Familial Risk of Lung Cancer among Nonsmokers and Their Relatives

Ann G. Schwartz, Ping Yang, and G. Marie Swanson

The role of family history of lung cancer in predicting lung cancer risk among nonsmokers and their relatives was evaluated in a population-based family study conducted in metropolitan Detroit. Lung cancer risk factor data were collected through telephone interviews with 257 nonsmoking lung cancer cases 40–84 years of age diagnosed between 1984 and 1987, their 2,252 relatives, 277 nonsmoking controls, and their 2,408 relatives. Lung cancer in a first-degree relative was associated with a 7.2-fold (95% confidence interval 1.3–39.7) increased risk of lung cancer among nonsmokers in the 40- to 59-year-old age group. This significant increased risk remained after adjustment for the smoking, occupational, and medical history of each family member (relative risk = 6.1, 95% confidence interval 1.1–33.4). Offspring of nonsmoking cases comprised another lung cancer high risk group (relative risk = 7.2, 95% confidence interval 0.5–103). A positive family history did not increase lung cancer risk among nonsmokers 60–84 years of age or their relatives. These findings suggest that susceptibility to lung cancer in families of nonsmoking cases may be evident only in a subset of relatives of early-onset nonsmoking cases.

Lung cancer is the leading form of cancer diagnosed in the United States with an overall incidence rate of 58.2 per 100,000 population (1). It is estimated that 172,000 new cases and 153,000 deaths from lung cancer occurred in 1994 (1). Cigarette smoking has been identified as the major risk factor in the development of lung cancer (2). It is estimated that 90 percent of lung cancer incidence in males and 79 percent in females can be attributed to cigarette smoking (3). In addition to those lung cancers attributable to smoking, an estimated 24,400 lung cancers were diagnosed among nonsmokers (14 percent of all lung cancer) in 1994. Potential risk factors for lung cancer, other than cigarette smoking, include exposure to environmental tobacco smoke (4–8), a number of occupational exposures including asbestos, radon, mustard gas, polycyclic hydrocarbons, chloromethyl ethers, chromium, inorganic arsenic, diesel, exhaust, and farming (9–11), other respiratory diseases (12–18), and a family history of lung or other cancers (19–28).

The traditional approach to the study of familial risk of lung cancer has been to use a case-control design and compare the number of cases who have affected relatives with the number of controls who have affected relatives. For lung cancer, estimates of familial risk obtained using this approach may be confounded by cigarette smoking or a history of other pulmonary diseases, both of which are associated with risk of lung cancer and demonstrate familiality (14, 15, 19). To more clearly delineate genetic from environmental risk underlying family clusters, a population-based family study of lung cancer among nonsmokers was conducted. This study included the collection of information about environmental tobacco smoke exposures, smoking, occupation, industry, and pulmonary disease history for the probands (cases and controls), their spouses, and their first-degree relatives. Of particular interest in this study was the role of family history of lung cancer in predicting lung cancer risk among nonsmokers and their relatives.

MATERIALS AND METHODS

Cases

Eligible cases included newly diagnosed, nonsmoking, population-based African-American and Caucasian lung cancer cases between the ages of 40 and 84 years, identified retrospectively after their participa-
tion in the Occupational Cancer Incidence Surveillance Study (OCISS) (29, 30). Briefly, OCISS was developed to monitor occupational cancer risks among residents of metropolitan Detroit, functioning in conjunction with the Metropolitan Detroit Cancer Surveillance System, which participates in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. OCISS subjects were identified among metropolitan Detroit area residents with cancers of the lung, colon, rectum, urinary bladder, esophagus, eye, liver, salivary gland, stomach, or mesothelioma. For the present study, all lung cancers diagnosed among non-cigarette smokers (n = 401) November 1, 1984, through June 30, 1987, were eligible for inclusion from the 5,953 completed OCISS interviews (93.6 percent of the 6,359 lung cancer cases identified).

Controls

Control selection took place concurrently with case selection. Non-cigarette smoking, population-based controls aged 40–84 years were identified from the sample of controls participating in the OCISS. The OCISS controls without any type of cancer were selected through random digit dialing. Of the 3,372 controls completing OCISS interviews by the start of the present study, 1,429 were nonsmokers. Three hundred ninety-eight nonsmoking controls for this study were randomly selected from the pool of potential control subjects.

Data collection

Cases and controls or their proxies reported in the OCISS that they did not smoke cigarettes at any time in their lives. Smoking status was questioned again in this study. Additional contacts were made if any discrepancies in the reports of smoking status occurred. Eight cases and four controls were excluded because of uncertainties in smoking status. For analysis, we further restricted the sample by excluding cigar and pipe smokers, leaving 314 eligible cases and 345 eligible controls. Interviews, designed for the current study and conducted by telephone, were completed for 227 (81.9 percent) of the eligible cases. Subjects or proxies for interview could not be located for 11.5 percent of the cases, and 6.7 percent refused to participate. Due to the retrospective nature of case identification and the high case fatality associated with lung cancer, 83 percent of the case family interviews had to be conducted with proxies. Approximately 84 percent of the proxies completing interviews for cases were either spouses, siblings, offspring, or parents. For 24 percent of the case subjects, more than one individual was interviewed to obtain complete information. For the controls, 277 (80.3 percent) interviews were completed, 5.8 percent could not be located, and 13.9 percent refused. Proxy interviews were completed for 22 percent of the controls. More than one family member was interviewed for 6.5 percent of the control subjects.

The subject interview included questions about health history, smoking history, environmental tobacco smoke exposure, and occupational history. The section on family history included questions about the age, sex, race, birth year, residence, health history, cancer status, vital status, age at death, place of death, cause of death, smoking history, environmental tobacco smoke exposure history, and usual occupation and industry for each first-degree relative (parents, siblings, children) and spouse of the cases and controls. For those relatives with cancer and for those relatives who had died, additional questions were asked pertaining to when and where these events occurred. Questionnaire data for 2,252 family members of nonsmoking cases (8.8 per case) and 2,408 family members of nonsmoking controls (8.7 per control) were included.

Analysis

The present study focuses on risk of lung cancer associated with a family history of lung cancer among nonsmokers. Two analytic approaches were taken. First, a traditional case-control comparison was made to determine whether cases were more likely than controls to report a first-degree relative with lung cancer. The following variables were incorporated into unconditional logistic regression models (31): age at diagnosis/interview (as a continuous variable), race (dichotomized as African-American and Caucasian), sex, education (dichotomized as less than high school graduate and high school graduate or more), family history of lung cancer in a first-degree relative (yes or no), personal history at least 1 year before diagnosis/interview of allergies, pneumonia, tuberculosis, emphysema, chronic obstructive pulmonary disease, chronic bronchitis, and asthma, exposure to environmental tobacco smoke at home and at work, usual occupation, and usual industry. Occupation and industry were coded using 1980 US Census Bureau classification codes (32) and grouped into 84 occupations and 90 industries. Odds ratio (OR) estimates of relative risk were calculated from the regression coefficients in the logistic models. Family history was retained in all models, as were variables with ORs significantly different from 1.0 at the p = 0.1 level.
Separate models were fit for age-, sex-, and histology-specific strata when possible. Histologic classification was based on registry records.

To determine whether familial risk of lung cancer was present after taking into account risk factors among the relatives, the second analytic approach treated lung cancer status among first-degree relatives as the outcome in unconditional logistic regression models. In these models, the family history variable was defined by specifying whether the individual was related to a case or a control. Cases and controls were excluded from this analysis. The same variables described for the cases and controls were available for the family members with the addition of cigarette, pipe, and cigar smoking history. Age, sex, race, cigarette smoking, and relationship to case or control were retained in all models. Final models included these variables and any additional variables significant at the $p = 0.1$ level. Separate models were constructed after stratification by relationship to the proband, age of the proband, histologic type of lung cancer in the proband, and smoking status of the relatives.

RESULTS

The mean age of both the cases and controls interviewed was 69 years. Approximately 20 percent of all subjects were African-American. Females accounted for 72 percent of the cases and 64 percent of the controls. This sex difference arose after the exclusion of cigar and pipe smokers from the analysis. The distribution of the cases by histologic type was as follows: 14 percent squamous cell carcinomas, 60 percent adenocarcinomas, 5 percent small cell carcinomas, 7 percent large cell carcinomas, and 14 percent other or not specified. The age distributions for the cases and controls are presented in table 1. Overall, 12.5 percent of the cases reported a history of lung cancer in at least one first-degree relative, compared with 9.0 percent of the controls. Two case families each reported two first-degree relatives with lung cancer in addition to the case, as did one control family. One control family reported four siblings with lung cancer. The percentage of cases and controls reporting a history of lung cancer in at least one first-degree relative by age of diagnosis/interview is illustrated in figure 1. A bimodal distribution was apparent for the cases, with a peak at 55–59 years of age and then increasing again at age 70 years. In the youngest cases (ages 40–59 years), 19.2 percent reported a family history of lung cancer as compared with 4 percent of the controls in the same age group.

In a traditional case-control comparison, risk associated with family history, environmental tobacco smoke exposure, and history of respiratory diseases adjusting for age, race, and sex was evaluated (table 2). When these variables were considered simultaneously in multivariate logistic regression models, nonsmoking cases were more likely than nonsmoking controls to have a first-degree relative with lung cancer (OR = 1.4, 95 percent confidence interval (CI) 0.8–2.5); however, this finding was not statistically significant (table 3). Similar analyses were carried out after stratification by age of the proband, sex, and histologic type (table 3). A positive family history of lung cancer was the most important predictor of lung cancer risk in nonsmoking probands 40–59 years of age (OR = 7.2, 95 percent CI 1.3–39.7). Family history did not contribute to lung cancer risk in older nonsmokers (OR = 1.1, 95 percent CI 0.6–2.1).

No increased risk of lung cancer was associated with a first-degree family history of lung cancer among nonsmoking males (OR = 0.5, 95 percent CI 0.1–2.1) whereas among nonsmoking females, a 1.7-fold increased risk was observed (95 percent CI 0.9–3.3). Family history of lung cancer was associated with increased risk of adenocarcinoma of the lung (OR = 1.7, 95 percent CI 0.9–3.3). Slightly higher risk resulting from a positive family history was seen for adenocarcinomas among female nonsmokers (OR = 2.0, 95 percent CI 1.0–4.1).

In the next step of the analysis, logistic regression methods were used, treating lung cancer occurrence among relatives as the outcome of interest. Questionnaire data for 2,252 family members of nonsmoking cases and 2,408 family members of nonsmoking controls were included. Mean ages of first-degree relatives were 57.5 and 56.5 years for cases and controls, respectively. The occurrence of lung cancer in relatives by relationship to the proband (cases and controls) and smoking status is detailed in table 4. Mean age of lung cancer diagnosis and smoking prevalence were similar among first-degree relatives of cases and controls.

Risk of lung cancer was analyzed considering each relative's age, sex, race, smoking history, environmental tobacco smoke exposure at home and at work, usual occupation and industry, history of other respi-
ratory diseases, and relationship to a case or control. In these analyses, risk associated with family history of lung cancer in a nonsmoker was less than that observed in the more traditional case-control analyses. Relatives of cases were 30 percent more likely to develop lung cancer than relatives of controls (table 5). This excess risk of lung cancer was limited to relatives of nonsmoking lung cancer cases 40–59 years of age (relative risk (RR) = 6.1, 95 percent CI 1.1–33.4). No excess risk was observed among relatives of probands aged 60–84 years (RR = 0.9, 95 percent CI 0.5–1.6).

Lung cancer risk also was found to vary by relationship to the proband (table 5). Offspring of the nonsmoking cases had seven times the risk of lung cancer compared with offspring of nonsmoking controls (95 percent CI 0.5–103). Offspring with lung cancer were identified through six female cases and one male control. One case reported two offspring with lung cancer. This group of high-risk relatives did not overlap with the group identified through the early-onset nonsmoking cases.

No significant increased risk was observed for first-degree relatives of female cases (RR = 1.3, 95 percent CI 0.7–2.4), relatives of female adenocarcinoma cases (RR = 1.2, 95 percent CI 0.6–2.3), nonsmoking rel-

![Figure 1. Family history of lung cancer among nonsmoking lung cancer cases and nonsmoking controls by age of diagnosis/interview, metropolitan Detroit, 1984–1987.](image)

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td>Percentage with exposure (n = 257)</td>
<td>Odds ratio*</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>History of lung cancer in a first-degree relative</td>
<td>12.5</td>
<td>9.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Exposure to environmental tobacco smoke at home</td>
<td>66.8</td>
<td>63.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Exposure to environmental tobacco smoke at work</td>
<td>53.0</td>
<td>45.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Allergies</td>
<td>5.1</td>
<td>9.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Asthma</td>
<td>2.4</td>
<td>2.9</td>
<td>0.8</td>
</tr>
<tr>
<td>COPD†</td>
<td>1.6</td>
<td>0.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Emphysema</td>
<td>3.1</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>6.3</td>
<td>4.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14.0</td>
<td>14.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3.1</td>
<td>1.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

* Adjusted for age, race, and sex.
† COPD, chronic obstructive pulmonary disease.
TABLE 3. Risk estimates for lung cancer among nonsmokers by age at diagnosis/interview, sex, and histologic type, metropolitan Detroit, 1984–1987

<table>
<thead>
<tr>
<th>Age at diagnosis/interview (years)</th>
<th>History of lung cancer in a first-degree relative</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>40–84</td>
<td>30/232</td>
<td>25/274</td>
<td>1.4*</td>
</tr>
<tr>
<td>40–59</td>
<td>9/46</td>
<td>2/50</td>
<td>7.2†</td>
</tr>
<tr>
<td>60–84</td>
<td>23/189</td>
<td>23/223</td>
<td>1.1‡</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3/72</td>
<td>8/99</td>
<td>0.5§</td>
</tr>
<tr>
<td>Female</td>
<td>27/170</td>
<td>17/176</td>
<td>1.7†</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>21/139</td>
<td>25/274</td>
<td>1.7‡</td>
</tr>
<tr>
<td>Females with adenocarcinoma</td>
<td>19/113</td>
<td>17/176</td>
<td>2.0†</td>
</tr>
</tbody>
</table>

* Adjusted for age, race, sex, environmental tobacco smoke exposure at work, occupation, industry, and allergies.
† Adjusted for age, race, sex, and allergies.
‡ Adjusted for age, race, sex, environmental tobacco smoke exposure at work, occupation, industry, and chronic obstructive pulmonary disease.
§ Adjusted for age, race, education, occupation, and industry.
‖ Adjusted for age, race, environmental tobacco smoke exposure at work, chronic bronchitis, and allergies.

Risk estimates for lung cancer among nonsmokers by age at diagnosis/interview, sex, and histologic type, metropolitan Detroit, 1984–1987 (RR = 0.9, 95 percent CI 0.3–2.5), or smoking relatives (RR = 1.4, 95 percent CI 0.7–2.7).

DISCUSSION

A number of studies have demonstrated a familial component to lung cancer risk (21–25, 33). Evidence supporting familiality suggests that the etiology of lung cancer includes shared genes, shared environments, or both. In the study presented, we have taken a stepwise approach in evaluating the potential role of environmental exposures and medical histories within families. To remove the greatest environmental risk factor for lung cancer, we have restricted entry into this study to nonsmoking lung cancer cases, nonsmoking controls, and their families. In addition, we have included risk factor data for first-degree relatives.

The traditional case-control comparison demonstrated that nonsmokers with lung cancer were 40 percent more likely than nonsmoking controls to report a positive family history of lung cancer in a first-degree relative. Gender differences in family history were apparent, a finding that has been reported by others (19, 26). Two studies that have taken a case-control approach to the study of family history reported that, among nonsmokers, family history of lung cancer did not increase lung cancer risk; however, a positive family history among current smokers was associated with an approximately twofold increased risk (23, 24). Shaw et al. (24) showed highest risk associated with family history for adenocarcinomas (OR = 2.1), a finding similar to that reported here for nonsmokers. The numbers of nonsmokers with lung cancer in these studies were small and exposure data for relatives were not collected, leaving little power to detect an association between family history of lung cancer and lung cancer risk, if one exists.

Our findings demonstrate that the greatest contribution of family history to lung cancer risk among nonsmokers occurred in subjects 40–59 years of age, who had a sevenfold increased risk. Although this suggests...

TABLE 4. Characteristics of the family members of nonsmoking lung cancer cases and controls, metropolitan Detroit, 1984–1987

<table>
<thead>
<tr>
<th>Family members</th>
<th>Case families</th>
<th>Control families</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Spouses</td>
<td>2,252</td>
<td>58.7</td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>2,027</td>
<td>57.5</td>
</tr>
<tr>
<td>Mothers</td>
<td>253</td>
<td>72.5</td>
</tr>
<tr>
<td>Fathers</td>
<td>253</td>
<td>70.6</td>
</tr>
<tr>
<td>Siblings</td>
<td>900</td>
<td>60.9</td>
</tr>
<tr>
<td>Offspring</td>
<td>621</td>
<td>43.1</td>
</tr>
</tbody>
</table>

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TABLE 5. Risk estimates for lung cancer among first-degree relatives of nonsmokers by age of the proband and relationship to the proband, metropolitan Detroit, 1984–1987

<table>
<thead>
<tr>
<th>Age at diagnosis/Interview of the proband (years)</th>
<th>Case relatives with lung cancer/total relatives</th>
<th>Control relatives with lung cancer/total relatives</th>
<th>Relative risk*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–84</td>
<td>31/1,707</td>
<td>27/1,905</td>
<td>1.3</td>
<td>0.7–2.2</td>
</tr>
<tr>
<td>40–59</td>
<td>9/328</td>
<td>2/396</td>
<td>6.1</td>
<td>1.1–33.4</td>
</tr>
<tr>
<td>60–84</td>
<td>21/1,378</td>
<td>25/1,508</td>
<td>0.9</td>
<td>0.5–1.6</td>
</tr>
<tr>
<td>Relationship to the proband</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>8/382</td>
<td>9/451</td>
<td>1.1</td>
<td>0.4–2.9</td>
</tr>
<tr>
<td>Siblings</td>
<td>16/784</td>
<td>19/840</td>
<td>0.8</td>
<td>0.4–1.6</td>
</tr>
<tr>
<td>Offspring</td>
<td>6/602</td>
<td>1/676</td>
<td>7.2</td>
<td>0.5–103</td>
</tr>
</tbody>
</table>

* Adjusted for age, race, sex, smoking status, occupation, industry, chronic bronchitis, emphysema, and tuberculosis.

a strong genetic component to lung cancer, using a case-control approach to study the role of family history has many limitations. Even when cases and controls are similar in terms of family size and relatives' ages, it has been shown that positive family history may overestimate relative risk measures associated with individual relatives (34). This is illustrated in this study when comparing the case-control results with those obtained from a cohort approach to the analysis. All risk estimates for individual relatives were lower than the corresponding risk estimates using the case-control approach.

When lung cancer risk among relatives was evaluated after adjusting for individual exposures, a positive family history of lung cancer (being related to a case rather than to a control) was a statistically significant predictor of lung cancer development only in relatives of nonsmokers diagnosed between ages 40 and 59 years (RR = 6.1). Although not statistically significant, increased lung cancer risk also was apparent in offspring of nonsmoking lung cancer cases, who demonstrated a 7.2-fold increased risk.

The only other reported study of familial aggregation of lung cancer that utilized risk factor data for relatives included families of 336 persons dying from lung cancer in a 4-year period among residents of 10 parishes in Louisiana (26). After adjusting for age, sex, smoking history, and occupational exposures for each relative, a 2.4-fold excess of lung cancer was reported among first-degree relatives of lung cancer cases as compared with relatives of spouse controls. Despite differences in these studies, both the Louisiana study and our study suggest that familial aggregation of lung cancer does occur in some families, even after the major risk factors for lung cancer are accounted for among relatives.

It is possible that risk factors other than those included in this study cluster in families and account for some of the observed aggregation. It is also plausible that there is a genetic component to susceptibility to lung cancer in families of nonsmoking cases. This is supported by the finding of familial risk only in the families of early-onset nonsmoking cases. With increasing age, risk from other exposures, most notably cigarette smoking, may mask the genetic component.

The only segregation study published demonstrated that the pattern of lung cancer occurrence in families was consistent with mendelian codominant inheritance of a rare autosomal gene with variable age at onset (20). An additional review of these families revealed heterogeneity in inheritance patterns based on age at death of the lung cancer proband (35). The authors attribute this heterogeneity to environmental exposures. Sixty years of age was used as a cutpoint to account for the likelihood that the probands' parents smoked. The pattern of disease in the early-onset proband families was best explained by mendelian codominant inheritance, with 60 percent of the population susceptible. Mendelian models could not be distinguished for the late-onset proband families. Sellers et al. (35) suggest that inherited susceptibility is to the effects of tobacco smoke and that the trait is expressed only in the presence of this environmental factor. Segregation analyses based on our case families will provide important new evidence in elucidating the causal mechanism acting in families identified through nonsmokers (36).

Although it is possible that a candidate gene will be found that causes lung cancer, it is also likely that several susceptibility genes exist that modify risk in the presence of environmental carcinogens. Several genetically determined traits have been associated with lung cancer risk. Attention has focused on polymorphic genes coding for phase I and phase II enzymes that play a role in the activation and detoxification of carcinogens in tobacco smoke, i.e., CYP1A1, CYP2D6, CYP2E1, and GSTM1. Association studies have often yielded conflicting results (37–45). The
results from several studies suggest that the effects of a phenotype or genotype may be more evident at low levels of exposure to carcinogens (42, 46, 47), as might occur in these nonsmokers. Association studies of lung cancer risk and CYP1A1 and CYP2E1 polymorphisms among the nonsmokers in our study population are being conducted. It has also been hypothesized that interindividual variation in DNA repair (48, 49) and microsatellite instability in rare alleles at the Hras1 variable number of tandem repeats locus (50) can modify susceptibility to lung cancer. In all of these instances, a model involving gene-environment interaction is suggested.

This study has some limitations. The logistic regression methods used here to model exposure data for relatives are based on the assumption of independence of family members. Although it is unlikely that the correlation structure within families is such that the estimates of relative risk are invalid, more appropriate statistical methods that model the correlation structure within the family (51) are currently being used to analyze these data.

Another limitation of the study was the reliance on proxy reports of smoking, occupation, and health histories. Retrospective identification of the nonsmoking lung cancer cases and high case fatality rates required the use of proxy data. Family data for both case and control family members were derived from proxies for the family members. The use of proxy data in family studies is usually unavoidable because not all family members can be interviewed. Agreement between subject and proxy reporting has been shown to be very high for certain medical conditions including cancer (52–54) and lung disease (52, 55, 56), last and usual job (52, 57), and smoking variables (52, 56, 58, 59), the same type of data requested for subjects and relatives in this study. We have been successful in using primarily spouses and first-degree relatives as proxies. Proxies were able to answer questions pertaining to health problems and occupational and cigarette smoking histories of the cancer cases 98 percent of the time or more. The numbers of lung cancers reported for relatives of controls were very close to the expected numbers calculated using data from the Surveillance, Epidemiology, and End Results program for 1989–1991 (1). The expected number of lung cancers among siblings was 16.3 (19 observed), among offspring was 0.9 (one observed), and among spouses was 5.3 (seven observed). These are the groups of relatives most likely to experience lung cancer at the 1989–1991 rates.

Even though family members have been shown to provide accurate reports of family cancer history (53, 54), attempts are being made to verify the lung cancers reported among family members. Of the 63 lung cancers among first-degree relatives of cases and controls, 26 (41 percent) have already been confirmed through medical records, death certificates, or the Metropolitan Detroit Cancer Surveillance System. Additional analysis including only confirmed lung cancer cases among relatives is warranted.

In conclusion, familial aggregation of lung cancer was demonstrated in families identified through nonsmoking lung cancer cases diagnosed between ages 40 and 59 years even after the lung cancer risk factor profile among relatives was considered. An excess of lung cancer among offspring of nonsmoking cases also was observed. The role for a susceptibility gene is supported by the finding that familial aggregation occurred only in relatives of younger nonsmoking lung cancer cases and among younger relatives (i.e., offspring). Segregation studies are currently under way to determine whether there is a major gene affecting underlying the observed familial aggregation. The accumulation of biologic specimens from high risk families is needed to search for candidate genes for lung cancer. Additional characterization of high risk individuals and families should be undertaken in an effort to more clearly understand the role of genes and the environment in lung carcinogenesis.

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