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ORIGINAL ARTICLE

Is EGFR gene mutation testing necessary in smokers with non-small cell lung cancer?

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Abstract

Objective Previous studies have proven that cumulative smoking dose predicts the prevalence of epidermal growth factor receptor (EGFR) mutations. The aim of this study was to investigate the relationship between smoking-related factors and *EGFR* mutation status.

Methods Samples were collected from 195 smokers with non-small cell lung cancer (NSCLC) who underwent surgical resection and the presence of *EGFR* mutations (exons 19 and 21) were determined by real-time polymerase chain reaction (RT-PCR).

Results *EGFR* gene mutations were present in 33 (16.9%) patients who were smokers; the patients were divided into three groups according to the smoking index (SI). The incidence of *EGFR* mutations decreased from 38.9% in mild smokers to 8.1% in severe smokers (P = 0.001). Compared to daily smoking dose (P = 0.547), initial smoking age (P = 0.085) and duration of smoking history had a larger effect on *EGFR* mutation status (P = 0.002).

Conclusion Although there is a decrease in the incidence of mutations with increasing SI, there were still around 17% of smokers with NSCLC that harbored *EGFR* mutations, so it is necessary to test for *EGFR* mutation status in smokers with NSCLC.

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Gefitinib and erlotinib, reversible epidermal growth factor receptor tyrosine inhibitors (*EGFR*-TKIs), can improve the progression-free survival and response rates of patients with non-small cell lung cancer (NSCLC) [1–4]. *EGFR* mutation status is considered to be the best patient selection criterion for *EGFR*-TKIs therapy [5–7]. However, it is not feasible to test for *EGFR* mutation status in all NSCLC patients due to a lack of appropriate tissue. For these patients, some clinical characteristics can be used as predictors of *EGFR* mutations and thus it is important to analyze the relationship between *EGFR* mutations and clinical characteristics.

Previous studies have demonstrated that *EGFR* mutations occur more frequently in non-smokers [1, 8–9]. Therefore, it may not be necessary to detect *EGFR* gene mutation status among smokers with NSCLC, but other studies have shown that there are still around 10% of smokers harbored *EGFR* mutations [10–11], so it is necessary to analyze the relationships between *EGFR* mutations and smoking-related factors.

Materials and methods

Tumor tissues were obtained from the patients who underwent surgical resection and the presence of *EGFR* mutations in exon 19 and 21 was determined by real-time polymerase chain reaction (RT-PCR) as previously described [12]. Patients were categorized as mild smokers [smoking index (SI) ≤ 10 pack-years],

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moderate smokers (10 pack-years > SI < 40 pack-years), and severe smokers (≥ 40 pack-years) [11]. The other smoking-related factors collected, including initial smoking age, daily smoking dose, and duration of smoking history, were analyzed by median value.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software. A chi-square test was performed to compare the associations between the *EGFR* mutation status and smoking-related factors. A two-sided probability value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

Smokers with NSCLC (4 women and 191 men), aged from 29 to 85 years (median, 59 years), were recruited to our study. According to the WHO classification, 122 patients had adenocarcinoma and the non-adenocarcinoma patients included 64 cases of squamous cell carcinoma, 3 cases of adenosquamous carcinoma, 2 cases of lympho-epithelioma-like carcinoma, 2 cases of large cell carcinoma, and 2 cases of sarcomatoid carcinoma. The other clinical-pathologic characteristics of the patients were listed in Table 1.

Table 1 The characteristics of *EGFR* mutation status in smokers with NSCLC.

Characteristics	*n*	*EGFR* mutation		*P* value
		Number	%	
Age (years)				0.438
≤ 60	116	22	19.0	
> 60	79	11	13.9	
Gender				0.527
Male	191	32	16.8	
Female	4	1	25.0	
Histology				≤ 0.001
Adenocarcinoma	122	32	26.2	
Non-adenocarcinoma	73	1	1.4	
Tumor location				0.032
Upper lobe of right lung	56	10	17.9	
Middle lobe of right lung	7	4	57.1	
Lower lobe of right lung	31	3	9.7	
Upper lobe of left lung	69	9	13.0	
Lower lobe of left lung	32	7	2.2	
PTNM stage				0.087
IA	22	7	31.8	
IB	59	7	11.9	
IIA	15	2	13.3	
IIB	18	1	5.6	
IIIA	52	9	17.3	
IIIB	12	1	8.3	
IV	17	6	35.3	

Relationship between the clinic-pathological characteristics and *EGFR* mutations

The prevalence of EGFR mutations in smokers was 33/195 (16.9%), including exon 19 deletion mutations in 13 and exon 21 point mutations in 20 samples. *EGFR* mutations occurred significantly more often in patients with adenocarcinoma (≤ 0.001); by tumor location, tumors located in the middle lobe of the right lung had the highest mutation rate 4/7 (57.1%). There was no difference for the presence of an *EGFR* mutation by sex (P = 0.527) (although the number of women was very low at 4) and a similar result was seen for age (P = 0.438; Table 1).

Relationship between *EGFR* mutation and smoking-related factors

The incidence of *EGFR* mutations decreased with an increasing SI. Among patients who smoked for more than 75 pack-years, only one had an *EGFR* mutation. According the SI, *EGFR* mutations were present in 7/18 (38.9%) of patients who were mild smokers, 18/78 (23.1%) of patients who were moderate smokers, and 8/99 (8.1%) of patients who were severe smokers (P = 0.001; Fig. 1). Patients who smoked more than 30 years demonstrated a lower *EGFR* mutation rate compared with those who smoked less than 30 years (7.2% vs 24.1%; P = 0.002; Fig. 2).The other SRFs, such as initial smoking age and daily smoking dose, showed no statistical significance, as shown in Table 2.

Discussion

Previous studies have demonstrated that non-smokers with NSCLC is a distinct disease, with special molecular and biological characteristics [13–14]. Smoking status has a significant association with *EGFR* mutations in NSCLC; the rate of *EGFR* mutations in never-smokers is around 51%–68% and in contrast, only 10% in smokers [15–17].Never-smokers has been recognized as an effective predictor for EGFR-TKIs sensitivity in clinical practice; however, around 40% of all patients with *EGFR* mutations would be missed if testing were restricted to never-smokers [18–19].

In our study, the prevalence of *EGFR* mutations was 16.9% in smokers with NSCLC. We also found that the incidence of *EGFR* mutations decreased from 38.9% in mild smokers to 8.1% in severe smokers (P = 0.001). Therefore, *EGFR* mutations should be tested for in all NSCLC patients, including smokers with NSCLC.

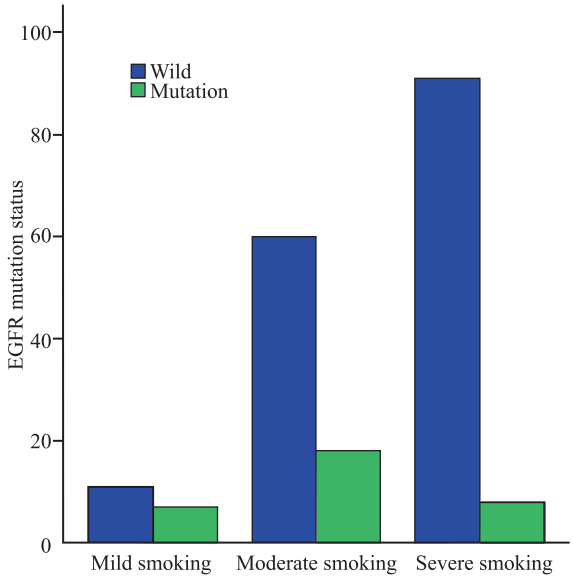

Fig. 1 EGFR gene mutation status in different smoking index.

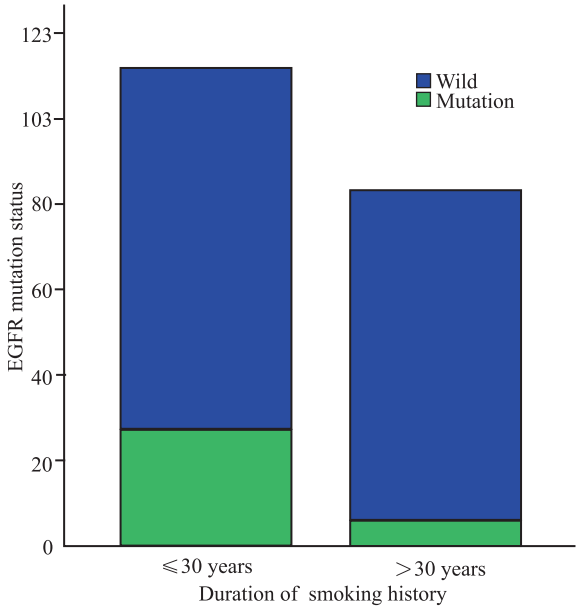

Fig. 2 EGFR gene mutation status in different duration of smoking history

The rate of *EGFR* mutations in smokers with NSCLC decreases when the number of pack-years increases [10–11, 16–17]. In the present study, an *EGFR* mutation was present in 7/18 (38.9%) patients who were mild smokers, 18/78 (23.1%) patients who were moderate smokers, and 8/99 (8.1%) patients who were severe smokers (P = 0.001), categorized by SI. Further analysis showed that among the smoking-related factors including SI, duration of smoking history, initial smoking age, and daily smoking dose, SI and duration of smoking history were highly correlated with *EGFR* mutations in smokers.

Table 2 The correlation between *EGFR* mutation status and smoking-related factors

Characteristics	*n*	*EGFR* mutation		*P*
		Number	%	
Initial smoking age (years)				0.085
≤ 24	105	13	12.4	
> 24	90	20	22.2	
Daily smoking dose				0.547
≤ 1.0 pack	132	24	18.2	
> 1.0 pack	63	9	14.3	
Duration of smoking history (years)				0.002
≤ 30	112	27	24.1	
> 30	83	6	7.2	
SI				0.001
Mild smoking	18	7	38.9	
Moderate smoking	78	18	23.1	
Severe smoking	99	8	8.1	

The relationship between *EGFR* mutations and sex is controversial; some studies showed that *EGFR* mutations occurred more frequently in female patients [8, 15], but other studies did not support this result [20–21]. The reason for this might be that among Asians most smokers were men. In our data, the rate of *EGFR* mutations in male and female smokers was 16.8% and 25.0%, respectively (P = 0.527). It seems that smoking status rather than sex was associated with *EGFR* mutation status. However, there were only 4 female patients who were smokers in our study.

The mechanism of how smoking affects *EGFR* mutations in NSCLC is unclear. The presence of other molecular alterations, including *K-RAS* mutations [22], *P53* mutations [23], and LKB1 alterations [24], might influence *EGFR* mutations in smokers with NSCLC. The above studies suggest that smoking itself might not cause *EGFR* mutations.

The limitation of this study is that we focused only on relationships between *EGFR* mutations and smoking-related factors, and more studies should be designed to analyze the relationships between the other driver mutations and smoking-related factors.

In conclusion, although the incidence of *EGFR* mutations in smokers with NSCLC decreased as the number of pack-years increased, there were still around 17% of smokers with NSCLC harboring *EGFR* mutations. It is therefore necessary to test for *EGFR* mutation status in all NSCLC patients including smokers, and if the *EGFR* mutation status is unknown, the patient's smoking index should be taken into account before making decisions about targeted therapy.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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