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# Family history of lung cancer in never smokers with non-small-cell lung cancer and its association with tumors harboring *EGFR* mutations

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## Abstract

**INTRODUCTION—**Inherited susceptibility to lung cancer is understudied. Never smokers are an important subgroup of patients enriched for tumors harboring oncogene aberrations in the *EGFR* and *ALK* genes. We aimed to better characterize the incidence of family history of lung cancer among never smokers with NSCLC.

**METHODS—**Clinicopathologic data, tumor genotype, family history of cancer, and specifically family history of lung cancer from 230 consecutive never smokers was retrospectively compiled and analyzed.

**RESULTS—**In our cohort, the median age was 56 years, 67% were women, 75% were white, 59% had advanced NSCLC and 87% had adenocarcinoma histology. In these tumors, 98/230 (42%) had an *EGFR* mutation, 17/155 (11%) had *KRAS* mutations and 27/127 (21%) had an *ALK* translocation. Family history of any cancer was common (57%) and specific family history of lung cancer was present in 42/230 cases (18%). The percentage of cases with family history of lung cancer was higher in the *EGFR* mutated versus *EGFR* wild-type NSCLCs. Out of the cases with a family history of any cancer, 22/53 (41.5%) *EGFR* mutated, 1/5 (20%) *KRAS* mutated and 3/19 (15.5%) *ALK* translocated cohorts had a family history of lung cancer. The ratio of family history of lung cancer to family history of cancer was significantly higher in the *EGFR* mutated cohort when compared to the *ALK* translocated plus *KRAS* mutated cohorts (p=0.039).



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**CONFLICT OF INTEREST STATEMENT**

Daniel B. Costa has received consulting fees from Pfizer, Roche and AstraZeneca. David M. Jackman has received consulting fees from Genentech and Foundation Medicine. Elizabeth M. Gaughan, Beow Y. Yeap and Sarah K. Cryer have no conflicts to disclose. No other conflict of interest is stated.

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**CONCLUSIONS—**Family history of lung cancer is common in never smokers with NSCLC, and there seems to be a particular link in families in which the proband has an *EGFR* mutated tumor when compared to *ALK* translocated or *KRAS* mutated tumors. Further study of families with *EGFR*-mutated NSCLC may yield insights into the pathogenesis of this tumor type.

### Keywords

lung cancer; non-small-cell lung cancer; family history; never smokers; epidermal growth factor receptor; EGFR; anaplastic lymphoma kinase; ALK; KRAS

## INTRODUCTION

Lung cancer remains the most common cause of cancer death in the United States (1). While cigarette smoking has been clearly established as the major risk factor for this malignancy, approximately 10–20% of lung cancers develop in never smokers (<100 cigarettes/lifetime) (2). The last decade of research in lung cancer has yielded important advances in the understanding of molecular pathways involved in tumorigenesis and in the development of targeted therapies. Specifically, mutations in the epidermal growth factor receptor (*EGFR*) gene and translocations involving the anaplastic lymphoma kinase (*ALK*) gene are part of the pathogenesis of some lung cancers, predominantly in never smokers, and predict for improved outcomes with tyrosine kinase inhibitors (TKIs) targeting these aberrant oncogenes (3).

A family history of lung cancer has been associated with an increased risk of non-small-cell lung cancer (NSCLC), for both smokers and never smokers, in several studies (4–7). There is interest in determining those at high risk for the development of lung cancer in order to appropriately apply screening techniques and further elucidate the genetic variants that predispose to this cancer. As the epidemiology, natural history and response to TKIs of tumors harboring actionable genetic aberrations differs from tumors without these genetic changes, we hypothesized that the incidence of family history of lung cancer may be different in patients with tumors with *EGFR* mutations, or V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations or *ALK* translocations. We, therefore, aimed to better characterize the incidence of family history of lung cancer among never smokers with NSCLC and correlate it with tumor genotype.

## MATERIALS AND METHODS

### Patient selection

Patients with a diagnosis of NSCLC, who were seen by our providers and whose tumors were genotyped for at least *EGFR* mutations were identified through ongoing Institutional Review Board (IRB) approved protocols at Beth Israel Deaconess Medical Center (BIDMC2009-P-000182) and Dana-Farber Cancer Institute (DFCI02-180). Patients were excluded if there was insufficient tissue for genotype analysis or if genotyping was not performed. There were 230 never smokers (as defined by <100 cigarettes/lifetime), evaluated between 2004 and 2011, with NSCLC retrospectively identified.

### Tumor genotype

*EGFR* and *KRAS* mutation analysis was performed using standard DNA sequencing techniques, as previously published (8;9). In the case of *EGFR*, exons 18 to 21 were sequenced (8;9). *ALK* translocation status was analyzed using a fluorescence in situ hybridization (FISH) break apart probe for *ALK*, as previously described (10). Tumor genotype was performed in baseline diagnostic specimens prior to patient exposure to EGFR or ALK TKIs.

### Data collection

Clinical, pathologic and tumor genotyping for *EGFR* and *KRAS* mutation status and *ALK* translocation status was collected. Family history of any cancer, specifically lung cancer, was collected based on patient self-report and physician notes available in the electronic medical records of both institutions. A family history of cancer was classified as "positive" or "negative" and was considered positive if there was any report of cancer in a genetically linked first of second degree relative as determined by chart review; however due to the retrospective nature of this chart abstraction and the non-standardized template for acquisition of family history in our datasets, further quantitative sub-classification of familial heritage was not performed. Positive cases were subdivided into "family history of lung cancer" or "family history of other cancers". The specific type of cancer, outside lung cancer, was not collected for this analysis. Smoking status and lung cancer histology of afflicted family members were not available.

### Statistical methods

Differences between clinical, pathological, tumor genotypes and family history of cancer were compared among groups using Fisher's exact test. Wilcoxon rank-sum test was used to compare differences in age.

## RESULTS

### Patient and tumor characteristics

Table 1 summarizes the clinical and pathological characteristics of our patients. All (100%) had their tumor tested for *EGFR* mutations, 67% had *KRAS* mutation analysis and 55% had *ALK* FISH (Table 1). Out of all tumors tested for an actionable oncogene genotype, 98/230 (43%) had an *EGFR* mutation, 17/155 (11%) had *KRAS* mutations, 27/127 (17%) had an *ALK* translocation, and an additional 45/101 (44%) were wild-type for these alterations. Out of the 98 *EGFR* mutated NSCLCs, 40 had exon 19 deletions, 33 had the exon 21 L858R point mutation, 9 had exon 20 insertions and 16 other *EGFR* mutations. In almost all tumors, mutations were mutually exclusive; however, in 2 patients' tumors concurrent mutations were identified (1 with an atypical *EGFR* mutation + *KRAS* mutation, and 1 with *ALK* translocation + *KRAS* mutation). These were excluded from further analysis by subgroup. The clinical and pathological characteristics of only *EGFR* mutated, only *KRAS* mutated, only *ALK* translocated and "triple-negative" groups are depicted in Table 2.

### Family history of cancer and lung cancer

Family history was available for all patients. For the cohort, 131/230 (57%) had a family history of any cancer, including 42 patients (18%) with a family history of lung cancer (Table 1). When we analyzed the cases with family history of any cancer in the *EGFR* mutated (53/98, 54%) versus *EGFR* wild-type (78/132, 59%) NSCLCs, there was no discernable difference (p=0.501). However, the percentage of cases with family history of lung cancer was more frequent in the *EGFR* mutated (22/98, 22%) versus the *EGFR* wild-type (20/132, 15%) NSCLCs (p=0.170); suggestive of a trend towards this genotype's association with a family history of lung cancer. The latter observation prompted us to analyze subgroups with different genotypes to determine which group had the highest percentage and ratio of a family history of lung cancer.

### Family history of lung cancer in affected by tumor genotype

Of the 97 patients with tumor genotype revealing only an *EGFR* mutation, 53 (55%) patients had a family history of any cancer and 22/97 (23%) had a family history of lung cancer. 26 patients had tumors harboring only an *ALK* translocation and 19 of these patients (73%) had

a family history of any cancer, including three patients (3/26; 12%) with a family history of lung cancer. A family history of cancer without lung cancer was more common in the *ALK* translocated than *EGFR* mutated cohort (Table 2). There were 15 patients found to have only a *KRAS* mutation in their tumor. Of this group, 5 patients (5/15; 33%) had a family history of any cancer, including only one patient (7%) with a family history of lung cancer (Table 2). Of the patients with a tumor genotype wild-type for all three mutations, 29/45 (64%) patients had a family history of any cancer and 9 (20%) a family history of lung cancer (Table 2).

### Proportion of family history of lung versus other cancers by tumor genotype

In the specific subgroup of patients with an *EGFR* mutated tumor and a family history of cancer, 41.5% of the family histories included at least one person with lung cancer (Table 3). Among patients with any family history of cancer, patients with *EGFR* mutation were significantly more likely to have a family history of lung cancer as compared to patients with an *ALK* translocation or a *KRAS* mutation (41.5% vs. 16.5%, p=0.039). The difference between the proportion of family history of lung cancer in patients with *EGFR* mutation and those who were wild-type for all three genetic alterations was less striking (p=0.475, Table 3).

### Family history of lung cancer in *EGFR* mutated lung cancers with *EGFR*-T790M and in women

Out of the total 98 patients with *EGFR* mutated tumors, 3 (3%) had a concurrent *EGFR*-T790M in addition to other *EGFR* mutations in their baseline diagnostic specimen. Of these 3 patients, only 2 (66%) had a family history of lung cancer. The percentage of family history of lung cancer in patients with tumors with or without *EGFR*-T790M and an *EGFR* mutation was numerically different (2/3 [66%] vs 20/95 [21%], respectively; p = 0.125). Out of the 72 women with *EGFR* mutated NSCLC in our cohort, 38 had a family history of cancer and 15 of lung cancer. There were no major differences in the incidence of a family history of lung cancer by gender (15/72 [21%] in women vs 7/26 [27%] in men; p = 0.586).

## DISCUSSION

The development of lung cancer in never smokers is a complex clinical problem. Several potential risk factors have been implicated, including second-hand smoke and other environmental exposures (2;6). Among these factors, a family history of lung cancer is not an insignificant risk and indeed is part of most lung cancer risk prediction models. Large scale population-based cohort studies have demonstrated an association between a family history of lung cancer, specifically in first degree relatives, and an increased risk of lung cancer (5). A family history of overall cancer has not been associated with an increased risk of lung cancer in the same studies. The degree of association between family history and development of lung cancer in never smokers has not been clearly defined. The International Lung Cancer Consortium provided a pooled analysis that included 24 case-control studies to address this issue, and individuals with a first-degree relative with lung cancer had a 1.51 fold increase in the risk of lung cancer, after adjustment for smoking and other potential confounders (5). In this large pooled analysis, never smokers had a lower association with positive familial history of lung cancer, than smokers. In contrast, one Japanese study (7) showed that the strongest association between family history of lung cancer occurred in women (hazard ratio [HR] of 2.65) and in never smokers (HR of 2.48). These previously published data point towards a possible link between family history of lung cancer and incidence of lung cancer in never smokers.

Genome wide association (GWA) studies related to the risk of lung cancer in unselected patients were first published in 2008 (4) and provided strong evidence of a susceptibility region in chromosome 15q25.1 (a locus with a common minor allele), with and odds ratio (OR) of around 1.30. The 15q25 region contains coding regions for three cholinergic nicotinereceptor genes (*CHRNA3*, *CHRNA5*, and *CHRNB4*) that encode nicotinic acetylcholine receptors, and these may increase addiction to tobacco, and, therefore, exposure to tobacco carcinogens (4). Indeed, this 15q25 region is associated also with peripheral arterial disease, chronic obstructive pulmonary disease and with head and neck cancers (4). The aforementioned susceptibility region was not associated with lung cancer in never smokers (4). The Genetic Epidemiology of Lung Cancer Consortium reported on families with three or more cases of lung or larynx cancer, and identified a susceptibility locus in 6q23–25.42 (11), which contains the *RGS17* gene (4). GWA studies and family linkage studies have been performed on never smokers with lung cancer in an attempt to identify potential causative variants, and many different areas have been identified. For example, in 2010 a genetic variant at 13q31.3, which alters the expression of the *GPC5* gene, was associated with a combined OR of 1.46 (12).

None of the aforementioned studies have evaluated tumor genotype as a factor associated with the frequency of family history of lung cancer in never smokers or if a specific tumor genotype alteration can cluster in families with lung cancer. Therefore, our work provides novel information. In our cohort of never smokers with NSCLC, almost one fifth (18%) of patients had a family history of lung cancer. These percentages are similar to previously published incidence rates of lung cancer in never smokers (6). The demographic characteristics of our patients with tumors harboring different tumor genotypes were similar to previously published data (3). *EGFR* mutations were the most frequent genotype (43%), followed by *ALK* translocations (17%) and *KRAS* mutations (10%) in these mostly Caucasian never smokers. We did not test for other actionable oncogene mutations/ translocations that are also found in never smokers, including *ERBB2* mutations, *ROS1* and *RET* translocations (13).

Our goal was to evaluate for a possible link between tumor genotype and a family history of lung cancer in never smokers. Patients with *EGFR* mutated tumors had a numerically higher percentage of a family history of lung cancer (22%). In the group of patients with a family history of any cancer, patients with an *EGFR* mutation were more likely to have a family member with lung cancer than patients with tumors harboring an *ALK* translocation or a *KRAS* mutation (Table 3). Within the limits of this small cohort, the retrospective data collection, the potential recall bias in never smokers, the lack of smoking data on afflicted family members, the lack of information on second hand smoke or other environmental or socio-economic factors, and the inherent difficulty in confirming a family history of lung cancer (if NSCLC or other) from chart extraction of non-standardized formats for family history data collection, our data suggests a possible link between a family history of lung cancer in patients with tumors harboring *EGFR* mutations. A larger, prospective study, with specific guidelines on family history collection would be needed to confirm these findings. There is a paucity of literature addressing genetic risk factors for *EGFR* mutations in lung cancer. Case-control studies have shown that smoking is not a risk factor for *EGFR* mutated NSCLC in Japan (OR 0.73), but women had a higher risk (OR 2.19) than men (14). The association of women with an incidence of *EGFR* activating mutations has been confirmed by others, suggesting hormonal elements that may interact with other factors in the development of *EGFR* mutated NSCLC (15). In our cohort, a family history of lung cancer was not associated with female gender in the *EGFR* mutated cohort. *EGFR* gene polymorphisms, including intron 1 CA repeats, have also been associated with tumor with *EGFR* mutated NSCLC (16), but these have never been linked to a family history of lung cancer. Another potential inherited susceptibility risk factor for lung cancer in *EGFR*

mutated NSCLC is the presence of a germline *EGFR*-T790M mutation, since this has been reported in kindreds with *EGFR* mutated NSCLC (17;18). However, this seems to be a rare allele in never smokers and is only found in less than 1% of patients with *EGFR* mutated NSCLC as a germline mutation (19;20). In our cohort, we identified that 3% of the tumors had baseline *EGFR*-T790M – although we did not have access to germline genotype data, the T790M tumor alteration is perhaps an indication of a germline alteration (18) - and the frequency of family history of lung cancer was higher in these patients than in those without *EGFR*-T790M in their baseline tumor specimen. A single family with multiple members with *EGFR* mutated NSCLC without germline *EGFR*-T790M mutation has been reported (21). Much remains to be learned about the genetic and inherited factors that contribute to *EGFR* mutated lung cancers and to NSCLCs in never smokers (22) and other cohorts of patients, such as younger patients with lung cancer (23).

In summary, we found a family history of lung cancer is common in never smokers with an *EGFR* mutated NSCLC. If this assertion proves to be true in future studies, then family members of a patient with *EGFR* mutated lung cancer may be considered for screening for early detection of lung cancer and these families may provide ideal kindreds for genetic linkage or GWA studies to define the genetic factors that lead to *EGFR* mutations in lung cancer.

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## Table 1

Patient, Tumor and Other Characteristics of the Overall Study Group

| | **Overall** |
|---|---|
| | **(n=230)** |
| Site | |
| BIDMC | 60 (26%) |
| DFCI | 170 (74%) |
| Age (years) | |
| Median (range) | 56 (25–88) |
| Sex | |
| Female | 153 (67%) |
| Male | 77 (33%) |
| Ethnicity | |
| White | 173 (75%) |
| Asian | 35 (15%) |
| Black | 14 (6%) |
| Hispanic/Other | 8 (3%) |
| Stage | |
| I–III | 94 (41%) |
| IV | 136 (59%) |
| Histology | |
| Adenocarcinoma | 199 (87%) |
| Squamous cell | 6 (3%) |
| Other | 25 (11%) |
| *EGFR* mutation testing | |
| Yes | 230 (100%) |
| No | 0 (0%) |
| *KRAS* mutation testing | |
| Yes | 155 (67%) |
| No | 75 (33%) |
| *ALK* FISH testing | |
| Yes | 127 (55%) |
| No | 103 (45%) |
| Family History | |
| Any Cancer | 131 (57%) |
| Lung Cancer | 42 (18%) |
| Other Cancer | 89 (39%) |

BIDMC, Beth Israel Deaconess Medical Center; DFCI, Dana-Farber Cancer Institute; EGFR, epidermal growth factor receptor; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization

**Table 2**

Patient, Tumor and Other Characteristics by Tumor Genotype

| | ***EGFR* mutation**[+] | ***KRAS* mutation**[+ ^] | | ***ALK* translocation** [^] | | ***EGFR* WT/*KRAS* WT/*ALK* FISH negative** | |
|---|---|---|---|---|---|---|---|
| | **(n=97)** | **(n=15)** | **p** | **(n=26)** | **p** | **(n=45)** | **p** |
| Age (years) | | | 0.627 | | 0.011 | | 0.168 |
| Median (range) | 57 (26–83) | 61 (31–74) | | 47.5 (29–81) | | 54 (26–79) | |
| Sex | | | 0.135 | | 0.092 | | 0.327 |
| Female | 70 (72%) | 8 (53%) | | 14 (54%) | | 29 (64%) | |
| Male | 26 (28%) | 7 (47%) | | 12 (46%) | | 16 (36%) | |
| Ethnicity | | | 0.070 * | | 0.781 * | | 0.239 * |
| White | 71 (73%) | 13 (86%) | | 19 (73%) | | 34 (76%) | |
| Asian | 19 (19%) | 0 (0%) | | 4 (15%) | | 5 (11%) | |
| Black | 5 (5%) | 1 (7%) | | 0 (0%) | | 4 (9%) | |
| Hispanic/Other | 2 (2%) | 1 (7%) | | 3 (12%) | | 2 (4%) | |
| Stage | | | <0.001 | | 0.350 | | 0.014 |
| I–III | 28 (29%) | 12 (80%) | | 10 (38%) | | 23 (51%) | |
| IV | 69 (71%) | 3 (20%) | | 16 (62%) | | 22 (49%) | |
| Histology | | | 0.378 # | | 1.000 # | | 0.410 # |
| Adenocarcinoma | 87 (90%) | 12 (80%) | | 24 (92%) | | 38 (84%) | |
| Squamous cell | 2 (2%) | 1 (7%) | | 0 (0%) | | 2 (4%) | |
| Other | 8 (8%) | 2 (13%) | | 2 (8%) | | 5 (11%) | |
| Family History | | | | | | | |
| Any Cancer | 53 (55%) | 5 (33%) | 0.167 | 19 (73%) | 0.117 | 29 (64%) | 0.361 |
| Lung Cancer | 22 (23%) | 1 (7%) | 0.300 | 3 (12%) | 0.278 | 9 (20%) | 0.829 |
| Other Cancers | 31 (32%) | 4 (26%) | 0.773 | 16 (62%) | 0.011 | 20 (44%) | 0.188 |

*Asian versus non-Asian;

#Adenocarcinoma versus non-adenocarcinoma

+ one patient with a tumor with *EGFR* mutation and *KRAS* mutation was excluded from analysis

^ one patient with a tumor with *ALK* translocation and *KRAS* mutation was excluded from analysis

EGFR, epidermal growth factor receptor; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization

**Table 3**

Proportion of Family History of Lung versus Other Cancers by Selected Tumor Genotype

| | ***EGFR* mutation** [+] | ***KRAS* mutation plus *ALK* translocation** [+ ^] | | ***EGFR* WT/*KRAS* WT/*ALK* FISH negative** | |
|---|---|---|---|---|---|
| | **(n=53)** | **(n=24)** | **p** | **(n=29)** | **p** |
| Lung Cancer | 22 (41.5%) | 4 (17%) | 0.039 | 9 (31%) | 0.475 |
| Other Cancers | 31 (58.5%) | 20 (83%) | | 20 (67%) | |

[+] one patient with a tumor with *EGFR* mutation and *KRAS* mutation was excluded from analysis

[^] one patient with a tumor with *ALK* translocation and *KRAS* mutation was excluded from analysis

EGFR, epidermal growth factor receptor; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization