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ORIGINAL CONTRIBUTIONS

Family History of Cancer and Risk of Lung Cancer among Lifetime Nonsmoking Women in the United States

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In a multicenter study of lung cancer in lifetime nonsmokers in the United States, 646 female lung cancer patients and 1,252 population controls were interviewed regarding history of cancer in their first-degree relatives. A 30% increased risk (95% confidence interval 0.9–1.8) was found for a history of respiratory tract cancer in parents or siblings after adjustment for exposure to environmental tobacco smoke (ETS) in adult life. Lung cancer, which represented approximately two thirds of the respiratory tract cancers, occurred more frequently in first-degree relatives of lung cancer patients than in comparable relatives of population controls (ETS-adjusted odds ratio = 1.29, 95% confidence interval 0.9–1.9). In particular, a significant threefold increased risk for lung cancer was associated with lung cancer diagnosed in mothers and sisters. The increased risk in relation to family history of lung cancer was observed among parents and siblings who were smokers as well as in those who were nonsmokers. The association with family history of lung cancer was strengthened when the analysis was restricted to adenocarcinoma of the lung (ETS-adjusted odds ratio = 1.50, 95% confidence interval 1.0–2.2). However, there was no association between family history of other cancers and risk of lung cancer in nonsmokers. *Am J Epidemiol* 1996;143:535–42.

family health; lung neoplasms; women

Although tobacco smoke is a well-established causal factor for lung cancer, there is accumulating evidence that genetic factors also play a role in lung cancer development. Case-control studies have consistently found that lung cancer aggregates in family members of lung cancer patients (1–9). A few studies have also observed that all cancers (8, 10), other nonpulmonary smoking-related cancers (2, 9, 10), and reproductive cancers (11) occur significantly more often in first-degree relatives of lung cancer cases than in controls. The extent to which familial susceptibility to the development of lung cancer can be attributed to aggregation of smoking habits in families versus shared genetic susceptibility has been difficult to determine, because most lung cancer patients in these studies were smokers, and information on smoking by family members was generally absent. In a seminal study conducted by Tokuhata and Lilienfeld (1) in which information on smoking and history of cancer was obtained from both the index subjects and their family members, the familial effect was more marked in nonsmokers than in smokers with lung cancer, and

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Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; OR, odds ratio.

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the excess of lung cancer was observed in relatives irrespective of their smoking history. However, in two studies with small numbers of lung cancer cases in nonsmokers (less than 35 cases in each study), an increased familial risk was observed only among smokers with lung cancer, not among nonsmokers with lung cancer (8, 9). Using data collected in a recently completed case-control study designed to investigate the etiology of lung cancer in lifetime female nonsmokers (12), we compared histories of cancer in first-degree relatives of lung cancer patients and controls.

MATERIALS AND METHODS

Study methods have been described in detail elsewhere (12, 13). In brief, this was a population-based case-control study of lung cancer in female lifetime nonsmokers, defined as those who had smoked fewer than 100 cigarettes and had not used any other form of tobacco for more than 6 months. Women aged 20–79 years with a microscopically confirmed diagnosis of primary lung cancer who resided in one of five major metropolitan areas in the United States (Atlanta, Georgia; Houston, Texas; New Orleans, Louisiana; the San Francisco Bay Area; and Los Angeles County, California) comprised the case series. In Atlanta and Houston, eligible lung cancer cases were diagnosed from December 1, 1985, through November 30, 1988, whereas in New Orleans and the two California study centers, case accrual continued for 2 additional years. Controls were selected by random digit dialing. The control group was supplemented by random sampling from Health Care Financing Administration files for women aged 65 years or more. Controls were frequency-matched to lung cancer cases (2 : 1 ratio) on age, ethnicity, and study area and were lifetime nonusers of any tobacco products. We completed interviews with 83 percent of eligible lung cancer cases and 70 percent of population controls. During the first 3 years of the study, a second control group was selected from female colon cancer patients, mainly to evaluate potential recall or response bias associated with being diagnosed with cancer or being ill. In the first report on this study, results on environmental tobacco smoke (ETS) were similar when lung cancer cases were compared with colon cancer or population controls (13). Interviewing of colon cancer controls was not continued in the last 2 years of the study.

Lifetime smoking status was determined in a multistep procedure that included reviewing information on tobacco use from hospital charts and contacting the physicians of lung cancer cases and colon cancer controls. For subjects believed to be nonsmokers or for whom smoking status could not be determined from these sources, we contacted the subjects by telephone and asked specific questions on their lifetime use of tobacco products. The identical telephone screening questions were used for the population control group. At the time of interview, lung cancer cases and controls were again asked the tobacco use screening questions to confirm each subject's reported status of lifetime non-tobacco use. In addition, a urine sample was collected from all consenting subjects at the end of the interview to determine the level of urinary cotinine and creatinine, as a measure of their recent nonsmoking status (14). The histologic type of lung cancer was independently confirmed by a pulmonary pathologist (D. S. Greenberg, Department of Pathology, Baylor College of Medicine, Houston, Texas).

In the family history section of the interview, all subjects, self- and surrogate respondents, were first asked the number of brothers and sisters (including half-siblings) they had. Subjects were then asked whether there was a history of cancer in the immediate family, which included fathers, mothers, brothers, and sisters (full and half-siblings). We did not distinguish between full and half-siblings in our coding if there was a history of cancer. The specific type of cancer in the affected relative and the relationship of the affected relative to the index subject was determined. However, the report of cancer in relatives was not independently confirmed, and the relative's age at cancer diagnosis was not obtained. Although we did not specifically ask for the smoking history of affected relatives, in our assessment of lifetime ETS exposure we asked whether the mother, father, or any other household member(s) had smoked in the household of the index subject during her childhood. We classified lung cancer in parents according to whether the mother or father had smoked during the childhood of the index subject. We also classified lung cancer in siblings based on whether there were other smokers in the household (other than parents) during the index subject's childhood.

We investigated the association between risk of lung cancer and family history of all cancers combined, as well as specifically by cancer site or system, which included the lung, breast, prostate, female genital tract (excluding the cervix), respiratory tract, and digestive system. In addition, family history of all tobacco-related tumors (buccal cavity, larynx, esophagus, stomach, liver, pancreas, respiratory tract, cervix, bladder, kidney, and renal pelvis) was evaluated. Multivariate logistic regression methods were used to compute risk estimates for family history of cancer (15) by comparing lung cancer cases (self- and surrogate respondents combined) with population controls. In tables 1–4, two sets of odds ratios are presented.

The odds ratios in the first column (adjusted odds ratios) were adjusted for age (≤49, 50–59, 60–69, and ≥70 years), study area (Los Angeles County, the San Francisco Bay Area, and the southern study areas—New Orleans, Atlanta, and Houston), ethnicity (white, black, Asian, or Hispanic), education (<11, 12, and >13 years of schooling), and number of brothers and sisters. (Details regarding the distribution of cases and controls by these demographic parameters have been previously presented (12).) The second column of odds ratios (ETS-adjusted odds ratios) was also adjusted for an index of exposure to ETS (0, 1–11, 12–28, 29–47, and ≥48 smoke-years) during adult life (12). Potential confounders, including employment in potentially high-risk occupations (12), dietary intake of antioxidants, and dietary cholesterol, were considered. These factors did not confound the family history-cancer findings and were not included in the final models.

RESULTS

In table 1, data are presented on reported history of lung cancer among fathers, mothers, brothers, and sisters of lung cancer cases and population controls. The prevalence of any family history of lung cancer was 8.9 percent among lung cancer patients and 6.6 percent among controls (ETS-adjusted odds ratio (OR) = 1.29, 95 percent confidence interval (CI) 0.88–1.90). Mothers and sisters of lung cancer cases were approximately three times more likely to have a history of lung cancer than comparable relatives of controls; however, there was little difference in such a history among fathers and brothers of lung cancer patients and controls. The increased risk of lung cancer associated with a family history of lung cancer was present after adjustment for ETS exposure; this adjustment did not uniformly strengthen or weaken the risk estimates for lung cancer in families. The odds ratio associated with lung cancer in mothers was affected very little by adjustment for ETS exposure (adjusted OR = 2.74, ETS-adjusted OR = 2.81), whereas the odds ratio associated with lung cancer in sisters was reduced but remained statistically significant with adjustment for ETS exposure (adjusted OR = 3.58, ETS-adjusted OR = 2.78) (table 1). Few subjects reported a history of lung cancer in more than one family member, and there was no indication of increasing risk with increasing number of family members with a positive history. Analyses restricted to self-respondents produced risk estimates that were slightly stronger than those calculated for all respondents combined (data not shown).

TABLE 1. Family history of lung cancer and risk of lung cancer in lifetime nonsmokers, United States, 1985–1990

	No. of population controls	No. of lung cancer cases		All lung cancers			
		Self-respondents	All respondents	Adjusted* OR†	95% CI†	ETS†-adjusted‡ OR	95% CI
Any lung cancer							
No	1,158	366	570	1.00		1.00	
Yes	82	39	56	1.33	0.9–1.9	1.29	0.9–1.9
Family member with history of lung cancer							
Father	30	13	16	1.04	0.6–2.0	0.94	0.5–1.8
Mother	6	6	9	2.74	0.9–8.0	2.81	0.9–8.3
Brother	43	16	21	0.86	0.5–1.5	0.89	0.5–1.6
Sister	8	8	14	3.58	1.5–8.8	2.78	1.0–7.4
No. of family members with lung cancer							
1	74	34	49	1.34	0.9–2.0	1.31	0.9–2.0
≥2	8	5	7	1.29	0.5–3.7	1.14	0.4–3.6

* Adjusted for age (≤49, 50–59, 60–69, and ≥70 years); area (Los Angeles County, San Francisco Bay Area, and southern centers (Houston, Louisiana, and Atlanta combined)); ethnicity (white, black, Asian, or Hispanic); education (≤11, 12, or ≥13 years of schooling); and number of brothers and sisters. Thirty-eight subjects were excluded from all analyses because of missing information on education ($n = 25$) or number of brothers and sisters ($n = 13$).

† OR, odds ratio; CI, confidence interval; ETS, environmental tobacco smoke.

‡ Adjusted for age, area, ethnicity, education, number of brothers and sisters, and exposure to environmental tobacco smoke in adult life (0, 1–11, 12–28, 29–47, and ≥48 smoke-years).

To determine whether familial risk of lung cancer is associated with the active smoking habits of subjects' relatives, history of lung cancer among the parents and siblings of subjects was stratified by their respective smoking status (table 2). These results are presented for self-respondents only, because of likely incomplete knowledge by proxy respondents of the smoking habits of parents and siblings of index subjects (12). Risk of lung cancer was elevated among subjects whose parents had a history of lung cancer, irrespective of whether the parents were smokers or nonsmokers. Similarly, history of lung cancer among siblings was associated with an increased risk of lung cancer regardless of whether siblings were smokers or nonsmokers.

There was a 30 percent (95 percent CI 1.0–1.8) increased risk in relation to family history of any respiratory cancer (table 3). However, this was explained largely by the excess risk associated with lung cancers, which accounted for 68 and 66 percent of the respiratory cancers among lung cancer cases and population controls, respectively. There was no association between risk of lung cancer and family history of tobacco-related cancers combined (table 3). Respiratory cancers represented 62 percent of the tobacco-related cancers among lung cancer cases, compared with 47 percent among population controls. However, there was a deficit of digestive tract cancers among first-degree relatives of lung cancer cases in comparison with population controls. Mothers and sisters of lung cancer cases and population controls showed similar histories of cancer of the breast and of the female genital tract (excluding the cervix). History of prostate cancer did not differ between fathers and brothers of cases in comparison with comparable relatives of controls (table 3). Lung cancer cases and population controls did not differ with regard to family history of all cancers combined (excluding lung cancer) (adjusted OR = 1.00, 95 percent CI 0.8–1.2); there was no significantly increased risk in relation to a history of any cancer reported in three or more family members. Results were essentially the same when the analyses were restricted to self-respondents (data not shown) or adjusted for years of ETS exposure (table 3).

Approximately three fourths of the lung cancers in this study population were classified as adenocarcinoma (12). Results for any family history of lung cancer were statistically significant (ETS-adjusted OR = 1.50, 95 percent CI 1.0–2.2) when the analyses were restricted to adenocarcinoma of the lung (table 4). The odds ratios associated with lung cancer in mothers and sisters were further strengthened in analyses restricted to adenocarcinoma of the lung. Although the odds ratio for a family history of female genital tract cancers and risk of lung cancer was also greater, this result was not statistically significant. Lung tumors other than adenocarcinomas were few in number; analysis in this subgroup produced unstable risk estimates for family cancer (data not shown). We also examined the effect of family cancer by proband's age at diagnosis of lung cancer (or age at interview for controls). Despite few lung cancers diagnosed among subjects aged 54 years or younger, the risk estimates in

TABLE 2. Risk of lung cancer in lifetime nonsmokers, by parents' and siblings' history of lung cancer and smoking habits (self-respondents only), United States, 1985–1990

Lung cancer in relative	Relative(s) that smoked	No. of population controls	No. of lung cancer cases (self-respondents only)	Adjusted* OR†	95% CI†	ETS†-adjusted OR‡	95% CI
Parent							
No	No	512	175	1.00		1.00	
No	Yes	687	209	0.86	0.7–1.1	0.82	0.6–1.1
Yes	No	4	2	1.52	0.3–8.6	1.44	0.3–8.3
Yes	Yes	32	15	1.23	0.6–2.4	1.05	0.5–2.1
Sibling							
No	No	863	269	1.00		1.00	
No	Yes	242	88	1.15	0.9–1.5	1.10	0.8–1.5
Yes	No	37	17	1.48	0.8–2.7	1.17	0.6–2.3
Yes	Yes	13	7	1.39	0.5–3.7	1.49	0.5–4.0

* Adjusted for age (≤49, 50–59, 60–69, and ≥70 years); area (Los Angeles County, San Francisco Bay Area, and southern centers (Houston, Louisiana, and Atlanta combined)); ethnicity (white, black, Asian, or Hispanic); education (≤11, 12, or ≥13 years of schooling); and number of brothers and sisters.

† OR, odds ratio; CI, confidence interval; ETS, environmental tobacco smoke.

‡ Adjusted for age, area, ethnicity, education, number of brothers and sisters. and exposure to environmental tobacco smoke in adult life (0, 1–11, 12–28, 29–47, and ≥48 smoke-years).

TABLE 3. Risk of lung cancer in lifetime nonsmokers, by family history of cancer, United States, 1985–1990

Type of cancer in family	No. of population controls	No. of lung cancer cases		All lung cancers			
		Self-respondents	All respondents	Adjusted* OR†	95% CI†	ETS†-adjusted‡ OR	95% CI
Respiratory tract§							
No	1,115	349	546	1.00		1.00	
Yes	125	56	80	1.30	1.0–1.8	1.30	0.9–1.8
Tobacco-related cancers‖							
No	973	314	485	1.00		1.00	
Yes	267	91	141	1.06	0.8–1.3	1.10	0.9–1.4
Digestive tract¶							
No	1,055	356	550	1.00		1.00	
Yes	185	49	76	0.79	0.6–1.1	0.80	0.6–1.1
Breast cancer							
No	1,133	362	567	1.00		1.00	
Yes	107	42	58	1.10	0.8–1.6	1.09	0.8–1.6
Female genital tract (excluding cervix)							
No	1,216	393	608	1.00		1.00	
Yes	24	11	17	1.33	0.7–2.5	1.42	0.7–2.7
Prostate cancer							
No	1,180	388	599	1.00		1.00	
Yes	54	14	23	0.96	0.6–1.6	1.06	0.6–1.8
All cancers combined, excluding lung cancer							
No	707	231	362	1.00		1.00	
Yes	533	174	264	1.00	0.8–1.2	0.99	0.8–1.2
No. of family members with cancer, excluding lung cancer							
1	365	119	181	1.01	0.8–1.3	1.00	0.8–1.2
2	122	36	56	0.90	0.6–1.3	0.90	0.6–1.3
≥3	46	19	27	1.16	0.7–2.0	1.14	0.7–2.0

* Adjusted for age (≤49, 50–59, 60–69, and ≥70 years); area (Los Angeles County, San Francisco Bay Area, and southern centers (Houston, Louisiana, and Atlanta combined)); ethnicity (white, black, Asian, or Hispanic); education (≤11, 12, or ≥13 years of schooling); and number of brothers and sisters.

† OR, odds ratio; CI, confidence interval; ETS, environmental tobacco smoke.

‡ Adjusted for age, area, ethnicity, education, number of brothers and sisters, and exposure to environmental tobacco smoke in adult life (0, 1–11, 12–28, 29–47, and ≥48 smoke-years).

§ Includes sites listed under *International Classification of Diseases for Oncology* (29) codes 160–165.

‖ Includes cancers of the buccal cavity and larynx, esophagus, stomach, liver, pancreas, respiratory system, cervix, bladder, kidney, and renal pelvis.

¶ Includes sites listed under *International Classification of Diseases for Oncology* (29) codes 153, 154, 156, 158, 159.

relation to family history of lung cancer and respiratory tract cancer were stronger in the younger age group (≤54 years) than in the older age group (≥55 years). For example, the ETS-adjusted odds ratio for family history of lung cancer was 1.86 (95 percent CI 0.51–6.83) in younger subjects (≤54 years) and 1.26 (95 percent CI 0.83–1.90) in older subjects (≥55 years). However, a deficit of digestive tract cancers was only apparent in the older age group (ETS-adjusted OR = 0.79, 95 percent CI 0.57–1.09) and was not observed among younger subjects (ETS-adjusted OR = 1.00, 95 percent CI 0.36–2.81). There was, however, no statistically significant age interaction with family history of lung cancer, respiratory tract cancer, or digestive tract cancer (data not shown).

DISCUSSION

This study, to our knowledge, is one of the largest studies to date of family history of cancer in relation to lung cancer among lifetime nonsmokers. The population-based study design reduced the likelihood of se-

TABLE 4. Risk of adenocarcinoma of the lung in lifetime nonsmokers, by family history of cancer, United States, 1985–1990

Type of cancer	No. of population controls (n = 1,242)		No. of lung adenocarcinoma cases (n = 479)		Adjusted* OR†	95% CI†	ETS†-adjusted‡ OR	95% CI
	Yes	No	Yes	No				
Any lung cancer	82	1,158	48	428	1.52	1.0–2.2	1.50	1.0–2.2
Any lung cancer in family member								
Father	30	1,189	15	443	1.25	0.7–2.4	1.11	0.6–2.2
Mother	6	1,228	8	454	3.20	1.1–9.6	3.24	1.1–9.9
Brother	43	947	18	378	0.95	0.5–1.7	0.95	0.5–1.7
Sister	8	974	11	368	4.06	1.6–10.4	3.59	1.3–9.8
No. of family members with lung cancer								
1	74	1,158	41	428	1.50	1.0–2.3	1.49	1.0–2.3
≥2	8	1,158	7	428	1.72	0.6–4.9	1.52	0.5–4.8
Respiratory tract§	125	1,115	64	412	1.37	1.0–1.9	1.38	1.0–2.0
Tobacco-related cancers‖	267	973	110	366	1.08	0.8–1.4	1.15	0.9–1.5
Digestive tract¶	185	1,055	58	418	0.79	0.6–1.1	0.80	0.6–1.1
Breast cancer	107	1,133	47	428	1.17	0.8–1.7	1.17	0.8–1.7
Female genital tract (excluding cervix)	24	1,216	14	461	1.50	0.8–3.0	1.59	0.8–3.2
Prostate cancer	54	1,180	19	454	1.01	0.6–1.8	1.13	0.7–2.0
All cancers combined, excluding lung cancer	533	707	207	269	1.04	0.8–1.3	1.02	0.8–1.3

* Adjusted for age (≤49, 50–59, 60–69, and ≥70 years); area (Los Angeles County, San Francisco Bay Area, and southern centers (Houston, Louisiana, and Atlanta combined)); ethnicity (white, black, Asian, or Hispanic); education (≤11, 12, or ≥13 years of schooling); and number of brothers and sisters.

† OR, odds ratio; CI, confidence interval; ETS, environmental tobacco smoke.

‡ Adjusted for age, area, ethnicity, education, number of brothers and sisters, and exposure to environmental tobacco smoke in adult life (0, 1–11, 12–28, 29–47, and ≥48 smoke-years).

§ Includes sites listed under *International Classification of Diseases for Oncology* (29) codes 160–165.

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lection bias, particularly inasmuch as participation rates were high (12). All women with incident lung cancer in the five geographic areas were eligible for participation, and controls were randomly selected from the same geographic areas as the cases.

Our main results show a positive association between risk of lung cancer and history of reported lung cancer in first-degree relatives, particularly sisters and mothers. Although the mean number of full and half-siblings was slightly greater in cases (2.05 and 2.25 for brothers and sisters, respectively) than in controls (1.98 and 2.15 for brothers and sisters, respectively), all analyses were adjusted for numbers of brothers and sisters. Interpretation of this finding is limited by potential sources of bias. In particular, recall bias, pertinent to all case-control studies of familial lung cancer based on self-report, must be considered. However, the relative specificity of the association with lung cancer in a family member argues against a general bias of recall of all forms of cancer among lung cancer cases. In addition, first-degree relatives of lung cancer patients showed an excess of respiratory tract cancers and a deficit of digestive tract cancers compared with first-degree relatives of population controls and colon cancer patients (colon cancer patients were interviewed during the first 3 years of the study and served as a second control group) (data not shown).

The prevalence of family history of cancer was slightly greater among self-respondents than among surrogate respondents in this study. The lower estimate of family history of cancer among surrogate respondents may be due to their unfamiliarity with the family history of probands, although we cannot be certain of this. Because all controls and 61 percent of lung cancer patients were self-respondents, our estimation of risks using all lung cancer respondents combined may represent a conservative estimate of the association. In addition, the prevalence of lung cancer

in first-degree relatives of probands in this study was somewhat lower than that reported in previous studies. The greater prevalences of lung cancer in first-degree relatives (10–20 percent) reported in previous interview studies were probably due to the inclusion of smokers (6, 20) and males (20) with lung cancer in those studies. The present study was restricted to females who were lifetime nonsmokers.

Although a number of previous studies have shown a familial effect of lung cancer in smokers with lung cancer (2, 8–10), the data regarding such an association among nonsmokers with lung cancer are less consistent (1–3, 8–10). This study agrees with studies conducted in Baltimore, Maryland (1), and Connecticut (10), and suggests that there is a familial effect that is independent of the effect of tobacco smoke. The increased risk of lung cancer in relation to lung cancer in parents and siblings was observed irrespective of the smoking status of the relatives. In a study conducted in Louisiana with information on the smoking habits of relatives (3), the magnitude of risk associated with lung cancer in female relatives was comparable in case-control comparisons conducted separately for nonsmoker and smoker female relatives.

The present findings also suggest that having a female relative (mother or sister) with lung cancer increased the risk of lung cancer more than having a male relative (father or brother) with lung cancer, which is consistent with results from two previous studies (3, 9). Reasons for the higher risks associated with lung cancer in female relatives are not known. It may be that female subjects are more knowledgeable and accurate regarding family histories, particularly those of their mothers and sisters. However, the studies conducted by Ooi et al. (3) and Shaw et al. (9) included male and female lung cancer probands, so sex bias in recall is probably not the sole explanation. The greater strength of association among female relatives might be explained by a greater proportion of lung cancer among males being linked to environmental causes (i.e., smoking and occupational exposures) than to genetic predisposition. There are no known biologic reasons for an increased genetic predisposition to lung cancer in women as compared with men. Some studies (4, 16) have suggested that female hormones (i.e., an excess of estrogens) may result in an increased susceptibility to adenocarcinoma of the lung, although other studies (6, 7) do not concur with that suggestion.

In this study of lung cancer among female lifetime nonsmokers, only family history of lung cancer was associated with an increased risk, whereas there were no statistically significant associations with family history of all cancers combined or family history of other cancers. The present results are not entirely surprising if the aggregation of relatives with cancer (2, 5, 17–19), particularly smoking-related cancers (5, 9), denotes an aggregation of tobacco use in families or a genotypic susceptibility promoted by tobacco smoke. It is intriguing that there was a deficit of digestive tract cancers among first-degree relatives of lung cancer patients, although this deficit was observed only among subjects aged 55 years or older. A deficit of lung cancer among family members of hereditary nonpolyposis colorectal cancer patients has been reported in most previous studies (21, 22). To date, studies of lung cancer have disagreed regarding the prevalence of microsatellite instability in lung tumors (23–25). Because a very high percentage of hereditary nonpolyposis colorectal cancer patients show microsatellite instability (26), it would be of interest in future studies to evaluate whether the presence of microsatellite instability in lung tumors differs between lung cancer patients with and without a family history of digestive tract cancers.

The findings regarding any family history of lung cancer were strengthened when the analyses were restricted to adenocarcinoma of the lung. A family history of lung cancer was associated with a fourfold increased risk of adenocarcinoma of the lung in a case-control study of this specific cell type in women (6). Among other studies that included all lung cancer cell types, a stronger familial effect for adenocarcinoma of the lung in comparison with other cell types was reported in one article (18). However, in another study, a stronger effect was found for small cell carcinoma (20) compared with other cell types, and in a third study, the association was present for all histologic types of lung cancer (9). Finally, results of this study suggest that a family history of lung cancer tends to be stronger among subjects with early onset of lung cancer. These data are compatible with the segregation analyses conducted by Sellers et al. (27, 28), who found evidence for a major gene influencing earlier age at onset.

This analysis represents a first step in demonstrating that lung cancer in nonsmokers tends to run in families more than would be expected by chance. However, at present, we cannot determine what portion of the familial clustering is related to common environmental exposures or biologically inherited susceptibility. To further evaluate the contribution of environmental versus genetic factors to the familial clustering of lung cancer in nonsmokers, additional information on all family members (i.e., affected and unaffected), including their ages, specific smoking habits, age at lung cancer diagnosis (if relevant), and other lifestyle factors (e.g., dietary habits), will be needed. In addition,

segregation analysis will be necessary to determine whether the pattern of lung cancer among relatives is compatible with a single major gene, multiple genes, or simply a shared environment.

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