Recurrent sores by ill-fitting dentures and intra-oral squamous cell carcinoma in smokers

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Abstract

Objectives: To examine whether denture use and recurrent sores caused by ill-fitting dentures are associated with intra-oral squamous cell carcinoma (IO-SCC) in individuals exposed to tobacco.

Methods: We conducted a hospital-based case-control study. The study population comprised 124 patients with IO-SCC and the same number of controls (individually paired according to gender and age) recruited from outpatient units of the same hospital. Conditional logistic regression analysis assessed the effect of denture use and recurrent oral sores by ill-fitting dentures, adjusted by covariates on the lifetime exposure to alcohol and tobacco, socioeconomic standings, and dietary patterns.

Results: The use of dentures showed no association with IO-SCC [adjusted odds ratio (OR) 1.40, 95 percent confidence interval 0.51-3.87, $P = 0.513$] in an assessment controlled by socioeconomic position, lifetime exposure to alcohol and tobacco, and dietary patterns. However, the report of recurrent sores caused by ill-fitting dentures showed significant association with the disease (adjusted OR 4.58, 95 percent confidence interval 1.52-13.76, $P = 0.007$).

Conclusions: The association between recurrent oral sores caused by ill-fitting dentures and squamous cell carcinoma of the mouth in smokers is in agreement with the hypothesis that the chronic physical irritation of oral mucosa contributes to the topical carcinogenic effect of tobacco, which must be taken into careful consideration in the planning of dental services for adults and the elderly.

Introduction

Tobacco smoking and alcohol consumption are prominent risk factors for intra-oral squamous cell carcinoma (IO-SCC), the most incident neoplasm of the head and neck worldwide. Gender and age differences in incidence and mortality are also well documented (1). Epidemiologic studies have also acknowledged the etiologic contribution of dietary patterns to IO-SCC (2,3). Assessment of additional risk factors must be adjusted by conditions already known to be associated with the disease.

The assessment of association between mouth neoplasm and specific conditions of dental status has not produced conclusive results (4). Recurrent sores of oral mucosa caused by ill-fitting denture, tooth brushing frequency, use of mouthwash and teeth whitening products are some of these conditions, which inspired studies searching for factors potentially associated with the incidence of IO-SCC (5-7). Continuing efforts to elucidate the risk factors may represent an important implement for the prevention of IO-SCC and for the promotion of healthy lifestyles.

The objective of this study was to examine whether denture use and recurrent sores caused by ill-fitting dentures have association with IO-SCC in individuals exposed to tobacco.

Methods

This study used a hospital-based case-control design (8). Patients undergoing treatment for IO-SCC (C00.3 to C06, *International Classification of Diseases, 10th Revision*) in the

head and neck surgery center of a major Brazilian hospital (Hospital das Clínicas, School of Medicine, University of São Paulo) from July 2006 to June 2007 were eligible for the case group. This is a public, free-of-cost health-care facility, which assists mostly low-income patients.

Two specifically trained examiners interviewed 124 individuals (22 women and 102 men) presenting tumors at different sites of the mouth: cheek mucosa (5), retromolar area (6), lower lip, inner aspect (10), gum (11), palate (17), floor of mouth (27), and tongue (48). Fourteen percent of them were aged below 50 years, 37 percent from 50 to 59 years, 30 percent from 60 to 69 years, and 19 percent were aged 70 years or above. All participants of the study dwelled in urban settings of the city of São Paulo.

The control group comprised an equal number of patients assisted in outpatient-care units of the same hospital, without prior or current experience of cancer, and with treatment needs unrelated to dental status. Controls were individually paired according to gender and age ($\pm$5 years) with the cases. The hypothesis addressed the association between oral status and tobacco consumption; therefore, only current smokers and those who quitted after the diagnosis were included.

All patients were interviewed immediately after their clinical consultation in a separate room of the ambulatory. The study observed Brazilian and international statutes on ethics in research involving human beings; ethical clearance was given by the research committees of the participating institutions (School of Dentistry and School of Medicine, University of São Paulo).

Interviews were conducted using a 30-minute structured questionnaire on socioeconomic status (SES), behavior (patterns of diet, smoking, and alcohol drinking), and dental status. SES was assessed in terms of education (years of formal schooling) and family income (number of Brazilian minimum wages, a standard measurement of monthly income, roughly equivalent to US$165 during the study period). The assessment of dietary patterns used an extensive food frequency questionnaire specifically devised for a previous study (9) and comprising usual components of Brazilian dietary patterns. Subjects were instructed to answer taking into account their usual diet during adulthood, i.e., after 20 years of age, discharging modifications occurred during the year preceding the diagnosis. To avoid misinterpretation of respondents in the case group, separate annotations were made for the current restrictions of food intake associated with the disease or the onset of treatment. Similarly for the control group, answers related to the most recent year were not considered.

The hypothesis of dietary patterns potentially associating with IO-SCC was assessed by the frequency of intake of three food items: bacon, deep fried foods, and fruits. Usually added to beans (one of the most common food item in the Brazilian diet) for flavoring, bacon was used as a surrogate for animal fat consumption. Deep fried foods (saturated fat) referred to different items that are common in the Brazilian diet: French fries, manioc or cassava, deep fried pastries and stuffed tidbits, a high-fat hors d'oeuvres containing animal protein. The assessment of fruit consumption was unspecific; bananas, apples, and oranges are some of the most frequently consumed fruits in Brazil.

The assessment of lifetime consumption of tobacco and alcohol considered the frequency, duration, and type of product consumed. Tobacco was assessed in terms of packs comprising 20 cigarettes; a cigar was considered as corresponding to four cigarettes, and each pipe serve corresponded to three cigarettes (10). One standardized drink was considered to contain 15.6 mL of pure ethanol, which corresponds to 312 mL of beer, 130 mL of wine, 52 mL of liqueurs, and 38 mL of distilled spirits (11). Results were expressed in terms of daily-packs $\times$ year (tobacco), and daily-drinks $\times$ year (alcohol). Figures for the lifetime consumption of alcohol and tobacco were subsequently multiplied for each participant, thus assessing the concurrent effect of alcohol and tobacco consumption on IO-SCC. Covariates assessing the cumulative exposure to tobacco and alcohol were categorized by tertiles of the overall (cases and controls) distribution.

The main exposures of interest are denture use and recurrent sores of oral mucosa by ill-fitting dentures. Patients were asked to inform on these conditions as referring to adulthood (from 20 years of age up to the year that preceded the diagnosis); dental examinations were not performed because case-control studies require the retrospective assessment of exposures. Direct questions asked patients if they used dentures, if the use of ill-fitting dentures caused oral sores, and whether this complaint was frequent or not.

Explanatory variables were preferably classified into three categories, according to the progressive level of exposure. This strategy aimed at ordering the gradient of exposure to protective and deleterious factors, and thus to assess the effect of dose response in the distribution of cases and controls. For each explanatory variable, the lowest level of exposure was considered the reference category, whereas the remaining categories were classified into an ordinal scale expressing comparison groups with cumulative higher exposure to the socioeconomic and behavioral factors (8).

Data analyses used conditional logistic regression (12). The appraisal of associations used point and interval crude estimates for the odds ratio (OR), as calculated by maximum likelihood estimation for paired analysis, and unadjusted for the remaining covariates. For variables classified into ordinal scales, comparison groups were pooled in the regression analysis and one single OR was assessed for each covariate, which represents a simple exponential function of exposure (8).

The subsequent fitting of a multivariate model observed a conceptual framework organizing covariates into different

Table 1 Conceptual Framework of the Assessment of the Effect of Socioeconomic Status (SES), Behavior and Dental Status on Intra-Oral Squamous Cell Carcinoma in Smokers: Summary Steps. Conditional Logistic Regression Analysis, Paired According to Gender and Age

Model	Equation (explanatory variables)	Interpretation
Distal covariates: SES		
Level 1: education	Education	Overall effect of education; not adjusted for mediating variables
Level 2: family income	Family income + education	Effect of family income adjusted for the confounding role of education
Mesial covariates: behavior		
Level 1: tobacco and alcohol	SES + tobacco	Effect of tobacco adjusted for the confounding role of education and income
	SES + alcohol	Effect of alcohol adjusted for the confounding role of education and income
Level 2: food intake	SES + tobacco + alcohol + food intake	Effect of the frequent consumption of fruits, bacon, and deep fried foods adjusted for the confounding role of themselves and of education, income, tobacco, and alcohol
Proximal covariates: dental status	SES + behavior + dental status	Effect of the use of dentures and recurrent sores caused by ill-fitting dentures, adjusted for the confounding role of education, income, tobacco, alcohol, and food intake

levels (Table 1) (13). This analytical scheme allowed to assess the effect of denture use and recurrent sores of oral mucosa on the risk of IO-SCC as adjusted by previously known conditions associated with the disease. Gender and age were controlled by individual pairing of cases and controls. Education and family income were classified as distal determinants of disease, i.e., SES covariates were considered to influence both behavioral factors and dental status. Smoking, alcohol drinking, and diet were classified as mesial determinants of disease, i.e., behavioral factors were considered to influence dental status. At last, denture use and recurrent oral sores were classified as proximal determinants of disease, i.e., the influence of covariates on dental status on behavior and socioeconomic conditions was not considered in this study.

Two-sided *P*-values lower than 0.05 were considered indicative of significant association between covariates and the outcome. The statistical analysis used the Stata 8.0 2003 (Stata Corporation, College Station, TX, USA) software.

Results

A relatively poor socioeconomic profile affected both the case and control groups (Table 2). More than half of the cases earned less than two Brazilian minimum wages; 43 percent of controls reported less than 5 years of formal schooling. The unadjusted assessment of associations identified a higher likelihood of poor socioeconomic standings for cases than that for controls: education ranked an unadjusted OR of 0.40 (95 percent confidence interval: 0.21-0.76), income ranked OR 0.22 (95 percent CI 0.10-0.46).

Differential levels of tobacco smoking and alcohol consumption were identified for the case and control groups. Even though the sample exclusively comprised smokers, cumulative exposure to tobacco was higher for cases than for controls. Cumulative exposure to alcohol consumption was also indicated as risk factor for IO-SCC (Table 2). Usual

food items of the Brazilian diet also associated with the outcome, as related to the frequency of intake. Fruits were indicated as protective, whereas high-fat foods were identified as deleterious.

Poor dental status was largely prevalent in both samples: 63 percent of controls used dentures; 40 percent of cases complained of recurrent sores as a result of ill-fitting dentures (Table 2). The use of dentures, irrespective of being well- or ill-adjusted, and the self-report of oral sores associated significantly ($P < 0.05$) with IO-SCC in the assessment of crude ORs (Table 2).

However, the effect of proximal exposures (use of dentures, oral sores) was modified when distal socioeconomic and mesial behavioral characteristics were considered. When adjusted by income, education, tobacco and alcohol consumption, and dietary patterns, the association between denture use and IO-SCC was not statistically significant (OR = 2.09, 95 percent CI 0.88-4.94, $P = 0.090$, non-tabled result). When additionally adjusted by recurrent sores as a result of ill-fitting dentures, the OR related to the use of dental prosthesis reduced its magnitude and significance even further ($P = 0.513$, Table 3). Contrariwise, recurrent sores caused by ill-fitting dentures remained significantly associated with IO-SCC after being adjusted in the multivariate model ($P = 0.007$, Table 3).

Discussion

The most important finding of the study is the association between IO-SCC and the self-report of recurrent sores by ill-fitting dentures, in an assessment controlled by socio-demographic factors, lifetime consumption of alcoholic beverages and tobacco, and aspects of diet. As all patients were smokers, this result suggests that the chronic physical irritation of mouth epithelium by an inappropriately fitted denture may represent an effective adjunct for the topical

Table 2 Distribution of Cases and Controls According to Socioeconomic Status, Cumulative Exposure to Tobacco and Alcohol, Dietary Patterns, and Dental Status

Variables	Categories	Cases	Controls
Socioeconomic status			
Education	<5 years of study	73	53
	5-8 years of study	30	32
	>8 years of study	21	39
Income	<2 Brazilian MW*	63	41
	2-5 Brazilian MW*	49	40
	>5 Brazilian MW*	12	43
Behavior			
Cumulative consumption of tobacco	<20	37	51
(daily packs × year)	20-40	43	42
	>40	44	31
Cumulative consumption of alcohol	<12	23	58
(daily drinks × year)	12-180	38	43
	>180	63	23
Fruit intake, frequency	<3 times per week	90	48
	3-6 times per week	19	45
	>6 times per week	15	31
Bacon intake, frequency	None at all	23	69
	1-3 times per week	40	34
	>3 times per week	61	21
Intake of deep fried food frequency	<3 times per week	35	98
	≥3 times per week	89	26
Dental status			
Use of denture	No	29	46
	Yes	95	78
Recurrent sores by ill-fitting dentures	No	75	110
	Yes	49	14

* Brazilian MW (minimum wage) ≈ US$165.

carcinogenic effect of tobacco. Previous studies also reported poorly fitting complete dentures as significantly associated with IO-SCC in assessments controlled by relevant covariates (4,5,14).

Tobacco-derived carcinogens may be absorbed by oral tissues more easily in the presence of oral sores; an intact oral mucosa would reduce the ingress of dissolved carcinogens. Studies assessing the continued effect of ethanol on cellular structure and function suggest that a continued exposure of oral epithelia to alcoholic beverages contributes to the carcinogenic effect of tobacco, because alcohol may influence intracellular (endocytosis) and intercellular (permeability) pathways (15).

Dietary patterns also have topical effects on oral mucosa, which may either reduce or contribute to the absorption of carcinogenic components of tobacco. Greenwald *et al.* (16)

Table 3 Unadjusted and Adjusted Assessment of the Effect of Socioeconomic Status, Behavior and Dental Status on Intra-Oral Squamous Cell Carcinoma in Smokers. Conditional Logistic Regression Analysis, Multivariate Model, Paired According to Gender and Age

Covariates	Unadjusted odds ratio (95% confidence interval)	P-value	Adjusted odds ratio (95% confidence interval)	P-value
Education	0.40 (0.21-0.76)	0.005	0.40 (0.21-0.76)	0.005
Income	0.22 (0.10-0.46)	<0.001	0.26 (0.12-0.59)	0.001
Lifetime consumption of tobacco	1.94 (1.03-3.66)	0.039	2.21 (1.10-4.46)	0.026
Lifetime consumption of alcohol	10.01 (4.10-24.45)	<0.001	8.41 (3.18-22.20)	<0.001
Fruit intake, frequency	0.22 (0.11-0.46)	<0.001	0.30 (0.11-0.83)	0.020
Bacon intake, frequency	11.48 (4.68-28.15)	<0.001	5.24 (1.50-18.36)	0.010
Deep fried food intake, frequency	8.86 (4.27-18.43)	<0.001	4.08 (1.67-9.96)	0.002
Use of denture	2.00 (1.12-3.58)	0.020	1.40 (0.51-3.87)	0.513
Recurrent sores by ill-fitting dentures	4.89 (2.39-10.01)	<0.001	4.58 (1.52-13.76)	0.007

discussed the possible mechanisms through which fat intake may influence carcinogenesis, including effects on the cell membrane integrity, increase in lipid peroxidase, and impairment of nutrient metabolism. Woutersen *et al.* (17) stated that, although no general biological mechanism has been fully established to explain the modulating effect of fat on carcinogenesis, there are convincing indications that dietary lipids can significantly alter the membrane fatty acid composition of both normal and neoplastic cells, thus modifying the physical chemical environment of oral mucosa exposed to tobacco. These arguments are in agreement with the current observation of deleterious effects for the usual intake of fat foods in individuals exposed to tobacco, and the protective effect of fruits, which may cleanse the oral mucosa from residual fat. These arguments also justify the inclusion of covariates on diet as controls for the assessment of oral sores caused by ill-fitting dentures as a risk factor for IO-SCC.

The burden of oral cancer has already been reported to be associated with the socioeconomic position in the Brazilian context (18,19); thus, adjusting the current assessment by SES covariates is important. The unadjusted assessment indicated denture use to be significantly associated with the disease, although this association was confounded by the absent control for socioeconomic standings. When adjusted with education and income, this association led to a two-sided *P*-value higher than 0.05, because denture use was unequally distributed among socioeconomic strata, i.e., poorer individuals are more likely to use dentures, and controls presented a better socioeconomic profile than the cases. Furthermore, when concurrently adjusted with recurrent oral sores as result of ill-fitting dentures, the use of dentures reduced its association with the outcome even further, which reinforces the hypothesis that denture use is a safe condition, as refers to the risk of IO-SCC.

The absent association between denture use and the outcome variable in the multivariate model, even when the quality of fitting was not considered as a control variable, is reassuring against unjustified apprehension with dental prosthesis. This observation is in agreement with previous assessments performed in the same city (20), and in broader databases, which also focused on smokers (6).

Overall, patients were collaborative and willing to report on personal issues to the hospital staff. However, this study adopted restrictive eligibility criteria, which yielded difficulties for assigning a larger number of cases. A single hospital was assessed, and nonsmoker patients and those with pain or speech disabilities were not interviewed; no proxy respondent was allowed. Restrictive eligibility criteria resulted in a sample size too reduced to allow the specific assessment of risk factors by the site of neoplasm. However, a previous assessment of a larger sample concluded that denture sores (usually affecting the gum and buccal sulcus) associated with tongue

cancer (5), which suggests that the deleterious effect of ill-fitting dentures may spread to the whole stomatognathic system.

The biological mechanisms explaining how recurrent denture sores in specific sites of the mouth may contribute to carcinogenesis in other parts of the mouth cannot be ascertained by a case-control study, and demand further research. However, the literature raised the hypothesis that individuals recurrently affected by oral sores may have a higher risk of infection by *Candida albicans*, and that enzymes developed by these yeasts are capable of producing chemical carcinogens by nitrosination (21,22).

Being a case-control study, this study is subject to criticism regarding the selection bias (8). The sample is not representative of the Brazilian society; this limitation affects most clinical studies. Concerning the selection of controls, the exclusive enrolment of participants in units of outpatient care, without cancer, and presenting treatment needs unrelated to dental status are reassuring against selection bias.

Recall bias is also acknowledged as a relevant limitation of case-control studies (8). Patients diagnosed with IO-SCC may have spent some time pondering which habits or events would have contributed to the disease. Therefore, cases would be more likely to recall oral sores than the controls. This limitation is difficult to overcome in the scope of a case-control study. The experience of oral sores by ill-fitting dentures does not generate effective registers at population level, and clinical examinations of oral mucosa after the diagnosis of cancer cannot be considered in the assessment of etiological factors. Nonetheless, the identification of smoking and alcohol drinking as risk factors for oral cancer extensively relied on the self-report of patients as to the level of consumption in case-control studies.

In conclusion, this study confirmed the association between recurrent oral sores caused by ill-fitting dentures and IO-SCC in smokers. This observation is in agreement with the hypothesis that the chronic physical irritation of mucosa contributes to the topical carcinogenic effect of tobacco in the mouth, which must be taken into careful consideration in the planning of dental services for adults and the elderly. In addition to improving mouth function and quality of life, the appropriate application and monitoring of dental prosthesis represent a non-negligible scope for cancer prevention.

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