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Population-based Relative Risks for Lung Cancer Based on Complete Family History of Lung Cancer

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Abstract

Introduction: Published risk estimates for diagnosis of lung cancer based on family history are typically focused on close relatives, rather than a more diverse or complete family history. This study provides estimates of RR for lung cancer based on comprehensive family history data obtained from a statewide Cancer Registry linked to a high quality genealogy data resource that is extensive and deep. The risk estimates presented avoid common recall, recruitment, ascertainment biases, and are based on an individual's (proband's) lung cancer family history constellation (pattern of lung cancer affected relatives); numerous constellations are explored.

Methods: We used a population-based genealogical resource linked to a statewide electronic SEER cancer registry to estimate relative risk (RR) for lung cancer for an individual based upon their lung cancer family history. The family history data available for a proband included degree of relationship (first to third-degree), paternal or maternal family lung cancer history, number of lung cancer affected relatives and age at diagnosis of affected relatives. Over 1.3M probands with specific constellations of lung cancer were analyzed. To estimate RRs for lung cancer, the observed number of lung cancer cases among probands with a specific family history constellation was compared to the expected number using internal cohort-specific rates.

Results: 5,048 lung cancer cases were identified. Significantly elevated RR was observed for any number of lung-cancer-affected relatives among first-, second-, or third-degree relatives. RRs for lung cancer were significantly elevated for each additional lung cancer first-degree relative (FDR) ranging from RR=2.57 (2.39, 2.76) for >= 1 FDR to RR=4.24 (1.56, 9.23) for ≥3 FDRs affected. In an absence of FDR family history, increased risk for lung cancer was significant for increasing numbers of affected second-degree relatives (SDR) ranging from 1.41 (1.30, 1.52) for ≥ 1 SDR to 4.76(1.55, 11.11) for ≥ 4 SDRs. In the absence of affected FDRs and SDRs, there were

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significantly increased risks based upon lung cancer affected third-degree relatives (TDR) ranging from 1.18 (1.11, 1.24) for ≥1 affected TDR to 1.55 (1.03, 2.24) for ≥ 4 affected TDRs. RRs were significantly increased with earlier age at diagnosis of a first degree relative, and equivalent risks for maternal compared to paternal history were observed.

Discussion: This study provides population-based estimates of lung cancer risk based on a proband's complete family history (lung cancer constellation). Many individuals at 2-5+ times increased risk for lung cancer were identified. Estimates of RR for lung cancer based on family history are arguably very relevant clinically. The constellation RR estimates presented could serve in individual decision making to direct resource utilization for lung cancer screening, and could be pivotal in decision making for screening, treatment, and post treatment surveillance.

Keywords

Lung Cancer; Genetic Epidemiology; Hereditary Factors; Family History

INTRODUCTION

An inherited predisposition has been shown to contribute to a number of cancers.[1-4] Recognition of the role of inherited predisposition has only been more recently recognized for lung cancer, likely due to the strength of association with tobacco use.[5-7] Estimated relative risks (RR) for lung cancer based on family history have been published, but are typically restricted to first degree relatives only[6]. Traditional RR based on observation of lung cancer in the relatives of those affected with lung cancer have been previously published for the Utah population.[2,8-10]

Here we use a different approach to estimate RR for lung cancer based on an individual's complete family history from first- to third-degree relatives. These population-based RR serve as powerful estimates of an individual's risk for lung cancer based on all Utah probands with a similar family history. More precise estimation of an individual's risk for lung cancer allows identification of those at highest risk for lung cancer whether due to genetics or environment. Identification of these individuals at highest risk for lung cancer may further refine risk models and allow targeted screening and education efforts towards those most likely to benefit. This may aid not just those at highest risk for the development of lung cancer, but may help with identification of non-smokers at risk for the development of lung cancer; non-smoking lung cancer is the 6th leading cause of death of all cancers in the United States.[11]

DATA/METHODS

Utah Population Data Base

The Utah Population Data Base (UPDB) is a unique resource consisting of a computerized genealogy of the state of Utah from the mid 1800s to present day that has been linked to statewide medical and demographic data. The UPDB includes 1.3 million individuals who have linked genealogy for at least 12 of their 14 immediate ancestors (both parents, all four grandparents, and at least 6 of their 8 great grandparents). These individuals with deep ancestral genealogy data were analyzed. Pedigrees in the UPDB can extend to 16

generations and include tens of thousands of individuals descended from a pair of ancestors. The UPDB genealogy is linked to statewide cancer data recorded in the Utah Cancer Registry (UCR). The registry has collected data on all independent primary cancers diagnosed or treated in Utah from 1966, and became an NCI Surveillance, Epidemiology, and End-Results (SEER) registry in 1973. Linked UCR cancer records are available for 94,822 of the 1.3 million individuals with at least 12 immediate ancestors. The University of Utah Institutional Review Board approved this study.

Lung Cancer Cases

Lung cancer cases were identified from UCR data linked to UPDB genealogy data using ICD-Oncology Revision 3 coding with primary site indicating lung or bronchus, excluding those with histology indicating leukemia or lymphoma; the 5,408 lung cancer cases and all of their relatives with deep ancestral genealogy were analyzed. Tobacco use data was not available. Based upon the 2016 *Utah State Health Assessment* from the Utah Department of Health, Utah is recognized to have the lowest rate of tobacco use of any of the states, estimated at just above 9%.

Estimated Rates for Lung Cancer

Estimation of risk for lung cancer within the UPDB resource utilized lung cancer rates estimated from the 1.3 million individuals with deep ancestral genealogy data. All these individuals in UPDB with at least 12 of 14 immediate ancestors were assigned to sex-, 5-year birth year range-, and birth state (Utah or not) cohorts. Cohort-specific rates of lung cancer were estimated as the number of lung cancer cases in each cohort divided by the total number of individuals in each cohort. Because RR were estimated for family history, the set of individuals with no affected first, second, or third-degree relatives was used to estimate cohort-specific rates for lung cancer.

Estimation of Relative Risks for Lung Cancer based on Family History

Relative risks for lung cancer based on complete family history were estimated from all probands in the UPDB with a specific family history constellation including first degree relatives (FDR), second degree relatives (SDR), and third-degree relatives (TDR). For some constellations, some relative categories were ignored, and thus probands were included no matter how many affected relatives they had for the ignored relationship. For each constellation of affected relatives considered (e.g. 1 FDR, 1 SDR, and 1 TDR) all of the individuals in the UPDB with this family history were identified, and termed probands. The RR for lung cancer for this constellation was then estimated as the observed number of lung cancer cases among the probands, divided by the expected number of lung cancer cases among the probands. The expected number of lung cancer cases in the probands was estimated by counting all the probands by cohort, multiplying the number of probands in each cohort times the estimated cohort-specific rate of lung cancer (estimated in individuals with no family history of lung cancer, as described above), and summing over all cohorts. Twotailed 95% confidence intervals were constructed for each RR under the assumption that the number of observed cases follows a Poisson distribution with mean equal to the expected number of cases.

RESULTS

In the version of the UPDB analyzed there are 1,315,887 individuals who have genealogy data for at least 12 of their 14 immediate ancestors; of these, 5,408 have a diagnosis of lung cancer recorded in the UCR since 1966. This is the data set analyzed for lung cancer relative risks based on complete family history. Table 1 shows the overall frequency of lung cancer diagnoses for all individuals in the UPDB. 923,223 (70%) of the individuals analyzed have 0 first-degree, 0 second-degree, and 0 third-degree relatives diagnosed with lung cancer. These individuals with no family history of lung-cancer were used to estimate cohort-specific rates of lung cancer within the UPDB. It is already clear from Table 1 that individuals with any family history of lung cancer are over twice as likely to be diagnosed with lung cancer as those with no family history of lung cancer (0.68/0.30 = 2.28).

The 392,664 individuals shown in Table 1 who have a positive family history of lung cancer are further considered by specific family history constellations; estimated risks for probands with varying family history are presented in more detail below. Each table of estimated RRs lists the description of the family history constellation, the number of probands in UPDB with that constellation, the number of observed lung cancer cases among the probands (obs), the expected number of probands affected with lung cancer (exp), the relative risk (RR) for individuals with that specific family history constellation (RR), the significance value for the RR test (p-value), and the lower and upper bounds of the two-tailed 95% confidence interval for the estimated RR (95% CI). For constellations where some relationships are noted “ignored”, probands with any number of affected relatives in the category were included. For all RR estimates shown, relatives more distant than TDR were ignored.

First Degree Relative Family History

Table 2 shows estimated RR for lung cancer based on family history in FDRs, with SDRs and TDRs ignored. Significantly elevated RRs for lung cancer were observed in all groups considered. The elevated risk even in the absence of any affected FDR (RR=1.09, 95% CI: 1.06,1.12) indicates that more distantly related relatives (who were ignored in this estimation) significantly contribute to elevated risk for lung cancer.

Second Degree Relative Family History

Table 3 shows estimated RR for lung cancer based on family history in SDRs in the absence of FDR family history and ignoring TDRs. Even in the absence of a lung cancer diagnosis in a first-degree relative, any number of affected SDRs results in significantly elevated risk for lung cancer.

It is also of interest whether positive SDR family history for lung cancer further affects risk in the presence of FDR positive family history. Table 4 shows estimated RR for lung cancer based on number of affected SDRs in the presence of exactly 1 affected FDR. The estimated RR for at least 1 affected SDR in the presence of FDR = 1 (RR = 3.03; 95% CI 2.52, 3.60) was significantly elevated over the estimated RR for only FDR = 1, ignoring SDRs and TDRs (RR = 2.08; 95% CI 1.93, 2.25; data not shown), displaying the additional impact of a

positive family history contributed by SDRs in the presence of a positive FDR family history.

Third degree relative Family History

Table 5 shows estimated RR for lung cancer based on positive TDR family history with no affected FDRs or SDRs. Since individuals with no affected FDRs, SDRs or TDRs were used to estimate base population rates for “no family history”, the estimated RR = 1.0 for this group of probands, as observed in Table 5. RRs for one or more affected TDRs are all significantly elevated; even in the absence of any more closely related affected relatives and increased with increasing number of TDRs.

Age at lung cancer diagnosis

It is generally accepted that an earlier age at diagnosis for cancer is indicative of a higher likelihood of inherited risk. Table 6 shows the estimated RR for lung cancer in probands with at least one affected FDR, based on the earliest age at diagnosis for that FDR. As expected, RRs in the presence of earlier diagnosis of lung cancer in an FDR are higher. The highest RR was observed in probands with at least one affected FDR diagnosed age 50-60 years (RR 3.66; 95%CI 3.11, 4.28).

Risks for specific relationships

Table 7 shows estimated RR for specific first- and second-degree relationships. The RR observed for specific FDRs do not typically differ significantly from the estimated RR for >=1 FDR shown in Table 2 (RR=2.57 95%CI 2.39, 2.76)). The most striking departure is the RR for both mother and father affected (RR=7.29; 95%CI 1.50, 21.31) for which the estimated RR is even higher than the estimated RR for >=2 affected FDR as seen in Table 2 (RR = 3.97; 95%CI 3.17, 4.90).

While no significant difference was observed for >=1 female affected FDR (RR=2.73; 95%CI 2.41, 3.08) compared to >=1 male affected FDR (RR=2.55; 95%CI 2.34, 2.78), the estimated RR for >=1 affected sister (RR=2.95; 95%CI 2.56, 3.37) was significantly greater than the estimated RR for >=1 affected brother (RR=2.49; 95%CI 2.25,2.75), and the estimated RR for >=1 affected son (RR=3.52; 95%CI 2.76, 4.41) was significantly greater than the estimated RR for > = 1 affected daughter (RR=2.47; 95%CI 1.70, 3.47). Comparisons of risks by sex for SDR relationships, also shown in Table 7, did not identify such differences. Neither sex nor age of the proband was considered.

Risks for Paternal Compared to Maternal Relationships

Multiple paternal family history constellations were compared to the equivalent maternal history including avunculars, grandparents, and cousins. As seen in Table 7, there was no significant difference in RR for affected father (RR = 2.38; 95%CI 1.88, 2.96) compared to affected mother (RR=2.35; 95%CI 1.62, 3.30). Comparisons of the other paternal and maternal constellations considered similarly identified no significant differences.

While significantly elevated risks were observed for both an affected paternal or maternal grandmother, no significant elevated risk was observed for an affected paternal or maternal

grandfather, though the numbers of affected probands were small, probably due to the narrow window of cancer diagnosis (1966 – 2014), limiting data for affected individuals separated by 2 generations.

DISCUSSION

This study provides population-based estimates of risk for lung cancer based on an individual's specific family history of lung cancer from first- to third-degree relatives. These results show that risk for lung cancer is significantly increased in the presence of any number of lung-cancer-affected first-, second-, or third-degree relatives. Ignoring all other affected relatives, RRs for FDRs are estimated to range from 2.57 for at least 1 affected FDR to 4.24 for at least 3 affected FDRs; RRs for SDRs are estimated to range from 1.41 for a proband with at least 1 affected SDR to 4.76 for a proband with at least 4 affected SDRs; and RR for TDRs are estimated to range from 1.18 for a proband with at least 1 affected TDR to1.50 for a proband with at least 4 affected TDRs.

The Utah RR estimates based on family history differ somewhat from similar risks estimated from the Icelandic population[7], possibly primarily because the Iceland risks were estimated as relative to the population rates of lung cancer and the Utah results were estimated relative to individuals with no family history of lung cancer. Sample sizes also differed, with the Utah data set including 5,408 lung cancer cases and the Icelandic dataset including 2,756 cases. Basic RR estimates were similar in the two populations; Jonsson et al., estimated RRs for FDRs in the Iceland data as 2.69 for parents, 2.02 for siblings and 1.96 for children; RRs for SDRs were estimated as 1.34 for aunts and uncles and 1.28 for nieces and nephews; and RRs for TDRs were estimated as 1.14 for first cousins.

Consideration of the earliest age at diagnosis for at least one affected FDR showed significantly elevated and increasing RRs, from RR = 1.74 for a proband whose earliest diagnosis in an affected FDR was greater than 80 years, to RR = 3.66 for a proband whose earliest diagnosis age in an affected FDR was between 50 and 60 years. Jonsson et al[7] similarly reported higher risks for relatives of patients with early onset disease.

While no significant difference in risk was observed for at least 1 female FDR compared to at least 1 male FDR, the estimated RR for at least one affected sister was significantly higher than the RR for at least 1 affected brother affected, and the RR for at least 1 affected son was significantly higher than the RR for at least 1 affected daughter. A similar comparison for SDR did not show differences for affected daughters or sons of proband's sisters compared to proband's brothers, nor for affected mothers compared to affected fathers (Table 7). In a study of family history of lung cancer in China[12], Jin et al. reported that female relatives of lung cancer cases were at higher risk than male relatives, although they noted environmental carcinogen exposure due to smoky coal exposure and cooking habits are risk factors for lung cancer in Chinese women may have affected results. This Utah analysis did not consider sex or age of the proband in risk estimation.

Although RRs varied from 3.43 (95% CI 1.11, 8.00) for paternal grandmother to 1.37 (95% CI 1.29, 1.46) for paternal first cousin, no significant differences were observed for the 5

relationships for which the RR for paternal relatives was compared to the RR for maternal relatives (data not shown). Combined paternal and maternal risks were considered only for FDR; the RR for both mother and father affected (7.29; 95% CI 1.50, 21.31) was the highest observed for any constellation considered, and significantly exceeded the RR estimated for a proband with at least 2 affected FDR (3.97; 95% CI 3.17, 4.90).

Tobacco use is recognized as the strongest risk factor for lung cancer, followed by radon exposure.[13] (https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm). While family history of lung cancer is also recognized as a risk factor, it is possible that similar tobacco use habits, or shared home or work environment could confound contributions of shared genetics of relatives. Although Utah has the lowest rate of tobacco use in the nation, it is likely that the majority of the lung cancer cases diagnosed in Utah were associated with tobacco use.

In a pooled analysis of lung cancer risk from the International Lung Cancer Consortium[14], the RRs reported were lower than those reported here; again, one important reason is that the Utah RRs were estimated using the rates of lung cancer estimated from individuals with no family history of lung cancer (no FDRs, SDRs, or TDRs affected), not population lung cancer rates. They reported an overall RR of 1.51 (95% CI 1.39, 1.63) for FDR family history when adjusted for proband age, sex, ethnicity, education, smoking status and study, compared to the Utah unadjusted estimated RR 2.57 (95% CI 2.39, 2.76) for at least 1 affected FDR ignoring SDRs and TDRs. The Utah unadjusted estimate for FDR family history using UPDB population rates for all individuals is still higher, with a RR of 2.18 (95% CI 2.08, 2.34) (data not shown). Cote reported evidence of interaction between smoking status and FDR family history; ever-smoking individuals with an affected FDR had a 3.19-fold increased risk of lung cancer compared to never-smokers without an affected FDR after adjustments for proband's age, sex, ethnicity, and education.[14]

Strengths of this study include that the lung cancer phenotype available from the statewide Utah Cancer Registry with data from 1966 is complete, accurate and population-based, and all cancer cases were confirmed histopathologically. Because the Registry provided all diagnoses there is no recall, recruitment, or ascertainment bias. In addition, while most studies estimating risks based on family history use only first-degree relatives, and sometimes even only the presence or absence of any related cases, this study included a complete family history for each of 1.3 million probands from first- to third-degree relatives.

Limitations in this study include that the population represented in the UPDB resource is primarily of Northern European extraction; findings must therefore be limited to similar populations. Absolute risks for lung cancer could not be determined for the population represented in UPDB; because not all individuals in UPDB are necessarily still in Utah with updated data, neither numerators nor denominators for rate estimation can be assumed to be accurate. Relative risks, however, utilize the same rates and are accurate. Data censoring could have resulted from incomplete or incorrect record-linking, or lung cancers that occurred outside the state of Utah, or before 1966. In addition, genealogy may not have been available for some individuals; genealogy data might not always represent biological

relationships, and record linking for females is not as successful as for males given name changes that occur.

Several improvements to these RR estimations can be made. Integration of the proband's current age, sex, radon exposure, occupation, socio-economic status, tobacco use history, and histological subtype of a relatives lung cancer would allow an even more accurate estimation of an individual's risk for lung cancer. While histology was not evaluated in this study, a prior study supports evidence for a genetic predisposition for the subset of non-squamous, non-small cell lung cancer.[15]

Like most studies estimating RR for lung cancer based on family history, tobacco use data for the probands and their relatives was not available, and this may be the most significant limitation to this analysis. The RR estimates presented here for the Utah population, without taking tobacco usage into account, are similar to many other published risk estimates, few of which integrate tobacco use data. The Icelandic report of risk for lung cancer based on family history did not integrate tobacco usage for risk estimation but had very similar RR estimates.[7] A case-control study in Louisiana reported a 2.4 fold increased risk for individuals with a family history after controlling for tobacco smoking.[16] A smaller study of the UPDB using only lung cancer cases with a linked Utah death certificate allowed identification of those lung cancer cases whose death certificate classified the contribution of tobacco usage to the cause of death. Significant excess relatedness was reported for the smoking-related (n=1,747) and non-smoking-related (n=784) lung cancer cases[5], but when close relationships were ignored (closer than first-cousins), only the non-smoking cases showed significant excess relatedness.

If we assume that *all* Utah lung cancer cases occurred in individuals who did not use tobacco, then these RRs based only on family history would under-estimate risk for smokers; if we assume that *all* Utah lung cancer cases are associated with tobacco use then these estimated RRs would conversely over-estimate risk for non-smokers. Precise RR estimates would require knowing both the proband's tobacco use status and the tobacco use status of all of their affected relatives. While such data is not available today in the UPDB, patient-wide collection of personal tobacco use (self-reported) has begun in the University of Utah Health System and more precise risk estimates integrating tobacco use, and perhaps even radon and other exposures, will someday be possible for the UPDB resource.

The confounding of the contributions of both shared genetics and shared environment adds complexity to risk estimation for lung cancer based on family history. Tobacco usage might have elements of genetic predisposition, close physical proximity of relatives might provide second hand exposure to tobacco products, relatives may live in physical proximity that might affect radon exposure, and relatives may work in similar occupations, which might affect carcinogen exposures. It is difficult to integrate all of these overlapping complexities with shared genetics.

This analysis of the Utah population with genealogic data suggests that 30% of individuals of any age in the UPDB have a positive family history of lung cancer in first-, second-, or third-degree relatives (Table 1); half of the lung cancers in Utah occur in this one-third of the

population (2,659/5,408 = 49%), clearly indicating that there exist subsets of individuals at significantly elevated risk. Table 8 shows the various family history constellations for which significantly elevated RR (≥2.0, ≥ 3.0 and ≥4.0) were observed, and the estimated proportion of the population who fall into these categories.

The clinical significance of estimated risks for lung cancer based on family history in close and distant relatives is strong. Of all cancers, lung cancer carries the highest overall mortality and has been for men since the 1950s and for women since the late 1980s. The high rate of deaths from lung cancer is due in part to the fact that the disease is often detected late, at which point treatments can be far less effective. Early detection of lung cancer can save lives. The National Lung Screening Trial[17] (NLST) showed that low-dose computed tomography can reduce lung cancer mortality by 20% in high-risk populations (age >55 years and smoking history > 30 pack years). The American Cancer Society already recommends a discussion of screening for lung cancer with healthy patients over the age of 55 with a history of smoking.[18] Using family history and the risk estimates provided here, those at highest-risk of lung cancer can quickly and efficiently be identified. Identification of high-risk individuals would contribute to earlier detection with focused screening, and could aid prevention education. Selection of high-risk individuals for clinical trials could also increase the power and efficiency of tests of new medications or prophylactic measures.

To our knowledge this is the first population-based study using complete family history of lung cancer to estimate an individual's risk for lung cancer. The detailed tables of estimated RRs based on complete family history provide straightforward estimates of relative risk for lung cancer that can be used by both clinicians and patients. At a minimum, these results are appropriate for individuals whose genetic background is Northern European; whether they can be extended to other populations remains to be seen. The analysis suggests that 4 % of Utah individuals analyzed, of any age, are at twice the risk as those individuals with no family history for lung cancer (RR>2.0). A more focused screening and prevention plan targeting these highest risk individuals can reduce morbidity and mortality from this most fatal of cancers. Especially for diseases where genes or predictive markers have not been identified, family history is an inexpensive, efficient, and powerful method to risk estimation that should be utilized whenever possible.

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Table 1

Characterization of personal history and family history of lung cancer in UPDB.

Population Description	Number in UPDB (%)	Number with Lung Cancer (%)
All Individuals with Ancestors	1,315,887 (100)	5,408 (0.41)
No FDRs, SDRs, or TDRs Affected	923,223 (70)	2,749 (0.30)
Family History in at Least 1 FDR, SDR, or TDR	392,664 (30)	2,659 (0.68)

FDR – First Degree Relative; SDR – Second Degree Relative; TDR – Third Degree Relative

Table 2

Estimated RR for lung cancer based on proband's first degree family history, ignoring SDRs and TDRs

Number Affected FDRs	Number	Observed	Expected	RR	95% CI	p-value
0	1,273,106	4,657	4,287.9	1.09	1.06, 1.12	<0.00001
>=1	42,781	751	292.2	2.57	2.39, 2.76	<0.00001
>=2	2,559	85	21.4	3.97	3.17, 4.90	<0.00001
>=3	175	6	1.4	4.24	1.56, 9.23	<0.00001

FDR – First Degree Relative; SDR – Second Degree Relative; TDR – Third Degree Relative

Table 3

Estimated RR for lung cancer based on SDR lung cancer family history in the absence of affected FDRs (FDR = 0) and ignoring TDRs

Number of Affected SDRs	Number	Observed	Expected	RR	95% CI	p-value
0	**1,166,504**	**4,054**	**3,859.3**	**1.05**	**1.02, 1.08**	**<0.00001**
>=1	**106,602**	**603**	**428.6**	**1.41**	**1.30, 1.52**	**<0.00001**
>=2	**11,822**	**80**	**47.0**	**1.70**	**1.35, 2.12**	**<0.00001**
>=3	**1,649**	**14**	**6.4**	**2.20**	**1.20, 3.69**	**0.01**
>=4	**290**	**5**	**1.1**	**4.76**	**1.55, 11.11**	**<0.00001**

Table 4

Estimated RR based on SDR family history in the presence of 1 affected FDR; TDRs ignored

Number of Affected SDRs	Number	Observed	Expected	RR	95% CI	p-value
0	**33,300**	**539**	**228.8**	**2.36**	**2.16, 2.56**	**<0.00001**
>=1	**6,882**	**127**	**42.0**	**3.03**	**2.52, 3.60**	**<0.00001**
>=2	**1,283**	**14**	**7.0**	**2.00**	**1.09, 3.36**	**0.01**
>=3	**237**	**4**	**1.2**	**3.42**	**1.17, 8.75**	**0.03**

Table 5

Estimated RR based on TDR family history without any FDRs and SDRs

Number of Affected TDRs	Number	Observed	Expected	RR	95% CI	p-value
0	**923,223**	**2,749**	**2749.0**	**1.00**	**0.96, 1.04**	**1.00**
>=1	**243, 281**	**1,305**	**1,110.5**	**1.18**	**1.11, 1.24**	**<0.00001**
>=2	**49, 275**	**362**	**283.4**	**1.28**	**1.15, 1.42**	**<0.00001**
>=3	**10,855**	**96**	**70.3**	**1.37**	**1.11, 1.67**	**<0.00001**
>=4	**2,835**	**28**	**18.1**	**1.55**	**1.03, 2.24**	**0.02**

Table 6

Estimated RR based on at least 1 affected FDR, ignoring both SDRs and TDRs, considering the earliest age at diagnosis for lung cancer in an affected FDR

Age at Diagnosis	Number	Observed	Expected	RR	95% CI	p-value
< 50 years	**2,333**	**36**	**11.8**	**3.04**	**2.13, 4.21**	**<0.00001**
50 <= age < 60 years	**6,536**	**155**	**42.4**	**3.66**	**3.11, 4.28**	**<0.00001**
60<= age < 70 years	**13,601**	**265**	**94.0**	**2.82**	**2.49, 3.18**	**<0.00001**
70<= age < 80 years	**13,840**	**216**	**98.6**	**2.19**	**1.91, 2.50**	**<0.00001**
>= 80	**6,471**	**79**	**45.4**	**1.74**	**1.38, 2.17**	**<0.00001**

Table 7

Estimated RR for specific first- and second-degree relationships

Constellation Description	Number	Observed	Expected	RR	95% CI	p-value
First Degree						
>= 1 sibling	25,466	567	217.2	2.61	2.40, 2.84	<0.00001
>= 1 sister	8,360	210	71.3	2.95	2.56, 3.37	<0.00001
>= 1 brother	17,718	379	152.2	2.49	2.25, 2.75	<0.00001
>= 1 son	4,129	74	21.0	3.52	2.76, 4.41	<0.00001
>= 1 daughter	2,289	33	13.4	2.47	1.70, 3.47	<0.00001
>= 1 female FDR	14,435	268	98.2	2.73	2.41, 3.08	<0.00001
>= 1 male FDR	29,487	520	203.6	2.55	2.34, 2.78	<0.00001
Mother	3,853	33	14.0	2.35	1.62, 3.30	<0.00001
Father	8,028	79	33.2	2.38	1.88, 2.96	<0.00001
Mother and Father	103	3	0.4	7.29	1.50, 21.31	0.01
Second Degree						
>= 1 Brother’s daughter	7,622	71	42.8	1.66	1.30, 2.09	<0.00001
>= 1 Sister’s daughter	8,188	82	50.0	1.64	1.30, 2.04	<0.00001
>= 1 Brother’s son	13,989	111	69.9	1.59	1.31, 1.91	<0.00001
>= 1 Sister’s son	14,883	120	80.7	1.49	1.23, 1.78	<0.00001

Table 8

Specific Family History Constellations Associated with Significantly Increased Risk for Lung Cancer

Relative Risk	≥2.0 (4%)	≥3.0 (2%)	≥4.0 (0.04%)
	≥ 1 FDR	≥ 2 FDR	≥ 3 FDR
	0 FDR and ≥3 SDR	1 FDR and ≥1 SDR	0 FDR and ≥4 SDRs
	≥1 FDR dx 60-80 years	≥1 FDR dx <59 years	Mother and Father
	Maternal Grandmother	0 FDR and ≥4 SDR	≥1 FDR and ≥3 SDR
		≥ 1 son	
		Paternal Grandmother	