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Increased risk of lung cancer in individuals with a family history of the disease: A pooled analysis from the International Lung Cancer Consortium

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Abstract

Background and Methods—Familial aggregation of lung cancer exists after accounting for cigarette smoking. However, the extent to which family history affects risk by smoking status, histology, relative type and ethnicity is not well described. This pooled analysis included 24 case-control studies in the International Lung Cancer Consortium. Each study collected age of onset/interview, gender, race/ethnicity, cigarette smoking, histology and first-degree family history of lung cancer. Data from 24,380 lung cancer cases and 23,305 healthy controls were analyzed. Unconditional logistic regression models and generalized estimating equations were used to estimate odds ratios and 95% confidence intervals.

Results—Individuals with a first-degree relative with lung cancer had a 1.51-fold increase in risk of lung cancer, after adjustment for smoking and other potential confounders(95% CI: 1.39, 1.63). The association was strongest for those with a family history in a sibling, after adjustment (OR=1.82, 95% CI: 1.62, 2.05). No modifying effect by histologic type was found. Never smokers showed a lower association with positive familial history of lung cancer (OR=1.25, 95% CI: 1.03, 1.52), slightly stronger for those with an affected sibling (OR=1.44, 95% CI: 1.07, 1.93), after adjustment.

Conclusions—The increased risk among never smokers and similar magnitudes of the effect of family history on lung cancer risk across histological types suggests familial aggregation of lung cancer is independent of those associated with cigarette smoking. While the role of genetic variation in the etiology of lung cancer remains to be fully characterized, family history assessment is immediately available and those with a positive history represent a higher risk group.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide (1). Current and former smokers are at greatest risk, but lung cancer does occur among nonsmokers, with varying rates across countries (2). The association between cigarette smoking and increased risk of lung cancer is now undisputed. Despite this, less than 20% of smokers develop lung cancer, suggesting that the effect of tobacco smoke exposure is modified by other variables, including individual susceptibility (3). The search for a gene or genes associated with susceptibility is still nascent. Genome wide association studies have independently reported chromosomal region 15q24-25.1, which contains nicotinic acetylcholine receptor sub-unit genes, to be associated with increased risk of lung cancer in ever smokers (4-6). These findings have been replicated among individuals with a family history of lung cancer, and the relative risk of lung cancer associated with markers in this region are much higher for familial cases compared to the relative risk observed among sporadic cases (7). Linkage analysis in families with aggregation of lung cancer also described a region on chromosome 6q23-25 associated with risk of lung cancer (8). The clinical significance of these findings is still unclear. In the meantime, lung cancer risk models using epidemiologic data have been developed, and the most parsimonious models for both ever and never smokers include a family history of cancer variable (9).

Developing risk models for lung cancer are vital, given the report from the National Lung Screening Trial (NLST), which suggests that low-dose helical computed tomography (CT) scans may cut deaths from lung cancer by 20% (10). It should be noted these findings were among individuals 55-74 years of age, with a smoking history of 30+ pack years, and should not be extended to other populations (11). A crucial component to a successful screening program is defining a population at high risk. Until screening protocols have been developed, the main recommendations to reduce risk of lung cancer remain smoking avoidance, cessation, and limiting exposure to known carcinogens (e.g. radon, environmental tobacco smoke)(12).

Relatives of individuals with lung cancer may be at higher risk of lung cancer than the general population. Various smaller studies have provided evidence that familial aggregation of lung cancer exists after adjusting for the aggregation of cigarette smoking and type of family relatedness (13, 14). In this study, we performed a pooled analysis of data contributed to the International Lung Cancer Consortium, in order to describe in greater detail familial aggregation of lung cancer. Given the large sample size of this analysis, we were able to perform subgroup analyses examining risk by gender, race/ethnicity, histologic type, age at diagnosis, and smoking status.

Materials and Methods

Study Population

The International Lung Cancer Consortium (ILCCO) was established in 2004, with the goal of sharing compatible data from lung cancer epidemiology studies to achieve greater power than from single studies alone. To date, 57 lung cancer studies are included in ILCCO. Further details regarding the aims, guidelines and policies of ILCCO are described in Hung et al.(15).

To be included in the main analysis of familial aggregation of lung cancer, the following minimum criteria were set. Each study must have collected data regarding the lung cancer status, age at diagnosis, smoking status of the proband, and vital status (living/deceased) for the mother, father and siblings of every case and control proband. Additional analyses were performed in 5 studies that also collected smoking status on each relative in addition to the

minimum variables. Institutional approval and written informed consent from all subjects were obtained by the investigator at each study site for each original study and their de-identified data were submitted to ILCCO for pooling.

Statistical Methods

The individual-level data from each study included the following demographic variables for the case and control subjects (referred to as probands): gender, ethnicity, age at diagnosis (cases) or interview (controls), education, smoking status, and pack years smoked, and histological classification (cases only). Never smokers were individuals who reported smoking less than 100 cigarettes in their lifetime. Former smokers were individuals who reported smoking cessation at least 2 years prior to interview. Questions regarding these data were resolved by the original study investigator.

Relative risks of lung cancer associated with having a first-degree relative with lung cancer were assessed using unconditional logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals. Estimates were adjusted for variables that differed significantly between probands or have been previously shown to be associated with lung cancer (gender, education, ethnicity, smoking status, pack years) and for study site. Logistic regression models were created for having any first degree relative with lung cancer, and then stratified by relative type (father, mother, sibling). To examine interactions between family history and race, a multiplicative variable of these two factors was added to the regression model. For all subgroup analyses except for histology, the controls were restricted to those from the same population (e.g., in the Asian subgroup analysis, only Asian controls were used). For histology subgroups, all controls (n=23305) were used. For the sub-set of studies where individual-level information was collected on both affected and unaffected fathers, mothers, and siblings, in addition to the probands, generalized estimating equation (GEE) regression models were created to determine whether familial risk of lung cancer was present after adjustment for risk factors among the relatives of the probands. These models correct for the correlation between family members (16), and adjusted for gender and smoking status of each first-degree relative. First, the dataset was restricted to first-degree relatives, and a variable to indicate whether each individual was related to a case or control proband was assigned to each subject. GEE models were then constructed for estimating relative risks in case relatives compared to control relatives, adjusting for proband age, proband gender, gender of the relative, smoking status of the proband and smoking status of the relative. SAS (Cary, NC) Version 9.2 was used for all analyses.

Results

Information regarding family history of cancer in first-degree relatives was available for 24,380 cases and 23,399 controls. Of the 57 studies which have contributed data to ILCCO, 24 studies met inclusion criteria for the analysis. Studies from North America accounted for 54% of the datasets analyzed (n=13), 8 were from Europe and 3 were from Asia and Oceania (Table 1). Population-based controls were ascertained by 11 studies, 8 studies employed hospital-based controls, and 5 studies utilized both population and hospital-based control probands (mixed).

Table 2 describes characteristics of case and control probands included in the analysis. Men accounted for about half of the study population, and the majority of the population was white (82.3%), followed by Asian (6.8%), and African American (5.4%). Case probands were significantly more likely to be smokers compared to the control probands (p-value<0.0001), and among those who reported smoking, cases had a higher number of pack years compared to controls (p-value<0.0001).

Risk of lung cancer associated with having a family history of lung cancer in a first-degree relative (mother, father, sibling) is presented in Table 3. Associations between lung cancer and family history were found in nearly every stratum after adjusting for proband age, proband gender, ethnicity, education, smoking status of the proband, pack years, and study number. Overall, individuals with a first-degree relative with lung cancer had a 1.51-fold increase in risk of lung cancer compared to individuals without a family history, after adjustment (95% CI: 1.39-1.63). There is evidence of interaction between smoking status and family history of lung cancer, with ever smoking individuals with a family history of lung cancer in a first degree relative having a 3.19-fold increase in risk of lung cancer compared to never smokers without a first-degree family history of lung cancer after adjustment (95% CI: 2.03-5.00, data not shown). When stratified by relative type, the association was greatest for those with a history of lung cancer in a sibling (OR=1.82, 95% CI: 1.62, 2.05), compared to lung cancer in a father (OR=1.25, 95% CI: 1.13, 1.39) or mother (OR=1.37 95% CI: 1.17, 1.61). This pattern was similar in male and female probands. There was a significant interaction between race and family history of lung cancer (p=0.002, data not shown). The overall association was strongest among Asians (OR=2.38, 95% CI: 1.50, 3.82), then African Americans (OR=1.67, 95% CI: 1.16, 2.40) and whites (OR=1.46 95% CI: 1.34, 1.58). A family history of lung cancer was associated with lung cancer in every histological type examined, after adjustment. Among never smoking individuals, only a history of lung cancer in a sibling was associated with lung cancer (OR=1.44, 95% CI: 1.07, 1.93). For ever smokers, lung cancer was associated with history of lung cancer in a father (OR=1.27, 95% CI: 1.13, 1.43), mother (OR=1.40, 95% CI: 1.17, 1.66) and sibling (OR=1.91, 95% CI: 1.68, 2.17), after adjustment. The association was stronger in cases diagnosed before the age of 50 than in later onset patients (OR=1.83 and 1.45, respectively). Having a history of lung cancer in siblings among probands <50 years old strengthened the association even further (OR=3.72, 95% CI: 2.00, 6.90), double the odds ratio for the older cases (OR=1.86, 95% CI: 1.65, 2.09). The number of affected relatives among cases and controls, by strata, are available in Supplementary Table 1.

The association between lung cancer and family history increased as the number of first-degree relatives with lung cancer increased. The association between family history and lung cancer increased from 1.45 (95% CI: 1.34, 1.58) for those individuals who reported one first-degree relative with lung cancer to 1.97 (95% CI: 1.59, 2.45) for those individuals with 2 or more first-degree affected relatives (data not shown).

Tables 4 and 5 include studies where individual-level information was collected on both affected and unaffected fathers, mothers, and siblings, in addition to the probands. As seen in Table 4, data were available for mothers of 6297 cases and 5907 controls, with 240 case mothers having lung cancer (3.8%) and 171 control mothers having lung cancer (2.9%). Data were also available for 6,263 fathers of cases and 5,886 fathers of controls, with 453 case fathers having lung cancer (7.2%) and 363 control fathers having lung cancer (6.2%). Data were available for 18,948 siblings of cases and 16,625 siblings of controls, with 724 case siblings reported to have lung cancer (3.8%) and 282 control siblings reported to have lung cancer (1.7%). Similar mean ages at diagnosis were reported for case and control fathers (p-value=0.16), mothers (p-value=0.08) and siblings (p-value=0.72).

Table 5 presents the strength of familial aggregation of lung cancer after adjusting for proband age, proband gender, proband smoking status, relative's gender, and relative's smoking status. The association with family history was 1.55-fold greater in first-degree relatives of cases compared to relatives of controls (95% CI: 1.39, 1.73), after adjustment. The association between lung cancer and family history was elevated for case relatives in all subgroups compared to control relatives. Family history was a stronger risk factor for relatives of early-onset (<50 years of age) cases (OR=1.97, 95% CI: 1.51, 2.58) than for

those related to someone with later onset disease (OR=1.53, 95% CI: 1.36, 1.72). The association was greater for those who had a sibling with lung cancer (OR=1.96, 95% CI: 1.65, 2.34) compared to a father (OR=1.33, 95% CI: 1.13, 1.57) or mother (OR=1.39, 95% CI: 1.12, 1.75) with the disease. In a sub-analysis of siblings with never smoking parents, the association between having a first-degree relative with lung cancer and lung cancer risk remained (OR=2.18, 95% CI: 1.52-3.11) after adjustment (data not shown). Never smoking relatives of cases were somewhat more likely to have lung cancer compared to never smoking relatives of controls (OR=1.31, 95% CI: 0.96, 1.78), but this association was not statistically significant. Individuals who were ever smokers and related to a case were 1.57-fold more likely to have lung cancer than smokers who were related to a control (95% CI: 1.41, 1.76).

Discussion

The results presented here represent the most comprehensive analysis of the association between family history of lung cancer and lung cancer since the first strong evidence of familial aggregation was reported nearly 50 years ago (17). To date, this is the largest pooled analysis which incorporated a traditional case-control analysis and also used data from individual family members to examine risk adjusted for gender and smoking status of each relative. Individuals with family history in a first-degree relative are at an approximate 50% increased risk of lung cancer compared to those without a family history, and this association remains regardless of gender, race/ethnicity, histological type and after adjusting for other known lung cancer risk factors.

The majority of lung cancers are diagnosed in current or former smokers, and environmental tobacco smoke also increases risk (18, 19). Given the strong evidence linking lung cancer etiology to well-identified occupational or environmental sources, less research has focused on other causes of this disease, including the influence of family history. Twin studies, especially those that can compare concordance between monozygotic and dizygotic twins, can provide information on whether familial aggregation is due to inherited or environmental factors. Evidence of limited heritability of lung cancers has been reported from population-based registry data in Utah, Sweden, Denmark and Finland (20-22). Even in these large, population-based studies, power is limited for most cancers, including lung. The magnitude of risk associated with having a family history of lung cancer are similar to those associated with familial aggregation of colon cancer (23), prostate cancer (24), and breast cancer in non-BRCA families (25). Stronger associations have been reported when the relative had early-onset disease for these cancers (23, 26, 27), as well as for lung cancer (28-30). In this pooled analysis, the association was stronger for individuals who were diagnosed with lung cancer prior to age 50, or who had a family history of lung cancer in a relative under the age 50. The difference was most pronounced among siblings, with the odds in early-onset lung cancer nearly double the odds in later onset probands.

Overall, having a sibling with lung cancer conferred the strongest association, and siblings of cases were at increased risk compared to siblings of controls. Aggregation studies of other cancer types such as prostate (31, 32) and breast (25) also report evidence of a stronger association with affected siblings compared to parents, yet this is less established for colon cancer (33). The association between family history and lung cancer remained for siblings even after adjustment for cigarette smoking in the relative. Similarly, among never smoking probands, the association was greater for those who report lung cancer in a sibling, rather than a parent. The association also remained in siblings from non-smoking households (i.e. both parents were never smokers). Finally, after adjustment for smoking in both the proband and the sibling, there remained strong evidence of an association between family history and lung cancer in the siblings of cases compared to the siblings of controls. Relative type

should be considered when assessing risk associated with family history of lung cancer. In general, an elevated risk of disease in siblings signals a recessive effect (34). The elevated risk from affected siblings might be a result from shared environment exposures childhood, or indicate there are recessive genes involved. In the five studies that provided information on all siblings, cases were not more likely to have a sibling compared to controls (82.4% and 83.8%, respectively), and sibships were similar in size, with an average of three siblings for both cases and controls. Adjusting for number of siblings did not change our results. Nevertheless, another factor that needs to be considered when interpreting the strong sibling risk is the age distribution, as affected siblings often have younger ages of onset compared to the affected parents of the case probands. In our study, the mean age of diagnosis for affected siblings and affected parents of the index cases was 60.2 and 66.2, respectively. Therefore, the stronger familial relative risks observed in siblings might be partially associated with an earlier age of onset. These findings may also be the result of the proband having greater recall of the cancer status of their generation (versus their parent's generation) and better diagnostic techniques in later years, but could also represent evidence of the genetic contribution to lung cancer etiology.

Most studies of lung cancer and familial aggregation included mainly non-small cell lung cancers. While it is difficult to ascertain the histology of lung cancer in the relatives, we were able to ascertain the histological type of lung cancer for the probands and to stratify results according to type. Despite the different etiologies and outcomes associated with various histological types, the odds ratios fell in a fairly narrow range (ORrange 1.28-1.81). For example, the rare (~1%) carcinoid tumors of the lung, which are not considered to be smoking-associated and are characterized by an excellent overall survival (35), showed an association with a positive family history of lung cancer (OR=1.28, 95% CI: 1.13-1.45), confirming in a large dataset early reports from Hassan et al. (2008)(36). The association with more common (15%) and lethal small cell carcinomas (37, 38) is slightly higher (OR=1.51, 95% CI: 1.33, 1.70), as anticipated by a recent meta-analysis (39). Overall, the similar magnitudes of the effect of family history on lung cancer across various histological types suggest that familial aggregation may be independent of the association with cigarette smoking. The hypothesis that familial aggregation of lung cancer may be associated with traits which act independently of cigarette smoking has received support from the results of a follow up study of the chromosome 6q region which reports a lung cancer risk-associated haplotype irrespective of degree of smoking yielded similar risk in carriers (40). The search for other risk factors unrelated to smoking remains crucial, given the number of lung cancer seen among never smokers.

Global estimates suggest that approximately 25% of lung cancer cases world-wide occur among never smoking individuals (41, 42). In this analysis, approximately 14% of all lung cancers were diagnosed in never smokers, and family history of lung cancer was associated with having lung cancer. Various other exposures that were unmeasured in these populations may account for some of this risk, although studies among never smokers with lung cancer, even after adjusting for other known carcinogenic exposures, support family history as an important risk factor (43-45).

The association between having a family history of lung cancer in a first-degree relative and lung cancer varies by ethnicity. The associations were highest among Asians and lowest among whites, with estimates for African Americans falling in between. While some studies have reported differences in risk of lung cancer associated with cigarette smoking by race/ethnicity, (46-48) few report estimates for family history by race/ethnicity, as study populations of individual studies are relatively homogenous. In the current pooled analysis, odds ratios were higher for African Americans, but not statistically different from results in the white populations. Studies investigating Asian populations reported risk estimates for

familial aggregation of lung cancer similar to the 2-fold increases found in the present pooled analysis (49, 50). Lower background rates of disease may account for these apparently stronger associations in the Asian population. As smoking patterns, environmental and occupational exposures, diet, and genetics differ by race/ethnicity, it is not unexpected that the strength of the association between family history and lung cancer risk would also vary.

The findings presented are not without limitations. First, all studies relied on self-report of family history and thus may be prone to recall bias. Confirming each lung cancer among relatives would be ideal but time and cost-prohibitive. Studies that have validated the reported family history through another source consistently report high accuracy (sensitivity >0.80) for lung cancers (51-53). Similarly, we were unable to perform a standardized pathologic review to confirm histological type, in the probands or the affected relatives. Next, the methodologies used to ascertain controls differed among the studies. When we limited our analyses to studies using the same control source, findings were essentially the same. Only parents and siblings are included in our analysis, as six studies did not collect information on offspring, and another two studies were focused on early-onset disease, where the majority of the offspring were under 21 years of age. Lastly, pooled analyses are limited by the number of common variables collected by each study. Age, gender, ethnicity, education and smoking history were collected for all study subjects, which are the major known risk factors for lung cancer. It is possible that there remains residual confounding by smoking, as smoking status does not fully assess tobacco smoke exposure. Information on environmental tobacco smoke exposure (in childhood or as an adult) was not collected in a uniform manner, therefore we were not able to adjust for it in a standardize manner, hence our findings may be confounded by this omission. Relative information was more likely to be missing certain variables compared to proband data, and we did not adjust models for family size, as this was not available for the majority of the studies. When we restricted our analyses to those studies with a family size variable, the results were not significantly different.

In summary, family history is a simple proxy for genetic risk, and is influenced by both shared and individual environmental exposures. The association between lung cancer and family history of lung cancer remains even after adjustment for smoking. Unlike germline mutation testing, family history assessment is fairly straightforward and inexpensive to obtain while taking a patient's history. While the role of genetic variation in the etiology of lung cancer is not yet defined, family history assessment is immediately available and those with a positive history represent a higher risk group. A positive family history of lung cancer should possibly be one of the variables considered in the selection of a population eligible for lung cancer screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of the studies included in the pooled analysis of familial aggregation of lung cancer

Continent	Study/Study Center	Principal investigator	Control source	Study period	Location	Cases, n	Controls, n	Total, n
North America	Samuel Lunenfeld Research Institute (54)	J. McLaughlin	Mixed	1997-2002	Toronto, Ontario, Canada	445	948	1393
	University of California at San Francisco (55)	J.K. Wiencke	Population	1999-2002	San Francisco, USA	4314	933	5247
	Mayo (56)	P. Yang	Mixed	1997-2006	USA	3533	1674	5207
	*Harvard (57)	D.C. Christiani	Mixed	1991-ongoing	Boston, USA	2253	1529	3782
	*M.D. Anderson Cancer Center (58)	M.R. Spitz	Hospital	1992-ongoing	Houston, USA	1841	2000	3841
	*Wayne State University and the Karmanos Cancer Institute (59, 60)	A.G. Schwartz	Population	1984-2005	Detroit, USA	1587	1758	3345
	*NY Multicenter Study(61)	J.E. Muscat	Hospital	1969-1999	New York State, USA	1320	1400	2720
	University of California at Los Angeles(62)	Z.F. Zhang H. Morgenstern	Population	1999-2004	Los Angeles, USA	611	1040	1651
	Maryland Lung & Prostate Cancer Study (63)	C.C. Harris	Mixed	1998-2009	Baltimore Metropolitan Area, USA	551	735	1286
	H. Lee Moffitt Cancer Center (64)	P. Lazarus	Hospital	1999-2003	Florida, USA	498	899	1397
	New England Lung Cancer Study (65)	E. Duell	Population	2005-2008	New Hampshire, USA	276	251	527
	Memorial Sloan-Kettering (66)	I. Orlow	Hospital	2005-2008	New York, USA	102	101	203
Europe	Central Europe (67)	P. Boffetta	Hospital	1998-2002	Central/Eastern Europe	2633	2702	5335
	LUCAS (68)	I. Stucker	Hospital	1990-1992	Paris, E. France	310	302	612
	ESTHER (69)	H. Brenner	Population	2001-2003	Germany	206	206	412
	CREST- Cancer of the RESpiratory Tract biorepository(70)	M. Neri	Mixed	1996--ongoing	N. Italy	413	555	968
	The Nijmegen Lung Cancer Study(71)	L.A.. Kiemeney	Population	Cases: 2008-controls: 2002-	The Netherlands	535	2080	2615
	Spain (71)	J. I. Mayordomo	Hospital	2006--	Aragon, Spain	350	1366	1716
	Liverpool Lung Project (72)	J.K. Field	Population	1998-2006	Liverpool, UK	475	954	1429

Continent	Study/Study Center	Principal investigator	Control source	Study period	Location	Cases, n	Controls, n	Total, n
	ReSoLuCENT (73)	P.J. Woll	Population	2006-ongoing	N. Trent, UK	214	204	418
Asia and Oceania	Aichi (74)	K. Matsuo	Hospital	2001-2005	Japan	716	716	1432
	Kyushu (75)	C. Kiyohara	Population	1994-1996	Japan	190	108	298
	*Israel (29)	G. Rennert	Population	2005--	Israel	372	350	722
	Hawaii (76)	L. Le Marchand	Population	1992-1997	Hawaii, USA	635	588	1223
Total						24380	23399	47779

*Data from these study sites were included in the generalized estimating equations analysis (Tables 4 and 5). Note that sample sizes reported in early manuscripts for published studies are often smaller than what was included in this pooled analysis.

Table 2

Characteristics of probands included in the familial aggregation analysis

	Cases (n=24380)	Controls (n=23305)	p-value
Gender			
Men	13833 (56.7%)	12529 (53.8%)	<0.0001
Women	10547 (43.3%)	10776 (46.2%)	
Age			
<30	73 (0.3%)	476 (2.0%)	<0.0001
30 ≤age<40	551 (2.3%)	1388 (6.0%)	
40 ≤age<50	2551 (10.5%)	3236 (13.9%)	
50 ≤age<60	5458 (22.4%)	5764 (24.7%)	
60 ≤age<70	7813 (32.3%)	7012 (30.1%)	
70 ≤age<80	6480 (26.6%)	4689 (20.1%)	
80+	1454 (5.9%)	740 (3.2%)	
Race/Ethnicity			
White/Caucasian	20069 (82.3%)	19303 (82.8%)	<0.0001
Hispanic/Latino	440 (1.8%)	670 (2.9%)	
African American	1304 (5.4%)	1691 (7.3%)	
Asian	1656 (6.8%)	1282 (5.5%)	
American Indian and Alaskan Native	185 (0.8%)	33 (0.1%)	
Hawaiian/Pacific Islander	398 (1.6%)	150 (0.6%)	
Other	169 (0.7%)	152 (0.7%)	
Missing/Unknown	159 (0.7%)	24 (0.1%)	
Education *			
Low	6332 (26.0%)	4550 (19.5%)	<0.0001
Medium	9023 (37.0%)	7800 (33.5%)	
High	6459 (26.5%)	8513 (36.5%)	
Missing	2566 (10.5%)	2442 (10.5%)	
Type of Smoker			
Never	3301 (13.5%)	8497 (36.5%)	<0.0001
Ever **	20961 (86.0%)	14160 (60.8%)	
Former	7940 (32.6%)	7836 (33.6%)	
Current	9877 (40.5%)	5287 (22.7%)	
Missing	118 (0.5%)	648 (2.8%)	
Mean Pack Years † (SD)	44.3 (33.3)	20.4 (25.8)	<0.0001
Histology			
Small cell carcinoma	2358 (9.7%)		
Non-small cell carcinomas ‡	18616 (76.4%)		
Squamous cell carcinomas	5781 (23.7%)		

	Cases (n=24380)	Controls (n=23305)	p-value
Large cell carcinomas	1099 (4.5%)		
Adenocarcinoma	9285 (38.1%)		
Bronchioloalveolar carcinoma (BAC)	896 (3.7%)		
Non small cell carcinoma, not otherwise specified	1555 (6.4%)		
Carcinoma[§]	1797 (7.4%)		
Carcinoid	347 (1.4%)		
Others/missing	1262 (5.2%)		

[*] Low=less than high school, medium=high school diploma or equivalent or some college, high=college degree

[**] Includes former smokers, current smokers, and subjects who were either former or current smokers

[†] Pack years of smoking was missing for 9.61% of cases and 14.56% for controls

[‡] Non-small cell includes squamous cell, large cell, adenocarcinomas, bronchioloalveolar carcinoma , and non-small cell carcinoma, not otherwise specified

[§] No further detail available

Table 3

The association between family history of lung cancer and lung cancer, by relative type

	Family History of Lung Cancer in 1st Degree Relative	Family History of Lung Cancer in Father	Family History of Lung Cancer in Mother	Family History of Lung Cancer in Sibling
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Overall	1.51 (1.39,1.63)	1.25 (1.13,1.39)	1.37 (1.17,1.61)	1.82 (1.62,2.05)
Proband Gender				
Male	1.53 (1.37,1.70)	1.23 (1.06,1.43)	1.32 (1.05,1.66)	2.07 (1.76,2.45)
Female	1.48 (1.33,1.65)	1.27 (1.09,1.48)	1.43 (1.15,1.77)	1.59 (1.35,1.87)
Proband Ethnicity				
White	1.46 (1.34,1.58)	1.19 (1.07,1.34)	1.37 (1.16,1.62)	1.77 (1.56,2.00)
Black/African American	1.67 (1.16,2.40)	1.48 (0.87,2.54)	1.13 (0.55,2.30)	2.07 (1.19, 3.60)
Asian	2.38(1.50, 3.82)	2.82(1.54, 5.70)	0.97(0.39,2.38)	4.35(1.83,10.34)
Proband Histology				
Small cell carcinoma	1.51 (1.33,1.70)	1.33 (1.13,1.57)	1.31 (1.00,1.73)	1.63 (1.36,1.95)
Non-small cell carcinoma	1.58 (1.44, 1.73)	1.40 (1.23,1.59)	1.28 (1.07,1.54)	1.77 (1.55,2.02)
Squamous cell carcinoma	1.54 (1.39,1.72)	1.32 (1.14,1.53)	1.16 (0.91,1.49)	1.85 (1.59,2.16)
Large cell carcinoma	1.81(1.60,2.06)	1.55(1.30,1.92)	1.58(1.25,2.10)	1.23(1.78,2.56)
Adenocarcinoma	1.59 (1.45,1.74)	1.25 (1.10,1.43)	1.61 (1.34,1.93)	1.85 (1.61,2.12)
BAC	1.56(1.45, 1.69)	1.09(0.90, 1.35)	1.68(1.24,2.12)	1.93(1.64,2.70)
Non-small cell carcinoma, nos Carcinoma	1.78 (1.58,2.01)	1.48 (1.24,1.75)	2.24 (1.78,2.83)	1.73 (1.44,2.08)
Carcinoid	1.28(1.13, 1.45)	0.92(0.69, 1.10)	1.48(1.16, 1.92)	1.78(1.48, 2.42)
Others/missing	1.30(1.17, 1.48)	1.10(0.96, 1.35)	1.20(0.95, 1.62)	1.85(1.55, 2.30)
Proband Smoking Status				
Never Smokers	1.25 (1.03,1.52)	1.09 (0.82,1.45)	1.10 (0.74,1.66)	1.44 (1.07,1.93)
Ever Smokers	1.55 (1.42,1.68)	1.27 (1.13,1.43)	1.40 (1.17,1.66)	1.91 (1.68,2.17)
Former Smokers	1.46 (1.29,1.65)	1.23 (1.03,1.47)	1.26 (0.97,1.62)	1.83 (1.53,2.18)
Current Smokers	1.57 (1.37,1.79)	1.33 (1.11,1.59)	1.51 (1.15,1.99)	1.85 (1.48,2.32)
Proband Age at Onset				
<50	1.83 (1.47,2.28)	1.68 (1.28,2.20)	1.51 (1.04,2.20)	3.72 (2.00,6.90)
50+	1.45 (1.33,1.57)	1.10 (0.97,1.24)	1.27 (1.06,1.52)	1.86 (1.65,2.09)

All ORs are adjusted for age, gender, ethnicity, education, smoker type, pack years and study site, where appropriate.

Table 4

Characteristics of relatives included in the familial aggregation analysis using generalized estimating equations

	Case Relatives	Control Relatives	P-value
Mothers (n= 12204)	n=6297	n=5907	
Ever Smoker	2123 (38.0%)	2270 (40.4%)	0.009
Never Smoker	3465 (62.0%)	3349 (59.6%)	
Number (%) affected w/Lung cancer:	240 (3.8%)	171 (2.9%)	
Median age at diagnosis	68	70	
Mean age at diagnosis (±SD)	66.8±13.0	69.0±10.4	0.08
Missing age at diagnosis	6 (2.5%)	4 (2.3%)	0.92
Fathers (n= 12149)	6263	5886	
Ever Smoker	3945 (72.7%)	3939 (72.2%)	0.57
Never Smoker	1483 (27.3%)	1517 (27.8%)	
Number (%) affected w/Lung cancer:	453 (7.2%)	363 (6.2%)	
Median age at diagnosis	65	67	
Mean age at diagnosis (±SD)	64.8±10.4	65.9±10.8	0.16
Missing age at diagnosis	27 (6.0%)	12 (3.3%)	0.08
Siblings (n= 35573)	18948	16625	
Ever Smoker	9869 (59.1%)	8107 (51.5%)	<0.0001
Never Smoker	6819 (40.9%)	7635 (48.5%)	
Number (%) affected w/Lung cancer:	724 (3.8%)	282 (1.7%)	
Median age at diagnosis	60	61	
Mean age at diagnosis (±SD)	60.2±11.3	60.0±11.3	0.72
Missing age at diagnosis	27 (3.7%)	11 (3.9%)	0.90

Table 5

Odds ratios (95% confidence interval) of risk of lung cancer among first-degree relatives of cases compared to first-degree relatives of controls among subjects included in the generalized estimating equations analysis

	# affected relatives with lung cancer	# unaffected relatives	Lung Cancer Risk among First-Degree Relatives Adjusted OR (95%CI)
Overall	2233	57693	1.55 (1.39, 1.73)
Proband Gender			
Male	969	26230	1.34 (1.14, 1.58)
Female	1264	31463	1.74 (1.50, 2.00)
Proband Ethnicity			
White	2093	51842	1.53 (1.37, 1.71)
Black/African American	122	5306	2.09 (1.28, 3.42)
Proband Histology			
Small cell carcinoma	88	1973	2.45 (1.72, 3.48)
Non-small cell carcinoma	1167	24738	2.46 (2.02, 2.98)
Proband Smoking Status			
Never Smokers	393	14972	1.38 (1.08, 1.75)
Ever Smokers	1833	42634	1.57 (1.42, 1.74)
Ex-Smokers	989	20837	1.62 (1.38, 1.91)
Current Smokers	841	21670	1.61 (1.34, 1.93)
Proband Age of Onset			
<50	298	15184	1.97 (1.51, 2.58)
50+	1935	42509	1.53 (1.36, 1.72)
Relationship to Proband			
Father	816	11333	1.33 (1.13, 1.57)
Mother	411	11793	1.39 (1.12, 1.75)
Siblings	1006	34567	1.96 (1.65, 2.34)
Relative Smoking Status			
Never Smoker	177	24091	1.31 (0.96, 1.78)
Ever Smoker	1750	28503	1.57 (1.41, 1.76)

ORs adjusted for: gender of proband, proband ethnicity, proband histology, proband smoking status, proband age of onset, relationship to proband, gender of relative, smoking status of relative (where appropriate).