

Genetic and Epigenetic Alterations in Oral and Oropharyngeal Cancers Associated with Smoke and Smokeless Tobacco Exposure: A Systematic Review

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Oral and oropharyngeal squamous cell carcinomas are influenced by several variables, such as alcohol use, tobacco use and human papillomavirus (HPV) infections. Among them, tobacco usage is closely linked to squamous cell carcinomas of the oropharynx and oral cavity. Tobacco-induced genetic and epigenetic alterations are crucial contributors to carcinogenesis and their exact processes are still unknown. The aim of this systematic review was to compile the most recent information regarding the genetic and epigenetic changes caused by tobacco use that lead to the initiation and progression of oral and oropharyngeal cancers. Databases such as PubMed, Scopus, and Web of Science, Dentistry & Oral Sciences Source and AMED – The Allied and Complementary Medicine Database were used in a methodical search. Altogether 28 studies on tobacco-related oral/oropharyngeal malignancies that were published between 2014 and 2024 were included and focused only on *in-vitro* experiments. PRISMA guidelines were used to screen the articles. Key findings, tobacco usage, cell culture conditions, study type, and important molecular changes were considered during extraction and data analysis. Both smoke and smokeless tobacco products were analyzed collectively. SYRCLE's risk of bias tool was used for the risk of bias assessment since most of the studies were used both animal models and cell lines. We found that frequent mutation of *TP53*, *CDKN2A*, and *NOTCH1* genes in tobacco users. Hypermethylation of tumor suppressor gene promoters and changes in the expression of regulatory microRNAs like miR-21 and miR-155 were examples of epigenetic changes. Additionally, tobacco smoke has been connected to chromatin remodeling and histone de-acetylation, both leading to uncontrolled cell growth and invasion. The development of oral and oropharyngeal cancer was driven by certain genetic alterations and epigenetic dysregulation as a result of tobacco usage. These results provide promising insights into novel treatment approaches such as molecular biomarkers for early detection of tobacco-associated head and neck malignancies

Keywords: Tobacco, oral cancer, oropharyngeal cancer, genetic, epigenetics