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Impact of family history of cancer on the incidence of mutation in epidermal growth factor receptor gene in non-small cell lung cancer patients

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ABSTRACT

Background: Epidermal growth factor receptor (*EGFR*) activating mutation is an important predictive biomarker of *EGFR* tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC), while family history of cancer also plays an important role in the neoplasia of lung cancer. This study aimed to investigate the association between family history of cancer and *EGFR* mutation status in NSCLC population.
Methods: From February 2008 to May 2012, 538 consecutive NSCLC patients with known *EGFR* mutation status were included into this study. Amplification refractory mutation system (ARMS) method was used to detect *EGFR* mutation. The associations between *EGFR* mutation and family history of cancer were evaluated using logistic regression models.
Results: *EGFR* activating mutation was found in 220 patients and 117 patients had family cancer histories among first-degree relatives. *EGFR* mutation was more frequently detected in adenocarcinoma patients ($p < 0.001$), never-smoker ($p < 0.001$) and with family history of cancer ($p = 0.031$), especially who had family history of lung cancer ($p = 0.008$). In multivariate analysis, the association of *EGFR* mutation with family history of cancer also existed ($p = 0.027$).
Conclusions: NSCLC patients with family history of cancer, especially family history of lung cancer, might have a significantly higher incidence of *EGFR* activating mutation.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide [1,2]. Non-small cell lung cancer (NSCLC) accounts for about 80% of primary lung cancer cases and approximately two thirds of them are diagnosed at an advanced stage of the disease [2]. Chemotherapy has been standard first-line therapy for them. Without molecular selection, its efficacy is still dismal with a median overall survival of 8–11 months. The emerging of the molecular drugs provides a new promise to the treatment of advanced NSCLC. A good sample here is the epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs), such as gefitinib or erlotinib, which have been widely used as first line, maintenance and 2nd/3rd therapy in advanced NSCLC [3–6].

However, not all patients respond to the *EGFR*-TKIs. The response rate is about 10% in the Causcian population and 30–40% in the Asian Population [7,8]. ISEL study first found that patients of female, never-smoker, adenocarcinoma or East Asian ethnicity will benefit more from the treatment of *EGFR*-TKIs [9]. After that, several phase III prospective trials confirmed that *EGFR* mutation is the main predictive factor for *EGFR*-TKIs [3,4]. Subsequent studies found that it was smoking status and histology but not gender which affect the incidence of *EGFR* mutation and *EGFR* mutation is a unique entity for its predictive role for *EGFR*-TKIs [4,8,10–15].

Familial aggregation was found in varied cancers including lung cancer [10,16–21]. Familial aggregation of cancer may signal a hereditary predisposition for the development of these tumors. The causative gene defect has been identified for cancer syndromes, such as familial breast and ovarian cancer caused by germ-line mutations in the BRCA1 or BRCA2 tumor suppressor genes or familial adenomatosis polyposis coli caused by germ-line mutations in the APC gene [22,23]. It was hypothesized that family lung adenocarcinoma might be caused by germ-line mutation such as *EGFR* V843I or T790M [24,25]. Recently, a pool analysis [26] found that

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familial aggregation of lung cancer increased risk of lung cancer associated with cigarette smoking. Since incidence of *EGFR* mutation is highly correlated with smoking status, we hypothesis that *EGFR* mutation might be involved in the carcinogenesis of the NSCLC patients with familial cancer history.

In this study, we investigated the associations between *EGFR* mutation and family history of cancer in combination with other factors like sex, smoking status, age and histology for the presence of *EGFR* mutation in the Chinese population. We found that NSCLC Patients with family history of cancer, especially family history of lung cancer, might have a significantly higher incidence of *EGFR* activating mutation.

2. Patients and methods

2.1. Patients

Eligible patients were more than 18 years of age with histologically or cytologically confirmed NSCLC and had sufficient tumor samples to perform a molecular analysis. Patients were considered never-smoker in this study if they reported smoking less than 100 cigarettes in their lifetime. Histology was based on criteria of the World Health Organization, and the TNM classification was determined according to International Association for the Study of Lung Cancer staging system version 7. Family history of cancer was defined as patients had family history of cancer in first-degree relatives [27]. An exon 19 deletion or an exon 21 L858R point mutation or T790M mutation was regarded as an activating mutation in this study. This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University (Shanghai, China); and written informed consent was obtained from each participant before the initiation of any study related procedure. The patients were confirmed and checked clinical characteristics again before the clinical research. If the patients had died, we connected with their clients.

2.2. DNA extraction and EGFR mutation analysis

All mutational analyses were performed in Tongji University Medical School Cancer Institute (Shanghai, China). The QIAamp DNA FFPE tissue kit (Qiagen, Hilden, Germany) was used for DNA extraction of FFPE tissue according to the user manual. The QIAamp DNeasy blood & tissue kit was used for DNA extraction of fresh tissue. The DNA samples were qualified by NanoDrop 2000 Spectrophotometer (Thermo Scientific, Waltham, USA), and then were standardized to 2 ng/μl. EGFR mutation detection was performed using a Human EGFR Gene Mutation Fluorescence PCR Diagnostic Kit (Amoy Diagnostics Company Ltd., Xiamen, China). 4 of the most common mutations were detected, including 2 types of deletion of exon 19, T790M and L858R point mutation. All experiments were done according to the user manual from the manufacture. Briefly, 47 ng of standardized DNA was added to 25 μL PCR master mix which contains PCR primers, fluorescent probes, PCR buffer and DNA polymerase. PCR reaction was performed by Stratagene Mx3000P™ (Agilent Technologies Inc, Palo Alto, USA). After amplification cycles, the fluorescent signal was collected from FAM and HEX channels. The Ct values that we used to determine whether a sample was positive or negative were based on extensive validation. The details were described in our previous articles [28,29].

2.3. Statistical analysis

For statistical analyses, we used the SPSS statistical software package (version 13.0; SPSS, Inc; Chicago, IL). Chi-square tests or Fisher exact tests were used to analyze correlations between *EGFR* mutation status and clinicopathological variables. The exact 95% CIs for *EGFR* mutation rates in each category of clinicopathological parameters, such as age, sex, smoking, histology and pathological stage were calculated. The odds ratios for the risk of activating *EGFR* mutation were calculated in a multivariate logistic regression model, including gender, age, PS, smoking status, histology and family history of cancer in all the patients. All statistical tests were conducted at a 2-sided level of significance of $p < 0.05$.

3. Results

3.1. Patient characteristics

From February 2008 to May 2012, 538 consecutive NSCLC patients with known *EGFR* mutation status entered into this study. Among them, 300 (55.8%) were men and 238 (44.2%) were women. Mean age was 59 years. There were 236 (43.9%) never smokers. 531 (98.7%) were PS 0–1 and 7 (1.3%) were PS 2. 16 (3.0%) were stage I disease, 14 (2.6%) were stage II disease, 68 (12.6%) were stage III disease, and 440 (81.8%) were stage IV disease. 441 (82.0%) were adenocarcinoma, 45 (8.4%) were squamous cell carcinoma, 21 (3.9%) were adenosquamous carcinoma, and 31 (5.8%) were NSCLC. Among all patients, 220 (40.9%) had an *EGFR* mutation, 101 patients (18.8%) detected exon 19 deletion, 2 patients (0.4%) detected T790M mutation, 100 patients (18.6%) detected exon 21 L858R point mutation, 7 patients (1.3%) detected both exon 19 deletion and T790M mutation, 6 patients (1.1%) detected both exon 19 deletion and exon 21 L858R point mutation while 4 patients (0.7%) detected both T790M mutation and exon 21 L858R point mutation. 117 patients (21.7%) had family history of cancer and 43 patients (8.0%) of them had family history of lung cancer (Table 1).

3.2. Association of EGFR mutation rate or family history of cancer and clinicopathological factors

EGFR mutation was found in 118 (49.6%) female, 150 non-smoker patients (49.7%) and 198 (44.8%) adenocarcinoma, which is significantly higher than 34.0% in male ($p < 0.001$), 29.7% in smoker ($p < 0.001$) and 22.7% in non-adenocarcinoma ($p < 0.001$) respectively. No other significant differences were observed between *EGFR* mutation with age, performance status or stage. As for family history of cancer, no significant difference was found with the characteristics (Table 1).

3.3. Impact of family history of cancer in harboring of EGFR mutation

EGFR mutation was 49.6% (58 patients) in the patients with family history of cancer, which was significantly higher than 38.5% (162 patients) in those without family history of cancer ($p = 0.031$). When we further divided family history of cancer into family history of lung cancer and family history of other cancer, we found *EGFR* mutation was 62.8% (27 patients) in the patients with family history of lung cancer, which is significantly higher than 41.9% (31 patients) in those with family history of other cancer and 38.5% (162 patients) in those without family history of cancer (Table 2). In the Cox regression model, after adjusting for gender, age, tumor stage, smoking history, performance status and histological type, the odds ratio for tumor *EGFR* mutation was 0.62 (95% CI: 0.41–0.95; $p = 0.027$), 0.47(95% CI: 0.28–0.80; $p = 0.005$) and 0.77 (95% CI: 0.824–0.638; $p = 0.035$) in patients with family history of cancer, never-smoker and adenocarcinoma respectively. However, gender was no longer associated with the incidence of *EGFR* mutation (OR = 0.92, 95% CI: 0.55–1.54, $p = 0.745$) (Table 3).

The impact of family history of cancer on *EGFR* mutation was further stratified according to gender, age, smoking status and

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Table 1
Characteristics of the 538 patients and their relationship with family history of cancer or *EGFR* mutation status.

Items	Total	Family history of cancer			*EGFR* mutation		
		Yes	No	*p*	Positive	Negative	*p*
Gender, *n* (%)							
Male	300 (55.8%)	65 (21.7%)	235 (78.3%)	0.959	102 (34.0%)	198 (66.0%)	<0.001
Female	238 (44.2%)	52 (21.8%)	186 (78.2%)		118 (49.6%)	120 (50.4%)	
Age, mean	59	59	59		58	59	
<70	448	98 (21.9%)	350 (78.1%)	0.873	182 (40.6%)	266 (59.4%)	0.779
≥70	90	19 (21.1%)	71 (78.9%)		38 (42.2%)	52 (57.8%)	
Smoking status, *n* (%)							
Non-smoker	302 (56.1%)	66 (21.9%)	236 (78.1%)	0.946	150 (49.7%)	152 (50.3%)	<0.001
Smoker	236 (43.9%)	51 (21.6%)	185 (78.4%)		70 (29.7%)	166 (70.3%)	
Performance status (ECOG), *n* (%)							
0–1	531 (98.7%)	116 (21.8%)	415 (78.2%)	0.630	217 (41.9%)	314 (58.1%)	0.915
2	7 (1.3%)	1 (14.3%)	6 (85.7%)		3 (42.9%)	4 (57.1%)	
Lung cancer staging, *n* (%)							
I–II	30 (5.6%)	3 (10.0%)	27 (90.0%)	0.108	16 (53.3%)	14 (46.7%)	0.154
III–IV	508 (94.4%)	114 (22.4%)	394 (77.6%)		204 (40.2%)	304 (59.8%)	
Pathology, *n* (%)							
Adenocarcinoma	441 (82.0%)	102 (23.1%)	339 (76.9%)	0.098	198 (44.8%)	243 (55.1%)	<0.001
Non adenocarcinoma	97 (8.4%)	15 (15.5%)	82 (84.51%)		22 (22.7%)	75 (77.3%)	

Table 2
Association between EGFR mutation and family history of cancer.

	EGFR mutation		
	Positive	Negative	*p*
Family history of cancer, *n* (%)			
Yes	58 (49.6%)	59 (50.4%)	0.031
No	162 (38.5%)	259 (61.5%)	
Family tumor classification, *n* (%)			
Family history of lung cancer	27 (62.8%)	16 (37.2%)	0.008
Family other cancer history	31 (41.9%)	43 (58.1%)	
Without family history of cancer	162 (38.5%)	259 (61.5%)	

histology. In the subgroup of never-smoker and adnocarcinoma, *EGFR* mutation was 60.6% (40 patients) and 53.9% (55 patients) in the patients with family history of cancer, which was significantly higher than those without family history of cancer ($p = 0.044$ and $p = 0.037$ respectively). However, no other significant difference was found between family history of cancer and *EGFR* mutation in the other subgroups (Fig. 1).

4. Discussion

As far as we know, this is the first study to investigate the impact of family cancer history on *EGFR* mutation in 538 Chinese NSCLC patients. We found that patients with family cancer history among first-degree relatives might also have a higher incidence of *EGFR* activating mutation, especially in the subgroup with family history of lung cancer. The multivariate analysis also showed that family history of cancer was an independent predictive factor to *EGFR* mutation, just like smoking status and histology.

Table 3
Multivariate analysis for prediction of tumor *EGFR* mutation.

Variables	Multivariate logistic regression		
	Odds ratio	95% CI	*p*
Gender (male vs female)	0.92	0.55–1.54	0.745
Age (<70 vs ≥70)	1.08	0.67–1.74	0.760
PS (0–1 vs 2)	0.97	0.45–2.08	0.930
Stage (I–II vs III–IV)	0.82	0.64–1.06	0.138
Smoking status (non-smoker vs smoker)	0.47	0.28–0.80	0.005
Pathology (adenocarcinoma vs non adenocarcinoma)	0.77	0.82–0.64	0.035
Family history of cancer (with vs without)	0.62	0.41–0.95	0.027

Personalized medicine emphasizes molecular analyses of tumor tissue obtained before therapy to select the proper treatment. However, most of the NSCLC patients were first diagnosed at an advanced stage and could not get enough tissue for genotyping of *EGFR* in NSCLC patients. In the IPASS study, only 56.1% of the enrolled patients provide the tissue samples to do the molecular analyses and 35.9% could be evaluated [15]. Also, a large national survey conducted in China mainland in 2011 and found that only 9.6% of the patient underwent the *EGFR* mutation, the main reason of the lower testing rate come from the shortage of the tumor sample [30]. Thus, clarifying the clinicopathological features of *EGFR* mutation so as to preferring choice of *EGFR*-TKIs in the enriched population is still needed in the clinical practice.

In this study, *EGFR* mutation status were detected in 40.9% in all the patients, while exon 19 deletion and L858R point mutation accounted for 94.1% of all mutations included. For most of the enrolled patients were never-smoker or adnocarcinoma, these results are consistent with the previous published data [4,9,28,31,32]. Pulmonary adenocarcinoma among Asian women who were non-smokers was regarded first as a separate entity in the Iressa Survival Evaluation in Lung Cancer study. In that preselected population, *EGFR* mutation (i.e., deletions in exon 19 and L858R point mutation in exon 21) was enriched and was highly associated with increased sensitivity to *EGFR*-TKIs [9]. IPASS study told us it was not gender status but smoker status or histology affected the incidence of the *EGFR* mutation [15]. The latest results from the PIONEER trial further confirmed the results from the IPASS study [33]. Our findings were consistent with these results, *EGFR* mutation was significantly higher in patients with adenocarcinoma ($p < 0.001$) or never- smoker ($p < 0.001$) or of female ($p < 0.001$) in the univariate analysis, however, gender no longer had a significant effect on the incidence of *EGFR* mutation in the multi-factor analysis.

Various studies have provided evidence that familial aggregation existed in nearly all kinds of cancer [10,16–21]. Recent study further demonstrated that familial lung cancer aggregation also exists after adjusting for the aggregation of cigarette smoking and type of family relatedness [26]. Moreover, patients with family history of cancer were found more frequently to have germline HOXB13 mutation, BRCA1 and BRCA2 mutations in familial prostate cancer and breast cancer respectively [34,35]. In our study, we found that patients with family history of cancer, especially in the subgroup of with family history of lung cancer, also have a significantly higher *EGFR* activating mutation, and the difference mainly existed in the never-smoker and adnocarcinoma subgroup. Similar to our result, Gaughan et al. reported a preliminary results and

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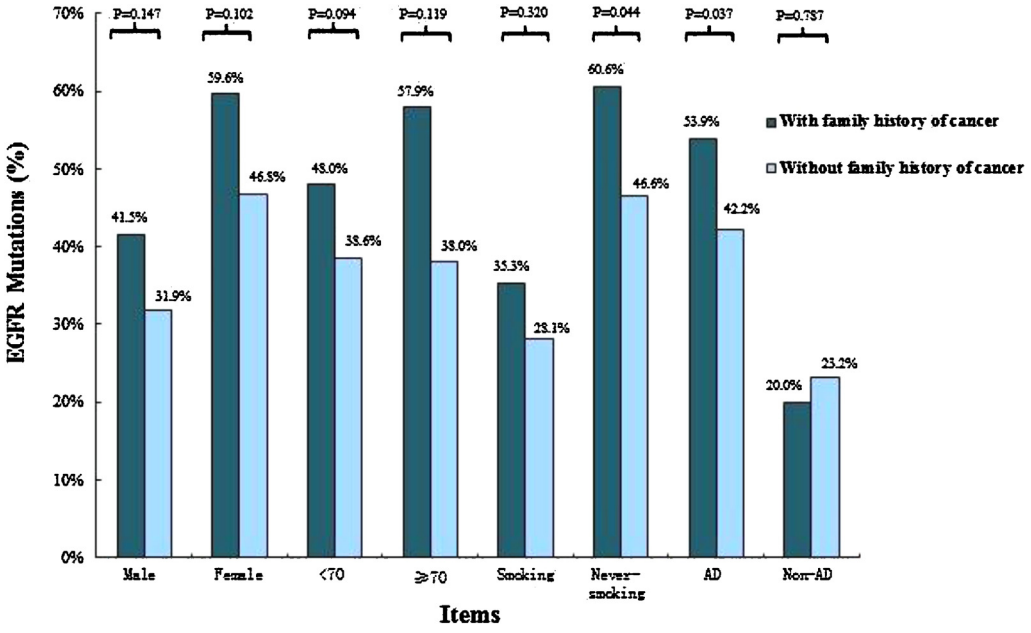

Fig. 1. Photograph showing the impact of family history of cancer on *EGFR* mutation was further stratified according to gender, age, smoking status and histology.

found that never-smoker NSCLC patients with *EGFR* mutation had a higher rate of family history of lung cancer when compared to the ALK translocated plus KRAS-mutated cohorts ($p = 0.023$), which meant that *EGFR* mutation was different from the other kinds of mutation drivers in the never-smoking lung cancer with family history of cancer [36]. The mechanism of the impact of family cancer history on the incidence of *EGFR* mutation is still unknown. Recently, the results from a follow up study found that a susceptibility locus on chromosome 6q region increased lung cancer risk-associated haplotype irrespective of degree of smoking yielded similar risk in carriers [37], which indicated that family history of cancer might play an important role in the family lung cancer aggregation in the never-smoker population. In addition, germ-line mutation *EGFR* T790M or V843I were reported to be an inherited susceptibility for lung adenocarcinoma respectively [24,25]. Moreover, patients with germ-line *EGFR* T790M or V843I mutation were more likely to have a secondary L858R mutation [24,25,38,39], which will result in the higher incidence of activated EGFR mutation in the patients. Therefore, we hypothesized that *EGFR* mutation might be an inherited susceptibility for lung cancer. Further large scale study of families with *EGFR*-mutated NSCLC is warranted and its fully clarifying may yield insights into the pathogenesis of this tumor type.

Our study has limitations that should be taken into consideration when interpreting the results. Firstly, our study is lack of validation for the family history of cancer inquiry because of the potential for recall bias by the patients. The misdiagnosis or missed diagnosis of their family history of cancer will result in a false negative family history. Secondly, all the enrolled patients came from a single institute, which will result in a selected bias and affected the final results. Thirdly, our study was lack of germ-line mutations detection in the whole population.

In conclusion, this study first investigated the impact of family history of cancer on the incidence of mutation in *EGFR* gene in Chinese NSCLC patients and found that family history of cancer, especially family history of lung cancer, together with smoking status and histology type were independent predictive factors to *EGFR* mutation, mainly in the never-smoker or adnocarcinoma subpopulation, which indicated that *EGFR* mutation might play an important role in the development of these subpopulations with family history of cancer.

Conflict of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.05.004.

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