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ASSOCIATION BETWEEN HUMAN PAPILLOMAVIRUS AND EGFR MUTATIONS IN NON-SMALL CELL LUNG CANCER

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Objective:

Aim: High-risk types 16 and 18 of human papillomavirus (HPV) are associated with the development and progression of various cancers. Unlike classical, the presence of rare mutations in epidermal



growth factor receptor (*EGFR*) gene in non-small cell lung cancer (NSCLC) is responsible for incomplete tyrosine kinase inhibitors response. The aim of this study was to determine the prevalence of HPV infection in NSCLC cytological smears in relation to the presence and frequency of *EGFR* gene mutations.

Methods: The two-year retrospective analysis included 67 NSCLC cytological smears obtained from lung cancer patients hospitalized at the Department of Respiratory Diseases Jordanovac, University Hospital Centre Zagreb. Cytological samples were routinely processed to obtain good quality smears with a sufficient number of malignant cells for PCR analysis. The DNA was extracted from NSCLC cytological smears stained by MGG using the Cobas DNA Sample Preparation Kit. Analyzed *EGFR* gene mutations were divided into classical (ex19del; L858R) and rare (G719X; ex20ins; S768I; T790M and ex21). The presence of HPV16 and/or HPV18 DNA was detected by amplifying the fragment of the *E7* gene. Expected PCR product size was 212 bp for HPV16, and 236 bp for HPV18. Prevalence of HPV infection in NSCLC patients with *EGFR* mutations compared to NSCLC patients without *EGFR* mutations was additionally examined by meta-analysis using data from this and six other studies.

Results: Among the 67 NSCLC cytological smears, 34 had mutations in the *EGFR* gene and 33 were free of it. More frequent HPV infection was observed in the NSCLC smears with *EGFR* gene mutations (HPV16, $n=11/34$, $p<0.05$; HPV18, $n=24/34$, $p<0.001$) compared to the NSCLC smears without *EGFR* gene mutations. Significant association between smoking and HPV16 infection was observed ($p<0.028$) in the group of NSCLC patients with *EGFR* gene mutations. Among 34 NSCLC cytological smears, 46 *EGFR* gene mutations were detected. Classical *EGFR* gene mutations were detected in 20 (58.8%) NSCLC smears, while rare mutations in five smears (14.7%). Nine (26.5%) NSCLC cytological smears had a combination of classical and rare *EGFR* gene mutations. The significant association between the presence of rare *EGFR* gene mutations and HPV16 and/or HPV18 infection ($p<0.05$) was observed. Meta-analysis confirmed that NSCLC patients with *EGFR* gene mutations have higher odds to have HPV infection than those without mutations.



Conclusion: The higher prevalence of HPV infection suggests the role of this virus in the etiology of NSCLC with *EGFR* gene mutations.