

Lung Cancer in Women: The Importance of Smoking, Family History of Cancer, and Medical History of Respiratory Disease¹

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ABSTRACT

The importance of smoking and other factors for lung cancer in women was investigated in a case-control study of women who had previously received a multiphasic health checkup at Northern California Kaiser Hospitals. Smoking and medical histories for 217 cases and matched controls were obtained from the multiphasic questionnaire. Odds ratios (ORs) and confidence intervals (CIs) associated with cigarette smoking were 35.1 (95% CI 4.8-256) for squamous and small cell and large cell carcinomas combined and 2.5 (95% CI 1.3-5.1) for adenocarcinoma. After adjusting for smoking, risk was increased in women with a family history of lung cancer (OR 1.9, 95% CI 0.7-5.6) and family history of any cancer (OR 1.8, 95% CI 1.0-3.2). A significant interaction existed between smoking and family history. Women with a history of bronchitis, pneumonia, or emphysema were at increased risk, whereas women with a history of asthma or hay fever experienced a significantly lower risk for lung cancer.

INTRODUCTION

In 1960, the male/female ratio of incident lung cancers began to decline, reflecting a rapid rise in the rate of increase in women and a leveling off of the rate of increase in men (1). By 1978, the male/female ratio had decreased from 6.6 to 3.1 and incidence rates for women aged 35-44 years equaled those for young men (2). Although recent Surveillance, Epidemiology, and End Results program data indicate a decline in incidence rates for women <45 years of age, rates for women >65 years have continued to increase by >10%/year (3). No longer regarded as primarily a disease of men, lung cancer is now the leading cause of cancer death in United States women (4).

Squamous cell carcinoma has been the predominant cell type found in men, whereas adenocarcinoma predominates among lung cancers in women (5). Based on this difference and differences in smoking habits between men and women, Kreyberg (6) hypothesized that smoking caused squamous, small cell, and large cell carcinomas but other risk factors were responsible for adenocarcinoma. While some case-control studies of women have indicated a stronger association with smoking for the former cell types than for adenocarcinoma (7, 8), others have shown no differences between cell types (9) or no association with smoking for adenocarcinoma (10, 11).

The difference between men and women in accumulated exposure to cigarettes has decreased with successive birth cohorts. Men and women born in the 1950s now smoke with equal frequency and intensity (12). On the basis of the observed relationship between smoking and cell type and the increase over time in smoking among women, one would expect a shift

in the histological distribution of lung cancers in women toward the male pattern with a predominance of squamous cell carcinoma. Instead, an increase in the frequency of adenocarcinoma in women not entirely explained by changes in diagnostic criteria has been observed (13-15).

To explain gender differences in the histological distribution of lung cancers, case-control studies have sought other causal factors for lung cancer. Associations with family history of lung cancer (16-22) and the occurrence of chronic obstructive pulmonary disease (8, 22-25) have been observed. In addition, a lower than expected incidence of lung cancer has been reported in persons with chronic asthma or allergy (26-31). The relationship of other risk factors to specific histological types of lung cancer has been infrequently studied. This study examined the importance of smoking, family history of cancer, and medical history of respiratory disease for specific lung cancer cell types in women who had attended the San Francisco or Oakland Kaiser Permanente Medical Centers for a multiphasic screening examination prior to diagnosis.

MATERIALS AND METHODS

All female cases of pathologically verified primary carcinoma of the lung diagnosed between 1969 and 1977 at Northern California Kaiser hospitals were identified from hospital discharge records and records of the California Tumor Registry. Cases who had received a multiphasic health checkup at the San Francisco or Oakland Kaiser Permanente Medical Centers prior to diagnosis were eligible for inclusion in the study. Microscopic confirmation was available for 217 of 252 eligible cases. Controls were selected from approximately 140,000 women who had attended the Kaiser screening between 1964 and 1977 but had not developed lung cancer. Each was matched for year of birth, race, and date of first multiphasic checkup.

The Kaiser multiphasic checkup, described in detail elsewhere (32), included a self-administered medical history questionnaire which provided demographic information, smoking habits, and medical and family histories for each participant. Most individuals received a multiphasic checkup more than once, completing a questionnaire at each visit. Because 10% of participants did not give a smoking history at the first multiphasic checkup, all questionnaires completed prior to the date of diagnosis (or for controls, the diagnosis date of the matched case) were examined. Cases and controls attended the multiphasic screening examination with equal frequency, an average of 2.7 and 2.5 times, respectively. Lung cancer cases first attended the multiphasic screening an average of 6.5 years before diagnosis. Only 10 cases (4.6%) had their first multiphasic checkup within 6 months of diagnosis.

The multiphasic questionnaire contained two sets of questions to characterize current and past smoking habits of an individual. These questions were combined by Friedman *et al.* (33) to classify women as current, ex-, or nonsmokers at each multiphasic checkup. Women who had quit at least 2 years prior to the diagnosis date were classified ex-smokers. Women who reported being nonsmokers at each multiphasic examination were classified as never-smokers. All others were considered current smokers.

Participants were considered to have a family history of cancer if they reported the occurrence of cancer in any first-degree relative (parents, siblings, or children) at any multiphasic checkup. Participants were asked whether they had ever had any of several respiratory diseases, including bronchitis, pneumonia, emphysema, asthma, or hay

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fever, more than 1 year prior to the multiphasic checkup. A positive answer at any checkup was considered a positive history. Education was coded as the highest level reported at any multiphasic examination.

All available pathology specimens were reviewed without prior knowledge of the initial diagnosis by Dr. Milton L. Bassis, Chief, Department of Pathology, Kaiser Permanente Medical Group, San Francisco, CA. Lung cancers were classified according to the 1967 World Health Organization criteria (34, 35) into five categories: squamous cell carcinoma, small cell carcinoma, adenocarcinoma including bronchoalveolar carcinoma, large cell undifferentiated carcinoma, and other and unknown carcinomas. Cases for whom no slides could be located (3%) were excluded from the analysis.

Data were analyzed using multivariate logistic regression methods for case-control data with pairwise matching (36). Conditional maximum likelihood estimates of the logistic coefficients were calculated by the Newton-Raphson method of iteration. The $OR,^3 \exp(B_i)$, was used to approximate relative risk. Confidence intervals were calculated for all ORs. Because socioeconomic status may be associated with the occurrence of respiratory disease and cancer independently of smoking (37), ORs for medical and family history variables were adjusted for education and quantity of cigarettes smoked. Case-control pairs with missing data were excluded from the analysis. Women with missing data did not differ with respect to age or smoking from those with complete data.

Because of the small number of never-smokers among some cell types, ORs were calculated for two groups of cell types consistent with the classification of Kreyberg (6) for lung cancers into tumors associated with smoking (Kreyberg I) and those thought to be caused by other factors (Kreyberg II). The first group, Kreyberg I, included 117 cases of squamous cell, small cell, and large cell carcinoma. The second group, Kreyberg II, consisted of 83 cases of adenocarcinoma and bronchoalveolar carcinoma. Classification by Kreyberg group showed good reliability. Following the pathology review, 88% of cases were classified into the Kreyberg group indicated by the original pathology report.

RESULTS

The racial composition of cases and matched controls (86% white, 11% black, and 3% Asian) resembled that of all women who attended the Kaiser multiphasic checkup (29). More cases than controls reported elementary school to be their highest level of education (21 compared to 14%). The risk associated with an elementary school education relative to at least 1 year of college was 2.1 (95% CI 0.9–9.3) after adjusting for smoking. Women with a high school, trade, or business education experienced no increased risk relative to college educated women (OR 0.8, 95% CI 0.5–1.5).

Adenocarcinoma was the most common cell type, accounting for 38% of cases. Squamous cell, small cell, and large cell carcinomas made up 17, 18, and 19% respectively. Lung cancer cases and controls (matched for year of birth) averaged 59 years at diagnosis. There were no differences between cell types in mean age at diagnosis.

Cigarette Smoking. The pathology distribution for cases who smoked was markedly different from that of never-smokers (Table 1). While one-third of the cases who smoked had adenocarcinoma, two-thirds of nonsmoker cases had adenocarcinoma. There were only 7 never-smokers among 117 women with squamous, small cell, or large cell carcinoma.

Table 2 presents age-adjusted ORs and 95% CIs by smoking and cell type. Lung cancer risk increased with quantity of cigarettes smoked, duration of smoking, and depth of inhalation for all cell types. A significant dose-response relationship existed for both Kreyberg I and Kreyberg II lung cancers. ORs

were distinctly higher for Kreyberg I than Kreyberg II lung cancers, and a steeper gradient in risk with increased smoking was observed.

Family and Medical History Variables. Seventeen cases and 9 controls reported a history of lung cancer in first-degree relatives (Table 3). The excess was seen only among smokers and was entirely accounted for by fathers and brothers of probands (14 cases, 5 controls). After adjusting for education and quantity smoked, women with a history of lung cancer experienced an increased risk for lung cancer of 1.9 (95% CI 0.7–5.6) (Table 4). Risk was increased in women older than age 55 years (OR 2.4) but not in younger women (OR 0.8). While the association appeared stronger for Kreyberg I than for Kreyberg II, neither OR differed significantly from unity.

Forty-one % of cases and 33% of controls reported a positive history of cancer at any site in first-degree relatives (Table 3). Cases who smoked more frequently reported having family members with both smoking-associated cancers and cancers not known to be associated with smoking than did controls who smoked. An excess of smoking-associated cancers only was seen in family members of nonsmoker cases compared to control nonsmokers. After adjusting for smoking and education, women with a family history of cancer had an increased lung cancer risk of 1.8 (95% CI 1.0–3.2) (Table 4). Women aged 55 years or younger experienced a greater increase in risk than older women (ORs 3.8 and 1.4, respectively). There were no differences between Kreyberg groups.

A significant interaction existed between cigarette smoking and family history of cancer (Table 5). Women who smoked more than one pack/day and reported a positive family history experienced an increase in risk >5-fold greater than the risk associated with heavy smoking alone (OR 47.4, 95% CI 22.2–101.2).

Both smokers and nonsmokers with lung cancer reported a history of bronchitis, pneumonia, or emphysema more frequently than did controls (Table 3). The adjusted OR was 1.7 (95% CI 0.9–3.1) for women with a medical history of respiratory disease compared to women with no history (Table 6). Odds ratios showed little variation with age or Kreyberg group and all confidence intervals included unity.

A history of asthma or hay fever at least 1 year before the multiphasic checkup was reported by 17% of cases and 29% of controls (Table 3). Women with asthma or hay fever were at significantly lower risk for lung cancer than women with no history of allergic disease (OR 0.5, 95% CI 0.3–1.0) (Table 6). ORs were lower than unity for both younger and older women (OR 0.2 and 0.8, respectively). No differences between cell types were observed.

DISCUSSION

The predominance of adenocarcinoma among lung cancer cell types in women has been observed in both case-control and

Table 1 Distribution of cases by smoking and cell type

Cell type	Ever-smokers		Never-smokers	
	No.	%	No.	%
Squamous cell	35	19	1	3
Small cell	40	22	0	0
Large cell	35	19	6	18
Adenocarcinoma	61	33	22	67
Other/unknown	13	7	4	12
Total	184	100	33	100

³ The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 2 Age-adjusted odds ratios associated with smoking

Smoking status	All lung cancer			Kreyberg I			Kreyberg II		
	OR	95% CI	Case/control	OR	95% CI	Case/control	OR	95%	Case/control
Never	1.0		33/109	1.0		7/58	1.0		22/43
Ever	6.7	3.7–12.0	184/104	35.1	4.8–256	112/61	2.5	1.3–5.1	61/40
Current	9.1	4.8–17.3	165/72	39.0	5.3–287	105/42	3.2	1.5–6.6	50/28
Former	2.5	1.1–5.9	19/32	12.6	1.4–113	7/19	1.7	0.5–5.3	11/12
Quantity ^a (pack/day)									
<1	2.5	1.2–5.2	35/55	12.1	1.5–96.3	18/31	0.9	0.3–2.7	14/24
≥1	12.6 ^b	6.2–25.6	149/47	71.2 ^b	8.3–609	93/29	3.8 ^b	1.6–8.8	47/15
Duration ^a (yr)									
≤20	1.6	0.7–3.5	23/47	4.9	0.5–44.6	11/26	0.7	0.2–1.9	10/20
>20	11.6 ^b	5.8–23.3	161–57	101.1 ^b	8.3–1230	101/35	4.1 ^b	1.8–9.4	51/20
Inhale ^a									
No	2.0	0.9–4.3	24/44	13.3	1.7–106	15/26	0.6	0.2–1.9	8/17
Yes	9.6 ^b	5.0–18.5	155/58	52.0 ^b	6.6–408	92/33	3.5 ^b	1.5–8.0	51/23

^a Relative to never-smokers.^b *P* (linear trend) < 0.001.

Table 3 Prevalence of family and medical history variables

	Never-smokers		Ever-smokers	
	Case	Control	Case	Control
Family history of lung cancer	1/31 ^a	4/105	16/177	5/103
Family history of any cancer	7/31	36/105	80/177	32/103
Cancer associated with smoking	4/31	6/105	26/177	9/103
Cancer not associated with smoking	1/31	21/105	40/177	17/103
Cancer of unknown site	2/31	9/105	14/177	6/103
Medical history of bronchitis, pneumonia, or emphysema	7/28	20/91	58/157	26/93
Medical history of asthma or hay fever	5/28	24/91	27/157	29/93

^a Number of cases or controls/total number.

population-based studies (38–41). The OR of 6.7 associated with ever-smoking is similar to that observed for women in Texas (OR 6.7) (42), New Jersey (OR 8.5) (43), and New Mexico (OR 9.4) (44) and only slightly lower than ORs observed for men (43).

The age-adjusted ORs associated with current smoking of 39.0 for Kreyberg I and 3.2 for Kreyberg II lung cancers confirm differences between cell types observed for women elsewhere (8, 42, 43, 45). While cigarette smoking was associated with 96% of squamous, small cell, and large cell carcinomas in women, only 45% of adenocarcinomas were associated with use of cigarettes. The data are somewhat limited in their ability to estimate the magnitude of the association between smoking and cell type. Because of the small number of nonsmokers with Kreyberg I tumors, confidence intervals for Kreyberg I ORs are wide, and it was not possible to calculate ORs for each cell type separately within this group.

The inverse association between education and lung cancer risk after adjusting for smoking confirms trends observed for both men and women in the Third National Cancer Survey (37). This difference may reflect occupational exposures in women with less education (8, 46) or failure to completely adjust for differences in smoking habits. Women employed in blue collar occupations smoke more than women employed in white collar jobs (12).

The results of this study confirm reports of an increase in lung cancer risk associated with family history of cancer (16–22). Tokuhata and Lilienfeld (16) were the first to report an increase in lung cancer mortality in relatives of cases compared

to relatives of controls. Subsequently, other studies have reported increased smoking-adjusted ORs of 2.0–5.3 associated with family history of lung cancer (19, 20, 22). A 2-fold increased risk associated with any cancer in relatives has also been observed (17, 20, 21). Although Sellers *et al.* (21) found that relatives of lung cancer cases experienced increased risks for both smoking-related cancers and cancers not caused by

Table 4 Odds ratios associated with family history of cancer

	Family history of lung cancer		Family history of any cancer	
	OR ^a	95% CI	OR ^a	95% CI
Total ^b	1.9	0.7–5.6	1.8	1.0–3.2
Age ^c (yr)				
≤55	0.8	0.1–11.5	3.8	0.9–16.2
>55	2.4	0.7–7.9	1.4	0.7–2.6
Histology ^d				
Kreyberg I	3.0	0.5–16.9	1.9	0.8–4.6
Kreyberg II	1.4	0.3–6.1	1.7	0.7–4.0

^a Adjusted for education and quantity smoked.^b Analysis based on 208 case-control pairs.^c Analysis based on 59 pairs aged ≤55 years and 147 pairs aged >55 years.^d Analysis based on 113 pairs for Kreyberg I and 81 pairs for Kreyberg II.

Table 5 Odds ratios for smoking and family history of cancer

Smoking	No family history		Positive family history	
	OR	95% CI	OR	95% CI
Never-smoker	1.0		0.7	0.2–2.3
<1 pack/day	2.3	0.9–5.9	2.2	1.1–4.5
≥1 pack/day	8.9	3.7–21.4	47.4	22.2–101.2

Table 6 Odds ratios associated with medical history variables

	History of bronchitis, pneumonia, or emphysema		History of asthma or hay fever	
	OR ^a	95% CI	OR ^a	95% CI
Total ^b	1.7	0.9–3.1	0.5	0.3–1.0
Age ^c (yr)				
≤55	1.1	0.3–4.2	0.2	0.0–0.7
>55	1.8	0.9–3.6	0.8	0.4–1.6
Histology ^d				
Kreyberg I	1.4	0.5–3.9	0.5	0.2–1.3
Kreyberg II	1.6	0.5–4.2	0.5	0.2–1.6

^a Adjusted for education and smoking.^b Analysis based on 184 case-control pairs.^c Analysis based on 48 pairs aged ≤55 years and 131 pairs aged >55 years.^d Analysis based on 98 pairs for Kreyberg I and 72 pairs for Kreyberg II.

smoking, most of the increased risk in this study was due to the occurrence of smoking-associated tumors in relatives. Only a small increase in risk associated with cancers not caused by smoking in relatives was observed. Stomach was the most common site reported in control relatives (in 22 of 68 families), however, casting doubt on the reliability of site data and conclusions drawn from them.

Heavy smokers who had a family history of cancer were nearly 50-fold more likely to develop lung cancer than non-smokers with no family history. A similar synergistic interaction between smoking and family history was observed by Tokuhata and Lilienfeld (16) and Horowitz *et al.* (18). Synergism between smoking and family history could be responsible for an earlier age at diagnosis in women with both risk factors. Consistent with a synergistic effect, younger women experienced a higher risk associated with family history of any cancer than did older women in this study and others (19, 20, 22).

Familial aggregation of cancer may reflect the importance of genetic factors or a common exposure to environmental carcinogens among family members. Cigarette smoking has been shown to cluster in families (47). Because no information was available concerning the smoking habits of relatives in this study, it was not possible to determine how much of the familial aggregation of lung and smoking-associated cancers was due to the clustering of smoking habits in family members. McDuffie *et al.* (48, 49), however, found that increased exposure to cigarette smoke among siblings of patients compared to those of controls was too small to account for familial aggregation of lung cancer. Clustering of smoking habits in relatives could explain the higher ORs associated with family history for Kreyberg I lung cancers compared to Kreyberg II tumors. Because of the higher proportion of smokers among Kreyberg I cases, relatives of women with Kreyberg I tumors are more likely to be smokers than relatives of women with Kreyberg II lung cancers.

Another possible source of bias in evaluating the significance of familial clustering is differences in family size between cases and controls. Persons with larger families have a greater chance of having a family member afflicted with cancer. Although cases and controls reported the same number of children (1.7 and 1.8, respectively), no information was available for the number of siblings. Similarities between cases and controls with respect to sociocultural factors which influence family size (race, religion, employment status) suggest that large differences in number of siblings are unlikely.

Both retrospective and prospective studies have found an association between lung cancer and chronic obstructive pulmonary disease that is independent of smoking (22–25). Wu *et al.* (8) noted a significant increased risk for adenocarcinoma and squamous cell carcinoma in women reporting a childhood history of pneumonia. A 2-fold increase in lung cancer risk associated with physician-diagnosed chronic bronchitis or emphysema was observed by Samet *et al.* (22) in a population-based case-control study of men and women. To explain an increase in prior lung disease in lung cancer cases and their family members compared to controls and their relatives, Cohen *et al.* (50, 51) hypothesized that impaired pulmonary function serves as a common familial precursor to both lung cancer and obstructive lung disease by allowing an increase in circulating toxins and carcinogens.

A number of investigators have reported an inverse association between allergic disease and cancer. Early observations included a smaller proportion of atopic individuals among lung

and other cancer cases than controls (28, 29). Patients with chronic asthma have been observed to develop less lung cancer than expected, although no adjustments were made for smoking (26, 27). Vena *et al.* (30) reported that women with a history of physician-diagnosed asthma, hay fever, hives, or other allergies experienced a nonsignificant decrease in lung cancer risk after adjusting for smoking. McDuffie *et al.* (31) found fewer positive skin reactions among lung cancer patients than controls. The protective effect associated with a history of allergic diseases may be due to enhanced immunological surveillance in atopic individuals secondary to an increase in IgE and/or other immune cells (52). Alternatively, the protective effect may be explained by an increase in the absorption of allergens and carcinogens at the mucosal level, resulting in more efficient handling by the immune system (53).

A frequent criticism of retrospective data is that exposure histories may be biased by prior knowledge of disease. In this study, all smoking, medical, and family histories were completed prior to the diagnosis of lung cancer. Although in a small percentage of cases it is possible that the diagnosis resulted from tests given at the multiphasic checkup, there was no indication that these women had any knowledge of their disease at the time they completed the questionnaire. In fact, controls were more likely than cases to report attending the multiphasic screening because they did not feel well (12% of controls *versus* 7% of cases). Although no attempt was made to confirm self-reports of medical or family histories, any bias in the accuracy of reporting would affect cases and controls equally.

Misclassification of histology is not likely to bias the results of this study. All slides were reviewed blindly by the same pathologist. Intraobserver variability was low. In a subsample of slides read at the time of diagnosis by M. L. B., 86% were given the same histological diagnosis after the blind review conducted for the study. Although the criteria of the World Health Organization for the classification of lung cancers has been updated since the pathology review was conducted for this study (54), a comparison of the classification schemes showed little difference between them (55).

The importance of cigarette smoking for all cell types of lung cancer in women is no longer in question. Nearly all cases of squamous cell, small cell, and large cell carcinomas of the lung in women were associated with use of cigarettes. More than half of all cases of adenocarcinoma, however, were not associated with smoking. This study was not able to identify additional risk factors specific for the different histological types of lung cancer. The family and medical history factors identified in this study appeared to be associated with all histological types of lung cancer. Because the excess risk associated with family history of cancer and the protective effect associated with history of asthma and hay fever were seen primarily in younger women, future research concerning lung cancer should include study of these risk factors and their effect on susceptibility to lung cancer.

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