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Risk Factors for Oral Tongue Cancer

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Abstract: ***Tongue squamous cell carcinoma (TSCC) is an aggressive subtype of oral squamous cell carcinoma characterized by early invasion and frequent cervical lymph node metastasis. This study reviews established and potential risk factors for TSCC, including tobacco smoking, alcohol consumption, chronic local trauma, human papillomavirus (HPV) infection, and genetic susceptibility. Tobacco and alcohol show strong dose–response relationships and synergistic effects and remain the most important preventable risk factors. Chronic mucosal trauma, particularly at the lateral border of the tongue, may contribute to carcinogenesis in patients without classical behavioral risk factors, although current evidence is inconsistent. Despite the established etiological role of HPV in oropharyngeal carcinoma, its prevalence and oncogenic activity in TSCC are low, and its causal contribution remains controversial. In contrast, genetic susceptibility and dysregulation of key molecular pathways appear to be more relevant in younger patients and in tumors arising without traditional risk exposures. TSCC therefore represents a multifactorial disease requiring integrated consideration of environmental, local, viral, and genetic factors to improve prevention, risk stratification, and early detection strategies.***

Keywords: Tongue squamous cell carcinoma; Oral cancer risk factors; Tobacco and alcohol; Human papillomavirus; Chronic mucosal trauma; Genetic susceptibility

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity, with tongue squamous cell carcinoma (TSCC) representing one of the most aggressive subsites, characterized by early invasion and frequent cervical lymph node metastasis. Tobacco smoking is a major etiological factor with a clear dose-dependent carcinogenic effect on the oral mucosa [1, 2, 3]. Smokers have a 3.34-fold higher risk of developing oral cancer compared with non-smokers, and risk increases with longer smoking duration [1, 3]. After smoking cessation, the relative risk decreases to 1.40 after one year [1], while passive smoking also contributes to increased oral cancer risk [2, 4, 5]. Alcohol consumption is another independent risk factor, showing a strong dose-response relationship with oral and pharyngeal cancers [6, 3]. Daily intake of 25 g, 50 g, and 100 g of distilled alcohol is associated with relative risks of 1.75, 2.85, and 6.01, respectively [7], and combined exposure to alcohol and tobacco significantly increases the risk of OSCC [8].

Chronic local trauma and persistent irritation of the oral mucosa have also been implicated in oral carcinogenesis [9, 10, 11, 12]. The lateral border of the tongue is the most frequently affected site, and in the absence of other major risk factors, chronic trauma is associated with an odds ratio of 9.1 for tongue cancer [12, 13]. Prosthetic appliances are most commonly reported as sources of chronic irritation [13, 12]; however, evidence regarding the role of fractured teeth and sharp dental edges remains limited, and some reviews do not confirm a clear association between chronic irritation and oral carcinoma [12, 11]. Human papillomavirus (HPV), particularly HPV16, is a well-established cause of oropharyngeal carcinoma [14], and its role in oral cancer has been increasingly investigated [15]. Oral HPV infection is detected in 4–5.5% of healthy adults [16, 17], and although HPV is more frequently detected in OSCC than in normal mucosa [18], its prevalence and oncogenic activity in TSCC are low, with reported infection rates of 1.9% and oncogenic activity in only 1.3% of cases [19, 20]. Consequently, the etiological role of HPV in tongue cancer remains controversial [21, 20, 19].

Genetic susceptibility contributes to the risk of head and neck squamous cell carcinoma, particularly in hereditary syndromes such as Li–Fraumeni syndrome, Fanconi anemia, Bloom syndrome, and dyskeratosis congenita, where cancer risk is increased by 700–1000 times [22, 23]. In sporadic cases, especially among young patients without classical risk factors, mutations in genes responsible for genomic stability and cell-cycle regulation, including TP53, CDKN2A, and Fanconi anemia pathway genes, are frequently identified [23]. Molecular studies further indicate that dysregulation of the WNT–CTNNB1–STK11 and CDKN2A–HGF–MET pathways may contribute to TSCC carcinogenesis [24]. The aim of the present study was to evaluate the association between established and potential risk factors—including tobacco use, alcohol consumption, chronic local trauma, HPV infection, and genetic susceptibility—and the development of tongue squamous cell carcinoma in the studied population.

2. Overview

Tobacco Smoking

Tobacco smoking has a dose-dependent carcinogenic effect in the oral cavity [1, 2, 3]. A meta-analysis [1] shows that the risk of developing oral cancer is 3.34 times higher in smokers compared to non-smokers, with the risk increasing proportionally with the duration of smoking [3]. After one year of smoking cessation, the risk decreases to 1.40 [1]. Passive smoking is also associated with an increased risk of oral cancer [2, 4, 5].

Alcohol

A dose-dependent effect on the development of oral cancer has been established [6, 3]. The risk of both oral and pharyngeal cancer increases with the amount of alcohol consumed [6]. A meta-analysis found that daily consumption

of 25 g, 50 g, or 100 g of spirits is associated with overall relative risks of 1.75, 2.85, and 6.01, respectively, for cancers of the oral cavity and pharynx [7].

Regular alcohol consumption is associated with a dose-dependent increase in the risk of developing oral cancer ranging from 2- to 14-fold [25, 26, 27, 28, 29, 30, 31]. Concomitant alcohol consumption and tobacco smoking significantly increase the risk of oral squamous cell carcinoma (OSCC) [8]. The effect of alcohol cessation on cancer risk remains unclear, with a significant reduction in risk observed only after 15–20 years [32].

Chronic Trauma or Local Irritation

There is evidence that factors leading to chronic trauma of the oral mucosa represent a significant risk factor for the development of oral carcinoma [9, 10, 11, 12]. The lateral border of the tongue is the most frequently affected site in cases of chronic trauma, and in the absence of other risk factors, the odds ratio reaches 9.1 [12, 13]. Prosthetic appliances are most commonly considered the traumatic agents [13, 12]. There are no studies specifically investigating the role of fractured teeth and sharp dental edges in the development of oral cancer [12]. Some literature reviews do not find an association between chronic irritation and oral carcinoma [12, 11].

HPV Infection

Human papillomavirus (HPV), particularly HPV16, is the predominant cause of oropharyngeal carcinoma [14], and in recent years HPV infection has also been considered a risk factor for oral cancer [15]. It has been established that a proportion of the healthy adult population is infected with HPV in the oral cavity, with prevalence ranging from 4% to 5.5% [16, 17].

HPV infection is 4.7 times more likely to be detected in OSCC than in healthy mucosa and represents a risk factor conferring a 3- to 6-fold higher risk of developing oral cancer [18]. Reported prevalence of HPV infection in oral squamous cell carcinoma ranges from 23.5% to 43.5% [33, 34], of which 68.2% are HPV16 and 34.1% are HPV18 [33]. There is high variability in infection rates depending on anatomical location [35]. In carcinoma of the tongue, HPV infection is rare; a prevalence of 1.9% has been reported in cancers of the oral tongue [19], with oncogenic activity detected in only 1.3% of cases [20]. The role of HPV infection in the development of tongue squamous cell carcinoma remains unclear [21]. An increasing number of studies do not find an association between HPV infection and carcinoma of the tongue [21, 20, 19].

Genetic Factors

A predisposition to head and neck squamous cell carcinoma (HNSCC) is observed in several hereditary syndromes, including Li–Fraumeni syndrome, Fanconi anemia, Bloom syndrome, and dyskeratosis congenita [23]. In these conditions, the incidence of HNSCC is 700–1000 times higher [22, 23]. In sporadic cases of HNSCC, in young patients and in the absence of classical risk factors, mutations leading to inactivation of genes responsible for genomic stability (p53, p16, FANCA–M) have been observed [23]. Some studies have found that these defects are relatively common in the population and may be inherited [36, 37, 23]. Molecular analyses of tongue squamous cell carcinoma indicate that dysregulation of the WNT–CTNNB1–STK11 and CDKN2A–HGF–MET pathways may contribute to carcinogenesis [24].

3. Conclusion

Tongue squamous cell carcinoma is a multifactorial disease in which both environmental exposures and individual susceptibility play important roles. Tobacco smoking and alcohol consumption remain the most significant and consistently confirmed risk factors, demonstrating strong dose–response relationships and synergistic effects when combined. These findings support the continued importance of public health strategies aimed at reducing tobacco and alcohol use as key measures for primary prevention of tongue cancer.

Local mechanical factors, including chronic mucosal trauma, may contribute to carcinogenesis, particularly in patients without classical behavioral risk factors, and the lateral border of the tongue appears to be especially vulnerable. However, the current evidence remains inconsistent, highlighting the need for well-designed prospective studies to clarify the true role of chronic irritation and specific dental factors in the development of TSCC.

Although HPV infection is a major etiological factor in oropharyngeal carcinoma, its contribution to tongue squamous cell carcinoma appears to be limited, with low prevalence and minimal oncogenic activity reported in tumors of the oral tongue. In contrast, genetic susceptibility and dysregulation of key molecular pathways may be particularly relevant in younger patients and in cases lacking traditional risk exposures. A better understanding of these interactions between environmental, local, viral, and genetic factors may improve risk stratification, support earlier diagnosis, and facilitate the development of targeted prevention and surveillance strategies for patients at increased risk of TSCC.

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