

# Characteristics of oral squamous cell carcinoma in users or non users of tobacco and alcohol

## Características do carcinoma bucal de células escamosas em usuários ou não usuários de tabaco e álcool

### Abstract

Tobacco and alcohol are the main extrinsic etiological factors for the genesis of oral squamous cell carcinoma (SCC), but it is still not clear if the presence of these factors interfere with clinical, pathologic and molecular characteristics or with the prognosis of the disease. In the present study, these characteristics were reviewed, establishing comparisons between the lesions of patients exposed and not exposed to tobacco and alcohol. We observed that oral SCC in non smokers and non alcohol drinkers occur mainly in female patients, under 50 or over 70 years old. The lesions tend to be less aggressive in this group of patients and have a better prognosis. The molecular characteristics of these malignant tumors also appear to be influenced by the presence of these habits, once mutations of p53 have been associated with tobacco and alcohol use. The understanding of the differences between the neoplasms of these two groups of patients can contribute to the management of this cancer, which could lead to advances in the determination of more appropriate therapeutic measures.

**Key words:** Oral cancer; risk factors; prognosis

### Resumo

O tabaco e o álcool são os principais fatores etiológicos extrínsecos associados à gênese do carcinoma bucal de células escamosas (CCE), mas não está claro se estes fatores interferem nas características clínico-patológicas, moleculares ou no prognóstico da doença. No presente estudo, essas características foram revisadas, estabelecendo-se comparações entre as lesões de pacientes usuários ou não de tabaco e álcool. Observou-se que carcinomas bucais de não fumantes e não etilistas ocorrem, preferencialmente, em pacientes do sexo feminino, em faixa etária inferior a 50 ou superior 70 anos. Neste grupo de indivíduos, as lesões tendem a ser menos agressivas e apresentam melhor prognóstico. O tabagismo e o etilismo também parecem influenciar as características moleculares do carcinoma bucal, uma vez que mutações da proteína p53 nas lesões têm sido associadas a esses fatores de risco. A compreensão das diferenças entre os CCE bucais desses dois grupos de pacientes pode contribuir para uma melhor abordagem e avanços no desenvolvimento de medidas terapêuticas mais adequadas frente a esta neoplasia.

**Palavras-chave:** Câncer bucal; fatores de risco; prognóstico

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## Introduction

Oral cancer represents the 7th most common type of malignancy in Brazil, with about 14,000 new cases diagnosed per year. Squamous cell carcinoma (SCC) is the most common malignant tumor of this anatomic site, and in approximately 80% of cases, it is associated with extrinsic factors such as the use of tobacco, alcohol or both (1,2). This cancer occurs preferentially in the tongue, buccal mucosa and gingiva, exhibiting predilection for men over 50 years old (2,3). In the last years, however, there has been an increase in the incidence of this lesion in younger patients, that is, under 45 years old (4,5).

Tobacco use constitutes the primary factor (90%) for the development of oral SCC. Tobacco contains about 50 substances with carcinogenic potential, such as nitrosamines and aromatic hydrocarbons (6). Besides, smoke raises the temperature of the mouth, which contributes to its deleterious effect. The involvement of alcohol is not so clear with respect to tobacco. While studies suggest that the risk of developing oral SCC in patients who are alcohol drinkers (non-smokers) is slightly higher (7), others demonstrate that excessive consumption of alcoholic beverages is an important factor for the occurrence of this cancer (8,9). Alcohol is associated with cell hyperproliferation (which increases vulnerability to inhaled or ingested carcinogens), production of metabolites with carcinogenic action, such as acetaldehyde, induction of enzymes that activate pro-carcinogens and reduction of retinoic acid (10). The consumption of alcohol, especially ethanol, interferes with DNA repair and can have an immunosuppressive effect (11).

Simultaneous exposure to tobacco and alcohol is significantly associated with a higher risk of developing oral SCC, because these substances show a synergistic effect (12-15). Despite the strong connection with the genesis of oral cancer, there are controversies about whether drinking alcohol and tobacco use is associated with clinical and molecular patterns of this lesion and with a better or worse prognosis in patients with the disease. In this study, we conducted a review of the clinicopathologic and molecular characteristics and biological behavior of head and neck SCC, with emphasis on oral cancer, comparing the lesions of smokers and alcohol drinkers with individuals not exposed to these risk factors.

## Clinicopathologic characteristics and prognosis

Studies have demonstrated that head and neck SCC in non alcohol drinkers and non smokers develops more often in the more advanced age group and in women (16-19). Lo et al. (20) found that in individuals exposed to risk factors (chewing tobacco, smoking and alcohol), the lesion developed a mean of 12 years earlier than in those not exposed. Meanwhile, Dahlstrom et al. (21) on evaluating 1303 individuals with SCC, observed that the group of non smokers and non alcohol drinkers was significantly

younger. Harris et al. (22) evaluated 78 young patients with SCC of this region, aged between 18 and 39 years. The non smokers and non alcohol drinkers had a lower mean age and women were more often affected in comparison to exposed individuals. However, in relation to age group for the development of SCC of head and neck in patients not exposed to these risk factors, age extremes seem to be more often observed, that is, individuals under 50 or over 70 years old are more affected (21).

In patients not exposed to the risk factors analyzed, the lesions develop primarily in the oral cavity, especially in the anterior tongue, alveolar ridge and gingiva (19,21,23). In individuals who smoke and drink alcohol, the tumors occur mostly in the larynx, hypopharynx, posterior tongue, retro-molar trigone and mouth floor (21,23). In relation to the size of the lesion and clinical stage, the studies yielded conflicting results on comparing patients exposed and not exposed to risk factors. Schmidt et al. (23) e Bachar et al. (5) did not observe a significant difference with respect to these clinical parameters between smokers and non smokers. Meanwhile, Dahlstrom et al. (21) e Harris et al. (22) found a greater percentage of tumors in stage I in patients not exposed to the risk factors. Kruse et al. (19) also found that the majority of oral SCC cases in non smokers and non alcohol drinkers were T1 or T2.

Link et al. (16) observed in a group of patients who were non smokers, more cases of moderately and poorly differentiated SCC. Meanwhile, more recent studies have demonstrated that in patients not exposed to smoking and alcohol the lesions tended to be classified as well or moderately differentiated, while in exposed individuals, a lower degree of cell differentiation has been observed (5,19).

Studies indicate that head and neck cancer in smokers can show a biologically more aggressive phenotype compared to patients who are non smokers. Mayne et al. (24) followed patients treated for oral, pharynx and larynx carcinoma and observed that smokers and alcohol drinkers showed a worse prognosis. Alcohol use increases risk of mortality in a dose-dependent way and after diagnosis, patients who continue with the alcohol habit show a worse survival.

A lower five-year survival rate was observed in patients who chewed tobacco, but no significant difference was found in survival between smokers and non smokers, nor between alcohol drinkers and non alcohol drinkers (20). Harris et al. (22) did not find a difference between groups of smokers/alcohol drinkers and non smokers/non alcohol drinkers with respect to the disease-free survival rate. However, they suggested a better general survival in 10 years for the group of individuals not exposed to the risk factors. On the other hand, Pytynia et al. (25) found that patients with head and neck SCC who did not smoke showed a longer mean time of general, disease-free survival compared to smokers. Ide et al. (14) and Fortin et al. (26) also demonstrated that smokers and alcohol drinkers, showed survival rates and local control of the disease that were inferior to that in patients not exposed to these risk factors. According to Girod et al. (27), female smokers with a diagnosis of oral and oropharynx cancer show a worse prognosis.

Patients who smoke also show greater rates of recurrence of the lesion in comparison to non smokers. Ex-smokers, in turn, show intermediate rates between the above groups (28). Do et al. (29) and Sassi et al. (30) observed that smokers and alcohol drinkers had a significantly greater risk of developing a second primary tumor in comparison to non smokers, especially if they continued the habit after diagnosis of the lesion. Meanwhile, on comparing the pattern of recurrence in cases of SCC of the tongue, Bachar et al. (5) did not observe a significant difference with respect to local and regional recurrence between patients exposed and not exposed to smoking and alcohol. The patients younger than 40 years, not exposed to the risk factors analyzed, showed a worse prognosis, suggesting that other factors besides smoking and alcohol drinking play a role in the pathogenesis of tumors of the tongue in this group of individuals.

Besides increasing the risk recurrence of the disease, smoking and alcohol drinking can reduce the efficacy of the treatment (31,32). Chen et al. (33) observed that non smokers showed a better prognosis after radiotherapy than did smokers who continued their habit. Patients who continue to smoke during radiotherapy have a poorer response to treatment, shorter post-radiotherapy survival, worse locoregional control of the disease and higher rate of complications with radiotherapy (34,35).

## Molecular characteristics

The detection of p53 protein, which implies the presence of stabilized mutated protein, has been associated with a poor prognosis of SCC of the head and neck. Siegelmann-Danieli et al. (36) did not find a significant association between the immunodetection of p53 protein in SCC of the tongue with consumption of alcohol and tobacco. On the other hand, Van Oijen et al. (37) and Farshadpour et al. (38) reported that the immunodetection of p53 protein in the mucosa adjacent to the tumor in head and neck SCC patients was significantly greater in those who were smokers and alcohol drinkers.

Studies have shown that p53 mutations are more frequent in head and neck SCC from smokers and/or alcohol drinkers (39-41). Brennan et al. (39) found mutations of p53 protein in 58% of patients with head and neck SCC who used tobacco and alcohol. In patients who were smokers the mutation occurred in 33% of cases, and in individuals not exposed to the risk factors, in 17% of cases. Hsieh et al. (40) also found that the neoplasms of patients who drank alcohol exhibited an increase in the incidence of mutation of p53. When alcohol consumption is associated with smoking, this mutation is more significant, demonstrating the synergistic effect of these risk factors. In addition to higher rates of mutation of protein p53, head and neck SCC from smokers showed percentage of infection by HPV lower, loss of heterozygosity in 3p, 4q, and 11q13 and the greater number of chromosome losses (41). Tumors of patients who did not smoke exhibit a lower frequency of common genetic alterations, suggesting that subjacent mutations can be unknown in these neoplasms (41).

Immunodetection of the marker Ki67 in head and neck SCC has been also compared between patients exposed and not exposed to risk factors. Van Oijen et al. (42) found an increase in cell proliferation in the oral epithelium of smokers, both patients with carcinoma and healthy individuals. Ex-smokers in both groups had a tendency toward increased cell proliferation, suggesting that even after quitting, the epithelial alterations persist. On the other hand, Farshadpour et al. (38) did not find differences in the immunodetection of Ki-67 in the mucosal epithelium adjacent to head and neck SCC from patients exposed and not exposed to tobacco and alcohol.

VEGF (vascular endothelial growth factor) have a positive association with a more advanced clinical stage of oral SCC and may have prognostic value in patients with this malignancy. Meanwhile, Faustino et al. (43) and Kyzas et al. (44) found no correlation between the immunoreactivity of that angiogenic marker with smoking and alcohol consumption in patients with oral SCC.

## Final considerations

The dental literature shows that tobacco and alcohol use plays a major role among the etiological factors involved in the genesis of oral SCC. When these substances are combined, the carcinogenic effect becomes potentiated due to their synergistic effect (12-15). However, it is not clear if the presence or absence of these habits affect the clinicopathologic and molecular characteristics of the tumor, as well as the prognosis of the patient. Previous studies demonstrated that SCC of head and neck in patients who are non smokers and non alcohol drinkers occurred predominantly in females and individuals under 50 or over 70 years are more affected (16-19,21,22).

The lesions of patients who are non smokers and non alcohol drinkers tend to show a less aggressive behavior, that is, the majority are classified as T1 or T2, and with respect to degree of histological differentiation, they are usually better differentiated (19,22,41,42). Besides, in these patients, the risk of tumor recurrence is lower and survival and prognosis are better (25,26,28,29). Response to radiotherapy also tends to be better in patients who are non smokers or who quit the habit during treatment (33-35).

The expression of proteins associated with the regulation of the cell cycle and mutations of various tumor suppressor genes have been investigated in oral cancer. However, few studies have compared the molecular characteristics of tumors of patients exposed and not exposed to tobacco and alcohol. The p53 protein is an established marker in the literature; its inactivation affects DNA damage repair and apoptosis, causing an increase in genetic instability which can lead to an accumulation of mutations. The expression of this protein appears to be influenced by tobacco and alcohol use, which causes its mutation (37,39,40). On the other hand, smoking and drinking habits do not seem to affect the immunodetection of VEGF, which is also considered a prognostic marker in patients with oral SCC (43,44).

The clinicopathologic patterns and biological behavior of SCC of the head and neck in smokers and alcohol drinkers compared to non smokers and non alcohol drinkers are distinct. Oral cancer can show a biologically more aggressive phenotype in smokers and alcohol drinkers. The analysis

of these patterns may contribute to the understanding and management of this neoplasm, which could lead to advances in the determination of more appropriate therapeutic measures and reduction of morbidity and mortality.

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