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.

Kew 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, retromolar 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 d predominately 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 to 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.

References

1. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612-9.
2. Andisheh-Tadbir A, Mehrabani D, Heydari ST. Epidemiology of squamous cell carcinoma of the oral cavity in Iran. J Craniofac Surg 2008;19:1699-702.
3. Pithan SA, Cherubini K, Figueiredo MA, Yurgel LS. Epidemiological profile of oral squamous cell carcinoma in patients attended at Stomatology Division of hospital São Lucas - PUCRS. Rev Odonto Ciênc 2004;19:126-30.
4. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya S. An analysis of risk factors for oral cancer in young people: a case-control study. Oral Oncol 2004;40:304-13.
5. Bachar G, Hod R, Goldstein DP, Irish JC, Gullane PJ, Brown D et al. Outcome of oral tongue squamous cell carcinoma in patients with and without known risk factors. Oral Oncol 2011;47:45-50.
6. Gupta PC, Murti PR, Bhonsle RB. Epidemiology of cancer by tobacco products and the significance of TSNA. Crit Rev Toxicol 1996;26:183-98.
7. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst 2007;99:777-89.
8. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer 2001;85:1700-5.
9. Polesel J, Dal Maso L, Bagnardi V, Zucchetto A, Zambon A, Levi F et al. Estimating dose-response relationship between ethanol and risk of cancer using regression spline models. Int J Cancer 2005;114:836-41.
10. Rossing MA, Vaughan TL, McKnight B. Diet and pharyngeal cancer. Int J Cancer 1989;44:593-7.
11. Gerson SJ. Oral cancer. Crit Rev Oral Biol Med 1990;1:153-66.
12. Talamini R, Bosetti C, La Vecchia C, Dal Maso L, Levi F, Bidoli E, Negri E, Pasche C, Vaccarella S, Barzan L, Franceschi S. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. Cancer Causes Control 2002;13:957-64.
13. De Stefani E, Boffetta P, Deneo-Pellegrini H, Ronco AL, Acosta G, Ferro G et al. The effect of smoking and drinking in oral and pharyngeal cancers: a case-control study in Uruguay. Cancer Lett 2007;246:282-9.
14. Ide R, Mizoue T, Fujino Y, Hoshiyama Y, Sakata K, Tamakoshi A et al. Cigarette smoking, alcohol drinking, and oral and pharyngeal cancer mortality in Japan. Oral Dis 2008;14:314-9.
15. Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C. Alcohol and tobacco use, and cancer risk for upper aerodigestive tract and liver. Eur J Cancer Prev 2008;17:340-4.
16. Link JO, Kaugars GE, Burns JC. Comparison of oral carcinomas in smokeless tobacco users and nonusers. J Oral Maxillofac Surg 1992;50:452-5.
17. Wiseman SM, Swede H, Stoler DL, Anderson GR, Rigual NR, Hicks WL Jr et al. Squamous cell carcinoma of the head and neck in nonsmokers and nondrinkers: an analysis of clinicopathologic characteristics and treatment outcomes. Ann Surg Oncol 2003;10:551-7.
18. Farshadpour F, Hordijk GJ, Koole R, Slootweg PJ. Non-smoking and non-drinking patients with head and neck squamous cell carcinoma: a distinct population. Oral Dis 2007;13:239-43.
19. Kruse AL, Bredell M, Grätz KW. Oral squamous cell carcinoma in non-smoking and non-drinking patients. Head Neck Oncol 2010;2:24.
20. Lo WL, Kao SY, Chi LY, Wong YK, Chang RC. Outcomes of oral squamous cell carcinoma in Taiwan after surgical therapy: factors affecting survival. J Oral Maxillofac Surg 2003;61:751-8.
21. Dahlstrom KR, Little JA, Zafereo ME, Lung M, Wei Q, Sturgis EM. Squamous cell carcinoma of the head and neck in never smoker-never drinkers: a descriptive epidemiologic study. Head Neck 2008;30:75-84.
22. Harris SL, Kimple RJ, Hayes DN, Couch ME, Rosenman JG. Never-smokers, never-drinkers: unique clinical subgroup of young patients with head and neck squamous cell cancers. Head Neck 2010;32:499-503.

23. Schmidt BL, Dierks EJ, Homer L, Potter B. Tobacco smoking history and presentation of oral squamous cell carcinoma. J Oral Maxillofac Surg 2004;62:1055-8.

24. Mayne ST, Cartmel B, Kirsh V, Goodwin WJ Jr. Alcohol and tobacco use prediagnosis and postdiagnosis, and survival in a cohort of patients with early stage cancers of the oral cavity, pharynx, and larynx. Cancer Epidemiol Biomarkers Prev 2009;18:3368-74.

25. Pytynia KB, Grant JR, Etzel CJ, Roberts DB, Wei Q, Sturgis EM. Matched-pair analysis of survival of never smokers and ever smokers with squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22:3981-8.

26. Fortin A, Wang CS, Vigneault E. Influence of smoking and alcohol drinking behaviors on treatment outcomes of patients with squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys 2009;74:1062-9.

27. Girod A, Mosseri V, Jouffroy T, Point D, Rodriguez J. Women and squamous cell carcinomas of the oral cavity and oropharynx: is there something new? J Oral Maxillofac Surg 2009;67:1914-20.

28. Khuri FR, Kim ES, Lee JJ, Winn RJ, Benner SE, Lippman SM et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. Cancer Epidemiol Biomarkers Prev 2001;10:823-9.

29. Do KA, Johnson MM, Doherty DA, Lee JJ, Wu XF, Dong Q et al. Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States). Cancer Causes Control 2003;14:131-8.

30. Sassi LM, Cervantes O, Schussel JL, Stramandinoli RT, Guebur MI, Ramos GH. Incidence of a second primary oral cancer tumors: a retrospective study. Rev Odonto Ciênc 2010; 25:367-70.

31. Berger MR, Zeller WJ. Interaction of nicotine with anticancer treatment. Klin Wochenschr 1988;66:127-33.

32. Dasgupta P, Kinkade R, Joshi B, Decook C, Haura E, Chellappan S. Nicotine inhibits apoptosis induced by chemotherapeutic drugs by up-regulating XIAP and survivin. Proc Natl Acad Sci USA 2006;103:6332-7.

33. Chen AM, Chen LM, Vaughan A, Farwell DG, Luu Q, Purdy JA et al. Head and neck cancer among lifelong never-smokers and ever-smokers: matched-pair analysis of outcomes after radiation therapy. Am J Clin Oncol 2011;34:270-5.

34. Chen AM, Chen LM, Vaughan A, Sreeraman R, Farwell DG, Luu Q et al. Tobacco smoking during radiation therapy for head-and-neck cancer is associated with unfavorable outcome. Int J Radiat Oncol Biol Phys 2011;79:414-9.

35. Browman GP, Wong G, Hodson I, Sathya J, Russell R, McAlpine L et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med 1993;328:159-63.

36. Siegelmann-Danieli N, Ben-Izhack O, Hanlon A, Ridge JA, Stein ME, Khandelwal V et al. P53 alteration in oral tongue cancer is not significantly associated with age at diagnosis or tobacco exposure. Tumori 2005;91:346-50.

37. van Oijen MG, van de Craats JG, Slootweg PJ. P53 overexpression in oral mucosa in relation to smoking. J Pathol 1999;187:469-74.

38. Farshadpour F, Hordijk GJ, Koole R, Slootweg PJ. Head and neck squamous cell carcinoma in non-smoking and non-drinking patients with multiple tumors: etiologic significance of p53 and Ki-67 in non-tumorous epithelium. J Oral Pathol Med 2008;37:549-54.

39. Brennan JA, Boyle JO, Koch WM, Goodman SN, Hruban RH, Eby YJ, Couch MJ, Forastiere AA, Sidransky D. Association between cigarette smoking and mutation of the p53 gene in squamous-cell carcinoma of the head and neck. N Engl J Med 1995;332:712-7.

40. Hsieh LL, Wang PF, Chen IH, Liao CT, Wang HM, Chen MC, Chang JT, Cheng AJ. Characteristics of mutations in the p53 gene in oral squamous cell carcinoma associated with betel quid chewing and cigarette smoking in Taiwanese. Carcinogenesis 2001;22: 1497-503.

41. Koch WM, Lango M, Sewell D, Zahurak M, Sidransky D. Head and neck cancer in nonsmokers: a distinct clinical and molecular entity. Laryngoscope 1999;109:1544-51.

42. van Oijen MG, Gilsing MM, Rijksen G, Hordijk GJ, Slootweg PJ. Increased number of proliferating cells in oral epithelium from smokers and ex-smokers. Oral Oncol 1998;34:297-303.

43. Faustino SE, Oliveira DT, Nonogaki S, Landman G, Carvalho AL, Kowalski LP. Expression of vascular endothelial growth factor-C does not predict occult lymph-node metastasis in early oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2008;37:372-8.

44. Kyzas PA, Geleff S, Batistatou A, Agnantis NJ, Stefanou D. Evidence for lymphangiogenesis and its prognostic implications in head and neck squamous cell carcinoma. J Pathol 2005;206:170-7.