Risk for Smoking-Related Cancer among Relatives of Lung Cancer Patients

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ABSTRACT

Studies of familial aggregation of cancer provide indirect evidence for the role of genetic predisposition to cancer. In an ongoing case-control study, we evaluated whether first-degree relatives of lung cancer cases are at increased risk of lung and other cancers. Smoking-related cancers were defined as cancers of the lung, bladder, head and neck, kidney, and pancreas. The 806 probands included in this analysis were patients referred to The University of Texas M. D. Anderson Cancer Center (Houston, TX). We identified 663 controls, matched to the cases on age (±5 years), sex, ethnicity, and smoking history, who were recruited from a local multispecialty physician practice in the Houston metropolitan area. Self-reported cancer family history data were available for 6430 first-degree relatives of the cases and 4936 first-degree relatives of the controls. An excess of cancer in relatives was evaluated by comparing the observed cancer cases among relatives of the cases with relatives of the controls. We conducted further analysis after stratifying on age of lung cancer onset (age at study registration for controls) and smoking status (never, former, or current) of the probands. We also conducted Cox regression analysis and compared time to cancer diagnosis among the relatives of the cases and controls adjusted for age and smoking status of proband and family members. Siblings [relative risk (RR) = 1.85; P = 0.003] of cases had a significant excess of lung cancer and an excess of smoking-related cancers (RR = 1.29; P = 0.01). We observed evidence of familial aggregation (RR = 1.71; P < 0.001) of lung cancer among relatives of late-onset lung cancer cases. From the Cox regression, we observed a moderate risk for development of lung (RR = 1.25; P = 0.09) and other smoking-related cancers (RR = 1.23; P = 0.05). After adjustment for smoking behavior of probands and their relatives, the risks of lung cancer (RR = 1.33; P = 0.03) and smoking-related cancers (RR = 1.28; P = 0.02) were statistically significant. We further stratified on age at onset and observed no evidence (P = 0.81) of familial aggregation of lung cancer among young onset (≤55 years of age) lung cancer cases. We also did not observe evidence of familial aggregation (P = 0.88) of smoking-related cancers in the same group. There was no evidence of increased risk (P = 0.77) of lung cancer among relatives of never-smokers. These findings support the need for additional study in the characterization and identification of genetic factors that influence and modulate cancer susceptibility in humans.

INTRODUCTION

Over 85% of lung cancers are attributed to smoking. However, because only a fraction of long-term smokers will develop lung cancer, interindividual variation in susceptibility to tobacco carcinogenesis must also be invoked to explain these differences in response to environmental exposures. Studies of familial aggregation provide suggestive evidence that hereditary factors may influence cancer risk (1–6). By incorporating exposure history of the probands and first-degree relatives into a familial aggregation study, the researcher is able to assess the level of familial risk of cancer while adjusting for the exposure. However, there are very few studies in the literature that incorporate tobacco exposure history of the family members into familial aggregation investigation (1, 7–10). The seminal study by Tokuhata and Lilienfeld (1) did not have the benefit of using modern quantitative methods for assessing the impact of smoking behavior on lung cancer risk. Later studies (7, 8, 10) had smaller sample sizes than the current study.

In this article, we describe the analysis of familial aggregation of lung and other smoking-related cancers among first-degree relatives of 806 lung cancer patients. The self-reported family history collected from these patients includes all cancers in first-degree relatives and age at diagnosis as well as smoking history of these first-degree relatives. We performed our analyses using similar family history data collected from controls recruited for an ongoing lung cancer case-control study. Our analysis takes into account not only smoking status of the probands but also smoking history of the first-degree relatives.

MATERIALS AND METHODS

Study Population. The case patients were recruited from The University of Texas M. D. Anderson Cancer Center (Houston, TX) from 1995 to 2000. All patients with newly diagnosed, histopathologically confirmed lung cancer were eligible for the study. The exclusion criteria were prior chemotherapy or radiotherapy, prior cancer, and any recent blood transfusion. After written informed consent was obtained from the subjects, an interviewer administered a structured questionnaire to collect detailed information on demographic data and lung cancer risk factors, including smoking status (never, former, recent quitter, or current) and family history. Smoking was defined as those who had smoked >100 cigarettes in their lifetimes, former smokers were those who had quit smoking >1 year before diagnosis, recent quitters were those who had quit smoking <1 year previously, and the remainder were defined as current smokers. Pack-years were calculated from duration and amount of smoking. Family history included cancer histories of first-degree relatives, i.e., parents, brothers, sisters, and biological children of cases. More specifically, year of birth, age at time of study, smoking status (yes or no), presence or absence of cancer (yes or no), type of cancer, age of diagnosis, and year of death were queried for each relative. The response rate for participation among the cases was 77.4% (11).

Control Population. Our control population was recruited from the Kelsey-Seybold Clinic, Houston’s largest private multispecialty physician group, which includes a network of 23 clinics and over 300 physicians and serves as the source of controls for ongoing case-control studies. Potential control subjects were first surveyed by a short questionnaire for willingness to participate in research studies and to provide preliminary data on matching characteristics, such as smoking behavior and demographics (12). The response rate for participation of these controls was 73.3% (11). Cases were matched to the controls on age (±5 years), sex, ethnicity, and smoking status.

Statistical Analysis. Descriptive statistical analyses were first conducted to characterize the study population of lung cancer cases and controls and their first-degree relatives. We computed point estimates and 95% confidence intervals for RR1 to determine whether there was an excess of lung and other smoking-related cancers (bladder, head and neck, kidney, and pancreatic cancers) among first-degree relatives of cases as compared with the controls. For these analyses, cancer diagnoses were classified according to International Classification of Diseases, 9th revision codes. The RRs, adjusted for person-years, were calculated using the methods described by Kahn and Sempos (13). Subsequent stratified analysis was performed based on the smoking status (never, former, recent quitter, or current) and age of diagnosis (<55 and ≥55 years) of the proband. We also conducted stratified Cox regression analysis (stratified by relation to proband) and compared time to cancer diagnosis

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1 The abbreviation used is: RR, relative risk.
FAMILIAL AGGREGATION OF SMOKING-RELATED CANCER

Table 1 Distribution of selected host characteristics for lung cancer patients and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (N = 806)</th>
<th>Controls (N = 663)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>432 (53.6)</td>
<td>363 (54.8)</td>
</tr>
<tr>
<td>Female</td>
<td>374 (46.4)</td>
<td>300 (45.2)</td>
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<tr>
<td>Smoking status</td>
<td></td>
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</tr>
<tr>
<td>Never</td>
<td>79 (9.8)</td>
<td>72 (10.9)</td>
</tr>
<tr>
<td>Former</td>
<td>360 (44.7)</td>
<td>349 (52.6)</td>
</tr>
<tr>
<td>Recent quitter</td>
<td>156 (19.4)</td>
<td>17 (2.6)</td>
</tr>
<tr>
<td>Current</td>
<td>211 (26.2)</td>
<td>225 (33.9)</td>
</tr>
<tr>
<td>Ethnicity</td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>656 (81.4)</td>
<td>550 (83.0)</td>
</tr>
<tr>
<td>African-American</td>
<td>82 (10.2)</td>
<td>65 (9.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>67 (6.3)</td>
<td>46 (6.9)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Continuous variables</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
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<tr>
<td>Age (yrs)</td>
<td>62 ± 10</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
<td></td>
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<tr>
<td>Former smokers</td>
<td>46 ± 31</td>
<td>45 ± 33</td>
</tr>
<tr>
<td>Current smokers</td>
<td>61 ± 36</td>
<td>48 ± 29</td>
</tr>
<tr>
<td>Recent quitters</td>
<td></td>
<td></td>
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<tr>
<td>Duration of cessation (yrs)</td>
<td>14 ± 10</td>
<td>16 ± 11</td>
</tr>
</tbody>
</table>

Table 2 Distribution of selected host characteristics for first-degree relatives of lung cancer patients

Table 3 Percent of ever smokers among all relatives, relatives reported to have a smoking related cancer, and relatives reported to have lung cancer

RESULTS

The demographic characteristics and smoking status of the 806 lung cancer probands and 663 controls are summarized in Table 1. Among the cases, there were slightly more men (53.6%) than women, and a majority (81%) of the probands were Caucasian. The average age of the cases was 62 years, and most (75%) were diagnosed with lung cancer after 55 years of age. The cases and controls were well matched on age, sex, and ethnicity. Approximately 90% of the cases and controls were ever-smokers (current smokers, recent quitters, or former smokers). There were fewer recent quitters and more current and former smokers among the controls. There was a higher percentage of never-smokers among women (16%) as compared with men (4%; data not shown). The former smoking cases and controls were matched well by pack-years; however, the current smoking cases reported significantly higher numbers of pack-years compared with controls. The average number of years since smoking cessation among former smokers was 14 for the cases and 16 for the controls.

Family history data were available for 6430 first-degree relatives of the cases and 4936 first-degree relatives of the controls, and their characteristics are summarized in Table 2. There were 260 reported smoking-related cancers and 661 non-smoking-related cancers among the first-degree relatives of the cases. Among the control first-degree relatives, there were 151 smoking-related cancers and 462 non-smoking-related cancers. Fathers of both cases and fathers of controls were most likely to be reported as having had lung cancer (N = 60 versus N = 40, respectively) or other smoking-related cancers (N = 16 and N = 18, respectively), followed by brothers and then mothers. There were only 10 reported cases of smoking-related cancers among offspring of cases, although there were no such cancers among control offspring. Prostate cancer was reported among 30 fathers of cases (35 of control fathers) and 27 brothers of cases (18 of control brothers; data not shown). There were no reports of prostate cancer among the sons. Breast cancer was reported among 53 mothers of cases (43 of control mothers), 48 sisters of cases (33 of control sisters), and 11 daughters of cases (0 of control daughters; data not shown).

Table 3 summarizes information regarding the smoking status of the relatives of the study participants. For both cases and controls, the majority of fathers (roughly 65%) and only slightly lower percentages of the brothers were ever-smokers, although the majority of mothers, sisters, and offspring were reported as never-smokers (≥40%). We stratified the relatives on reported cancer status and found that the proportion of ever-smokers was substantially higher in those with smoking-related cancers. For example, the proportion of ever-smoking fathers of cases and controls with a reported smoking-related cancer was higher (86.4% and 89.7%, respectively) compared with the overall group (65.5% case fathers and 68.7% control fathers) but not as high as the proportion for those with lung cancer (91.7% and 95%, respectively). Similar patterns were evident for other rela-
tives as well. The correlation of smoking status was low among the probands and family members (data not shown). For the lung cancer cases, the correlations ranged from 0.103 (for cases and fathers) to 0.156 (for cases and daughters), although all were statistically significant at the 1% level. The correlations of smoking status among the controls and their relatives ranged from 0.029 (for controls and mothers) to 0.092 (for controls and sons). Only the latter correlation was statistically significant at the 1% level.

We observed a moderate risk (RR = 1.08; P = 0.02) for all cancers (smoking-related and non-smoking-related cancers) among the first-degree relatives of lung cancer cases. The results from the RR analysis of all smoking-related cancers and lung cancer are summarized in Table 4. Significant excesses of smoking-related cancers were observed overall (RR = 1.29; P < 0.001) and among siblings of lung cancer cases (RR = 1.75; P < 0.001), older probands (RR = 1.54, P < 0.001), and current smokers (RR = 1.90; P < 0.001). Similarly, we observed a significant overall (RR = 1.30; P = 0.04) risk of lung cancer among first-degree relatives, siblings (RR = 1.85; P = 0.003), relatives of late-onset lung cancer cases (RR = 1.71; P < 0.001), and relatives (RR = 1.87; P = 0.003) of current smoking cases.

With the exception of siblings of lung cancer cases who had a significant excess (RR = 4.98; P = 0.019) of kidney cancer as compared with controls (actual counts given in Table 2), excess of other individual smoking-related cancers was observed but was not statistically significant. No bladder cancer was observed in mothers of lung cancer cases. In a series of articles (15–17), they report a 2.55 familial risk of lung cancer probands, with the effect being more pronounced among nonsmokers. Ooi et al. (7) reported that relatives of lung cancer probands were 2.4 times more likely to develop lung cancer compared with relatives of spouse controls in a study of 337 lung cancer probands in Louisiana. Shaw et al. (14) found a 2.8 increase in risk of lung cancer in two or more relatives of cases. In a series of articles (15–17), a team of investigators examined coaggregation of cancers using the Utah Cancer Registry. In their most recent publication (17), they report a 2.55 familial risk of lung cancer. These risk estimates are somewhat higher than we observed in this analysis (RR = 1.30).

Other investigators have reported familial aggregation of lung cancer among relatives of early-onset cases. Schwartz et al. (8) noted

### Table 4. Significant excesses of smoking-related cancers were observed overall (RR = 1.29; P < 0.001) and among siblings of lung cancer cases (RR = 1.75; P < 0.001), older probands (RR = 1.54, P < 0.001), and current smokers (RR = 1.90; P < 0.001). Similarly, we observed a significant overall (RR = 1.30; P = 0.04) risk of lung cancer among first-degree relatives, siblings (RR = 1.85; P = 0.003), relatives of late-onset lung cancer cases (RR = 1.71; P < 0.001), and relatives (RR = 1.87; P = 0.003) of current smoking cases.

### Table 5. RR (95% confidence interval (CI) and Ps) of smoking-related and lung cancers among first-degree relatives from Cox regression analysis.
that family members of non-smokers with early-onset lung cancer had a 6-fold-increased lung cancer risk. In a subsequent study involving 257 population-based probands, Schwartz et al. (9) also showed that family members of lung cancer cases had increased risk for cancers other than those of the lung. Kreuzer et al. (18) concluded that lung cancer in a first-degree relative was associated with a 2.6-fold increase in risk of lung cancer in young (<46 years of age) cases, with no elevated risk observed in the older group. In a study of 945 lung cancer cases and 983 controls in Germany, Bromen et al. (19) reported a 4.75-fold increase in risk of lung cancer among relatives of probands who were diagnosed with lung cancer at <50 years of age. Radzikowska et al. (20) reported stronger evidence of aggregation of cancers among 757 younger lung cancer patients in Poland.

In our investigation, we were unable to demonstrate such increased risk among relatives of early-onset cases using our own comparison group. The excess risk was restricted to relatives of probands >55 years of age. The difference in risk could be related to the distinct nature of referral patterns to our cancer center. For example, roughly 26% of our case probands were arbitrarily defined as early-onset (<55 years of age) cases. Alternatively, the difference could be attributable to the control population under study. The recruitment of early-onset cases is still ongoing; therefore, we will reanalyze these data after more early-onset cases have been recruited.

Very few studies were able to investigate smoking status-specific familial aggregation of lung cancer. Tokuhata and Lilienfeld (1) reported a 2.4-fold increase in lung cancer among never-smoking female relatives of cases. Ooi et al. (7) also showed an increased risk of lung cancer among never-smoking female relatives and among ever-smoking fathers. Sellers et al. (10) reported an excess of lung cancer among relatives after adjusting for pack-years. Schwartz et al. (8) focused on never-smoking lung cancer patients and observed an increased lung cancer risk among family members after adjusting for smoking history of the family members. We observed an increased risk of lung and other smoking-related cancers, even after adjusting for smoking behavior of the proband and family members. Specifically, we observed an excess of cancer among relatives of current smokers but did not observe an increased risk of a smoking-related cancer among relatives of never-smokers. However, <10% of our cases were never-smokers. Furthermore, the majority of fathers and brothers of cases and controls were ever-smokers, although the majority of mothers, sisters, and offspring of cases and controls were never-smokers. After stratification by reported cancer status, the majority of relatives with a reported smoking-related cancer or lung cancer were ever-smokers. As with the recruitment of early-onset lung cancer cases, recruitment of never-smoking lung cancer patients is still ongoing. Therefore, we will consider further assessment of smoking behavior and cancer risk among relatives.

Increased risk of breast cancer has also been reported among female relatives of lung cancer patients. Schwartz et al. (9) first found a moderate familial aggregation of breast cancer among relatives of lung cancer cases. In a subsequent study involving 118 lung cancer cases and 161 controls, Schwartz et al. (21) reported that first-degree relatives of individuals with early-onset (<40 years of age) lung cancer had 5.1 times the risk of developing breast cancer. Mayne et al. (22) also found a 2-fold increase in risk of breast cancer among mothers and a 2.07-fold increase in risk of breast cancer among sisters of 437 nonsmoking men and women with lung cancer. In our study, we similarly observed an increased risk of breast cancer among mothers of never-smoking lung cancer cases. We also found a 7-fold-increased risk of breast cancer among daughters of lung cancer cases. We plan to perform follow-up analysis and focus on familial aggregation of breast cancer among lung cancer probands.

A limitation of our study is that family history of cancers and smoking history of relatives was obtained only through self-reports from the probands; individual family members were not contacted to verify information. The probands also provided self-reported smoking history, including number of cigarettes/day, number of years smoked, and the former smoker’s self-reported years since cessation. Ziogas and Anton-Culver (23) observed that proband-reported family history of cancer was more accurate for first-degree relatives, and probands obtained through clinics had lower false positive family history report rates compared with population-ascertained probands. Bondy et al. (24) evaluated the accuracy of proband-reported cancer among family members by comparing reported cancer information with documentation available through medical records and death certificates. They noted high levels of accuracy between proband-reported and record-confirmed cancers of first-degree relatives. In our analyses, we only used smoking status of first-degree relatives (ever or never) and smoking status of the probands (never, former, or current). To minimize the effect of misreporting of smoking history on our analyses, we did not incorporate pack-years or years since cessation for the probands or relatives.

A second possible limitation of this study is that we did not use a population-based control group. The idea that controls must represent the entire population of nondiseased individuals has been debated. Rothman (25) argues that the selection of controls should be based on individuals who have the possibility of becoming cases. Fries and Sellers (26) maintain that control families need to be chosen carefully to minimize common familial exposure that might be wrongly interpreted as familial aggregation. Hence, control families should be as similar to case families for all unmeasured covariates. Our lung cancer cases were recruited through The University of Texas M. D. Anderson Cancer Center (Houston, TX). We therefore wanted to recruit controls from a population of healthy individuals who would have sought treatment at The University of Texas M. D. Anderson Cancer Center if they had developed lung cancer. Our controls were therefore recruited through a local multispecialty physician practice in the Houston metropolitan area.

The goal of this project was to investigate familial aggregation of lung and other smoking-related cancers to further define the role of genetic predisposition to cancer. To this end, we performed analyses after stratifying on smoking behavior of the proband, and we also completed Cox regression analyses in which risk of cancer among family members was assessed after adjusting for age and smoking behavior of the probands and family members and after stratification as well. With each type of analysis, we were able to draw conclusions regarding familial risk of smoking-related cancers in the presence or absence of tobacco exposure. However, the results from the Cox regression were most compelling because evidence of familial risk of cancer increased after adjustment for smoking behaviors of the probands and family members. This type of adjustment (i.e., smoking behavior of the family members) is not possible when using cancer registry data. Therefore, the collection of data from locally obtained controls as well as detailed family histories of cancer incidence and smoking behavior is crucial for additional studies in familial aggregation. These findings further support the need for continuing characterization and identification of genetic factors that influence and modulate cancer susceptibility in humans using locally recruited controls.

REFERENCES


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