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LETTER TO THE EDITOR

EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION STATUS: DOES YOUNGER MEAN MORE FREQUENTLY MUTATED?

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Dear Editor,

The median patients' age at diagnosis of non-small-cell lung carcinoma (NSCLC), is 65 years. The majority of advanced NSCLC patients require molecular diagnosis of tumor tissue for qualification to molecularly targeted therapies [tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR), ALK or ROS1]. The molecular background of NSCLC in different age groups (especially in the youngest and the oldest groups) is poorly studied. Recent data have suggested that *EGFR* mutations are associated with an older age at diagnosis (adenocarcinoma female patients of Asian origin) [1]. However, in small retrospective studies, a higher incidence of *EGFR* mutations in young patients has also been suggested [2-4]. More recent studies have suggested that age may not be as significant predictor of *EGFR* mutations status [4-6].

In this commentary, we will attempt to prove that *EGFR* mutation status in NSCLC is highly dependent on the patients' age. Our study enrolled the largest group of homogenous Caucasian NSCLC patients tested for *EGFR* mutations.

The studied group consisted of 12651 NSCLC patients (median age: 66 ± 7.5 years, range: 25-92 years) and included 94.3% of adenocarcinoma, 5.3% of not otherwise specified NSCLC, 0.3% of large cell carcinoma, <0.1% of adenosquamous carcinoma and <0.1% of squamous cell carcinoma patients. Patients were divided into 11 age groups (every 5 years). Routine diagnostics of *EGFR* status was performed with molecular probes for a real-time polymerase chain reaction (PCR) technique on a Cobas z480 (Roche Diagnostics AG, Basel, Switzerland) instrument.

The *EGFR* gene mutations were detected in 1109 patients (8.77%), including 573 exon 19 deletions (4.53%), 358 L858R substitutions (2.83%) and 178 rare or double mutations (1.41%). The *EGFR* gene mutations occurred significantly more frequently in female than in male patients (14.4 *vs.* 4.8%; $\chi^2 = 352.5$, $p < 0.00001$). In young patients (25 to <50 years old), the incidence of mutations was significantly higher (17.26 *vs.* 8.39%; $\chi^2 = 50.21$, $p < 0.00001$) than in older patients (>50 years old). The incidence of mutations was 23.4% in young women and 13.9% in older women ($\chi^2 = 19.24$, $p = 0.000012$) and 10.6% in young men and 4.6% in older men ($\chi^2 = 19.29$, $p = 0.000011$). The differences in *EGFR* mutation prevalence in different age groups were caused by the differences in the frequency of the exon 19 deletion in female ($\chi^2 = 17.46$, $p = 0.000029$) and male ($\chi^2 = 29.6$, $p < 0.00001$) patients. The frequency of the L858R substitution and rare or double mutations was similar in the studied age groups in both genders. Deletion in exon 19 was the dominant mutation in young men (deletion frequency 74.1%, L858R frequency 7.4%, rare or double mutations frequency 18.5% of all examined *EGFR* mutations). In older men and in young and older women, exon 19 deletion frequency was 51.8,

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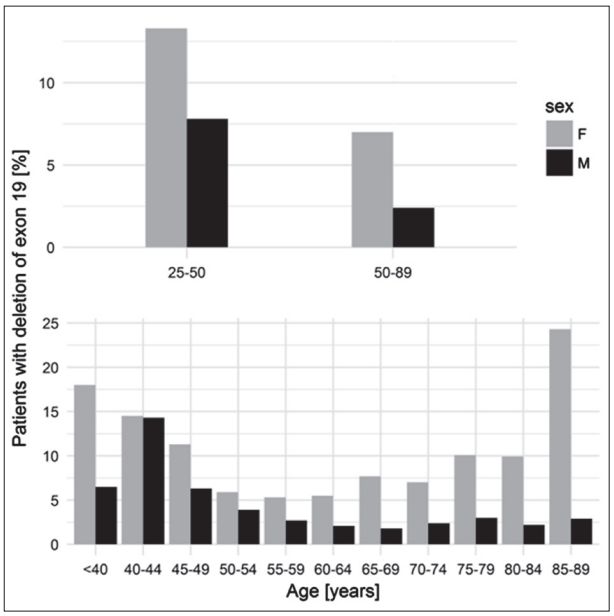

Figure 1. The prevalence of exon 19 deletions of *EGFR* gene in different age groups of patients with NSCLC.

56.9 and 50.2%, respectively, whereas the incidence of the L859R substitution was 30.6, 23.1 and 34.9%, respectively. The incidence of the exon 19 deletion gradually decreased along with increasing age of male patients. In women, the prevalence of the exon 19 deletion was highest in the youngest and the oldest age groups. Thus, clear trends were not observed for the L858R substitution and rare or double mutations (Figure 1).

Our results indicate the entity of hereditary molecular background for development of the exon 19 deletion in *EGFR* in young adults [our preliminary next-generation sequencing (NGS)] results indicate mutations in tumor suppressor genes, *e.g., MSH2*). However, smoking behavior may influence the presence of *EGFR* gene mutations in different female age groups. Moreover, diagnostics of *EGFR* mutations in young and older patients should be particularly careful and meticulous (correct sequence of genetic testing).

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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