepant values was reduced by 33%. In the SEER Program, large cell carcinoma was not categorized before 1978.

The reliability of the histological classification in the current study was not evaluated, although current efforts are under way to review a sample of slides representing all lung histological types. It is unlikely that there was extensive misclassification of large cell cancer in this series. Table 1 shows that the histological distribution of lung cancer in the overall case-control study is similar to that reported in the SEER system (Table 1). The epidemiology of large cell cancer has also been hindered because of the relatively few number of incident cases compared to other lung histological types. The few studies that examined the rates of large cell cancer by amount of cigarette smoking were inconclusive because of small sample sizes (7). One case-control study in Japan by Sobue *et al.* (8), which included 81 large cell lung cancer patients, did show evidence of a dose-response effect. Compared with subjects who smoked 1–29 years, the OR for large cell cancer was 1.3 for 30–39 years of smoking, 2.1 for 40–49 years of smoking, and 1.6 for 50+ years of smoking. In our previous report that included 97 men and 59 women with large cell lung cancer for the study period 1985–1990 (2), the OR of lung cancer associated with ≥20 CPD was calculated among current smokers using 1–19 CPD as the male and female referent groups, respectively. There were only three male cases and six female cases in these referent groups; this appears to have resulted in unstable relative risk estimates.

It is uncertain what carcinogenic agents in tobacco smoke cause large cell lung cancer. Experimental studies have not produced large cell carcinoma in the lungs of laboratory mice and rats (9). Autopsy studies by Auerbach and Garfinkel (10) show that large cell carcinomas are evenly distributed throughout the lung, in contrast to squamous cell cancers that arise primarily in the central lung bronchi and adenocarcinomas that occur almost exclusively in the peripheral lung. Experimental animal studies show that the most likely mechanisms of lung cancer induction in humans differ by the location of the tumor. The deposition of cigarette particulates containing polycyclic hydrocarbons in the major lung bronchi probably initiates the development of squamous cell carcinoma. The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a blood-borne carcinogen that is metabolized in the liver and induces lung adenocarcinoma in highly vascularized, peripheral lung tissue in animals and possibly humans. It may be that both particulate deposition and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone cause large cell cancer in humans.

An important public health concern is whether the "tar" content of cigarettes is related to the risk of large cell cancer. Studies have shown that the risk of lung cancer is lower in smokers of low tar filter cigarettes relative to smokers of the higher tar nonfilter cigarettes (11–13). Other studies have not shown this effect (14–16), however, and it has been suggested that the level of tar in cigarette smoke may be an important determinant of lung cancer only for some histological types (17). Our data confirm this hypothesis, showing a reduced risk of squamous cell carcinoma with filter cigarettes but no reduction for adenocarcinoma (18). Larger-scale studies are needed to determine whether the risks for large cell carcinoma vary between smokers of nonfilter and filter cigarettes.

The role of other possible risk factors for large cell cancer including air pollution (19, 20) should be explored. In a study of 755 lung cancer case-control pairs in Trieste, Italy, Barbone

Table 2 Age, education, and race in cases and controls, 1980–1995

Variable	Men				Women			
	Cases N = 228%		Controls N = 2545%		Cases N = 154%		Controls N = 1715%	
Age								
<45	12	5.3	198	7.8	19	12.3	150	8.8
55–64	47	20.6	435	17.1	33	21.4	366	21.3
65–74	89	39.0	995	39.1	55	35.7	582	33.9
>74	80	35.1	917	36.0	47	30.5	617	36.0
Education								
<12	72	31.6	555	21.8	34	22.1	296	17.3
12	69	30.3	669	26.3	68	44.2	636	37.1
13–15	33	14.5	434	17.1	27	17.5	364	21.2
>15	54	23.7	887	34.9	25	16.2	419	24.4
Race								
White	212	93.0	2332	91.6	144	93.5	1588	92.6
Black	14	6.1	205	8.1	9	5.8	124	7.3
Other	2	0.9	8	0.3	1	0.7	3	0.2

Table 3 Odds ratio for cigarette smoking and large cell cancer of the lung, 1980–95

Smoking category	Men				Women			
	Cases N = 228	Controls N = 2545	OR[a]	95% CI	Cases N = 154	Controls N = 1715	OR[a]	95% CI
Tobacco use								
Never	7	650	1.0		13	936	1.0	
Former	99	1113	7.9	3.7–17.2	41	431	7.2	3.8–13.5
Current	120	593	18.0	8.3–39.0	100	348	20.2	11.1–36.7
Cigar/Pipe	2	189	0.9	0.2–4.6	0	0		
CPD in current smokers								
0	7	650	1.0		13	936	1.0	
1–19	16	173	8.3	3.4–20.6	11	130	6.0	2.6–13.7
20–39	45	275	14.6	6.4–33.1	50	177	21.0	11.0–40.1
≥40	59	144	37.0	16.4–83.2	39	41	72.9	35.4–150.2
Trend				$P < 0.01$				$P < 0.01$
CPD in ex-smokers								
0	7	650	1.0		13	936	1.0	
1–19	16	291	4.8	2.0–11.9	11	199	4.2	1.9–9.6
20–39	41	490	7.4	3.3–16.9	19	154	9.9	4.8–20.7
≥40	42	331	11.1	4.9–25.0	11	77	10.5	4.5–24.4
Trend				$P < 0.01$				$P < 0.01$
Years of smoking								
0	7	650	1.0		13	936	1.0	
1–19	14	415	2.9	1.2–7.3	9	197	2.9	1.2–6.9
20–39	98	820	10.6	4.9–22.9	74	414	11.5	6.3–21.1
≥40	107	470	23.1	10.4–50.8	58	167	30.1	15.8–57.4
Trend				$P < 0.01$				$P < 0.01$
Years since quitting								
0	7	650	1.0		13	936	1.0	
>10	56	803	6.1	2.8–13.6	16	287	4.2	2.0–9.0
6–10	20	144	12.9	5.3–31.1	11	74	11.5	5.0–26.7
1–5	23	163	12.4	5.2–29.6	14	69	15.9	7.1–35.4
Trend				$P < 0.01$				$P < 0.01$

[a] Adjusted for age and education by logistic regression. Reference group is never smokers for all calculations.

et al. (20) found increased risks of large cell for residents living near iron foundries, incinerators, and shipyards. Poor nutrition may contribute to large cell lung cancer. Steinmetz *et al.* (21) found suggestive evidence that low consumption of vegetables and fruits was related to an increased risk in a cohort of women living in Iowa. These findings provide further leads in the epidemiology of large cell lung cancer.

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