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The relation between epidermal growth factor receptor mutations profiles and smoking patterns in patients with lung adenocarcinoma: A cross-sectional study

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Abstract

Background: Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases, with smoking being a critical risk factor. The identification of NSCLC patients harboring epidermal growth factor receptor (EGFR) mutations, sensitized to tyrosine kinase inhibitors, has revolutionized treatment plans, resulting in improved clinical responses and reduced chemotherapy toxicity. This study aimed to assess the relationship between EGFR mutations and smoking patterns in patients diagnosed with lung adenocarcinoma referred to major pathologic laboratories.

Methods: This cross-sectional study included 217 NSCLC patients aged above 18 years. Molecular abnormalities of the EGFR gene were analyzed by polymerase chain reaction amplification of exons 18–21 accompanied by Sanger sequencing. Then, the data were analyzed using the SPSS 26 software. Logistic regression analysis, χ^2 test, and Mann–Whitney *U* test were used to evaluate the relation between EGFR mutations and smoking patterns.

Results: EGFR mutations were identified in 25.3% of patients, predominantly involving deletion in exon 19 (61.8%). For most of the mutant EGFR patients, the majority were nonsmokers (81.8%), and 52.7% were female patients. Besides, the median duration of smoking was 26 years and the median frequency of smoking was 23 pack-years in the mutant EGFR group, both of which were lower compared to the wild mutant group. Moreover, female gender, current, and heavy smoking were significantly correlated with EGFR mutations based on the univariate logistic regression analysis (*p*: 0.004, 0.005, and 0.001, respectively).

Conclusions: Female gender and nonsmoker status were strongly associated with positive EGFR mutations. While guidelines traditionally recommended EGFR testing primarily for female nonsmokers with advanced NSCLC, our study in line with the recently published evidence has shown a significant prevalence of positive EGFR mutations among male patients and smokers. Therefore, routine mutation testing is

treatments.[7,28] The use of anti-EGFR TKIs has greatly improved patients' quality of life and extended their overall survival by approximately 12 months.[28] Nonetheless, not all EGFR mutations are sensitive to TKIs.[29] Specifically, those with an exon 21 or an exon 19 deletion mutations are sensitive, while those with an exon 20 mutation do not respond favorably.[29,30] Hence, determining the tumor's genotype has become crucial in planning treatment regimes in NSCLC patients, as the EGFR mutation status can predict the response to TKI drugs.[31]

Estimation of the probability of EGFR mutations using common demographic information has been proposed as a valuable adjunct to laboratory testing especially in developing countries and regions without enough facility.[32] Information on the epidemiology of EGFR mutations and smoking patterns in our region is limited. The single-center study evaluated EGFR mutations in 103 Iranian NSCLC patients and showed 24% mutation frequency mostly point mutation on exon 21 and never smokers.[33] Another study with 50 patients reported EGFR-positive mutations in 28% of patients. Females, nonsmokers, and deletion in exon 19 were more common in the EGFR-positive group.[34] Mohammadi et al. also reported a 20% frequency of EGFR mutations among patients with lung adenocarcinoma mostly on exon 19 and females.[35]

International guidelines recommend testing for EGFR mutations in all advanced nonsquamous NSCLC patients regardless of their gender, age, and smoking status. Additionally, it is recommended for all nonsmoker patients with advanced squamous NSCLC who are under the age of 50.[36] However, in different regions of our developing country, due to the need to optimize patient services, this test is currently limited to nonsmokers and female patients with NSCLC. Nevertheless, our findings have highlighted a remarkable percentage of male patients and smokers among NSCLC cases. Consequently, smokers and male patients may also benefit from EGFR mutation testing and subsequent targeted therapies. Therefore, it is imperative to update the previous paradigm of EGFR mutation testing to middle-aged, middle-eastern, nonsmoker females should be updated to all NSCLC patients as major advancements in targeted therapy and patient survival among NSCLC patients harboring EGFR mutations have been achieved in recent years.[37]

This study conducted in our region was the first and had the largest sample size to evaluate the relationship between smoking patterns and EGFR mutations. While the potential effect of ethnicity should not be underestimated, it is important to note that the study sample consisted of a homogenous group of patients from southern Iran, which enabled a more accurate analysis. Furthermore, the DNA samples were analyzed by highly expert pathologists in well-equipped and reliable laboratories.

Based on the findings of the present study, it is recommended that EGFR mutation testing be routinely performed for all patients diagnosed with NSCLC regardless of gender and smoking history considering that EGFR mutations were identified in a significant proportion (25.3%) of patients with lung adenocarcinoma and also it can still occur in nonsmokers and light smokers. This approach will ensure that patients who are eligible for targeted therapies based on their EGFR mutation status receive appropriate treatment options.

However, the study faced several limitations due to its retrospective nature. First, the small number of female patients could potentially affect the interpretation of the results. Second, although all the accessible data were collected from the laboratories and patients' records, information regarding cancer stage and grade was not available. Third, due to the poor health condition of some patients, as well as cases of mortality and changes in contact information, it was not possible to gather missing information from them. In addition to the aforementioned limitations, most of the patients had reduced their consumption of waterpipes (hookah) after their disease diagnosis. Consequently, accurate data on hookah usage status was not available.

5 | CONCLUSION

In conclusion, consistent with numerous published studies, a strong association was observed between positive EGFR mutations, particularly in exon 19, and female gender as well as nonsmoker status. Considering the detection of positive EGFR mutations in smokers and the survival benefits associated with targeted therapies, it is recommended that routine mutation testing be performed for all NSCLC patients, regardless of their clinical and demographic characteristics. This study presented the largest EGFR mutation database in our region, focusing on smoking profiles. Given the limited accessibility of well-equipped EGFR testing laboratories for a significant number of patients in developing countries, the findings of such epidemiological surveys can serve as valuable guidance in determining the optimal long-term treatment strategy.

AUTHOR CONTRIBUTIONS

Seyedeh Yasamin Parvar: Methodology; writing—original draft; writing—review and editing. **Alireza Rezvani**: Conceptualization; project administration; resources; supervision; validation. **Rezvan Ghaderpanah**: Data curation; formal analysis; writing—review and editing. **Mohammadhossein Hefzosseheh**: Data curation; Methodology; Writing—original draft. **Shakila Rafiei**: Data curation; writing—original draft. **Ahmad Monabati**: Conceptualization; supervision; validation.

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