








Association between oral hygiene and head and neck cancer in Brazil

Associação entre higiene oral e câncer de cabeça e pescoço no Brasil

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ABSTRACT: *Introduction:* Poor oral hygiene, regular use of mouthwash and absence of visits to the dentist could correspond to potential risk factors for the development of head and neck cancer. *Objective:* The objective of this study was to determine whether oral hygiene is associated with the occurrence of oral cavity and head and neck cancer in a Brazilian sample. *Method:* The variables of oral hygiene condition, such as toothbrushing frequency, dental loss, need and use of prosthesis, and regular visit to the dentist in a case-control study were analyzed in patients from five hospitals in the state of São Paulo, Brazil, paired by gender and age, from the multicenter project *Genoma do Câncer de Cabeça e Pescoço* (GENCAPO). *Results:* The most frequent malignancies in the 899 patients included were those of the tongue border (11.41%) and tongue base (10.92%). The multivariable statistical analysis found odds ratio values: Brushing once 0.33 (95%CI 0.25 – 0.44); Brushing twice 0.42 (95%CI 0.35 – 0.52); Flossing always 0.19 (95%CI 0.13 – 0.27); Flossing sometimes 0.19 (95%CI 0.15 – 0.24); Bleeding 2.40 (95%CI 1.40 – 4.09); Prosthesis 1.99 (95%CI 1.54 – 2.56); Visiting the dentist 0.29 (95%CI 0.22 – 0.37); Good hygiene 0.21 (95%CI 0.17 – 0.27); Regular hygiene 0.20 (95%CI 0.15 – 0.25); number of missing teeth (6 or more) 3.30 (95%CI 2.67 – 4.08). *Conclusion:* These data showed that, in the population studied, indicators of good hygiene such as brushing teeth and flossing were protective factors for mouth and head and neck cancer, while bleeding and many missing teeth were risk factors.

Keywords: Oral hygiene. Case-control studies. Mouth neoplasms. Head and neck neoplasms. Brazil.

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RESUMO: *Introdução:* Má higiene bucal, uso regular de enxaguante bucal e ausência de visitas ao dentista podem corresponder a potenciais fatores de risco para o desenvolvimento de câncer de cabeça e pescoço. *Objetivo:* Determinar se a higiene bucal está associada à ocorrência de câncer em cavidade oral e cabeça e pescoço em uma amostra brasileira. *Método:* O estudo caso controle analisou variáveis de higiene bucal, como frequência de escovação, perda dentária, necessidade e uso de prótese e visita regular ao dentista em pacientes de cinco hospitais do estado de São Paulo, pareados por sexo e idade, provenientes do projeto multicêntrico Genoma do Câncer de Cabeça e Pescoço (GENCAPO). *Resultados:* As neoplasias mais frequentes nos 899 pacientes incluídos foram: bordo de língua (11,41%) e base de língua (10,92%). A análise estatística múltipla encontrou os seguintes valores de *odds ratio*: escovar uma vez 0,33 (IC95% 0,25 – 0,44); escovar duas vezes 0,42 (IC95% 0,35 – 0,52); uso de fio dental sempre 0,19 (IC95% 0,13 – 0,27); uso de fio dental às vezes 0,19 (IC95% 0,15 – 0,24); sangramento 2,40 (IC95% 1,40 – 4,09); prótese 1,99 (IC95% 1,54 – 2,56), visita ao dentista 0,29 (IC95% 0,22 – 0,37); boa higiene 0,21 (IC95% 0,17 – 0,27); higiene regular 0,20 (IC95% 0,15 – 0,25); e número de dentes ausentes (6 ou mais) 3,30 (IC95% 2,67 – 4,08). *Conclusões:* Esses dados mostraram que, na população estudada, indicadores de boa higiene, como escovar os dentes e uso do fio dental, foram fatores de proteção para o câncer de boca e cabeça e pescoço, enquanto sangramento e muitos dentes ausentes foram fatores de risco.

Palavras-chave: Higiene bucal. Estudos de casos e controles. Neoplasias bucais. Neoplasias de cabeça e pescoço. Brasil.

INTRODUCTION

The main etiological factor for head and neck carcinomas is tobacco, and the association between the two may be exacerbated by the consumption of alcoholic beverages^{1,2}. However, as cancer is a multifactorial disease, there are other components associated with its development, such as nutritional factors³, inherited mutations, and immunological conditions⁴. Some viruses have carcinogenic potential, including the human papillomavirus (HPV); the effect of HPV has already been demonstrated for cervical cancer and has relevant associations with head and neck carcinomas, especially in the oropharynx⁵. Social factors and lifestyle, in addition to being risk factors, alter the prognosis of the disease⁶. Even with so many factors already known and studied, new relationships and hypotheses need to be investigated to manage the other possible etiological factors.

The literature indicates that poor oral hygiene, regular use of mouthwash, and absence of visits to the dentist could correspond to potential risk factors for the development of head and neck cancer, especially in the oral cavity^{7,8}. Biologically, this hypothesis is plausible because inflammation and microbiological dysregulation contribute to a favorable tumor environment⁹. A recent systematic review found that the use of alcoholic mouthwashes may increase the chances of having head and neck cancer among high-risk patients¹⁰. This finding is important for the identification of risk factors and protection from the disease, allowing to reflect on strategies that can be adopted to prevent such occurrences. Studies associating oral hygiene and head and neck cancer have shown some evidence of a relationship between them^{11,12}. Data from Latin American⁷ and the International Head and Neck Cancer

Epidemiology (INHANCE) Consortium indicated that poor hygiene was a risk factor for cancer of the oral cavity and esophagus¹³. The objective of this study was to determine whether oral hygiene, with exclusively Brazilian patients, is associated with the occurrence of oral cavity and head and neck cancer.

METHOD

The data originated from a multicenter project titled *Fatores ambientais, clínicos, histopatológicos e moleculares associados ao desenvolvimento e ao prognóstico de carcinomas epidermóides de cabeça e pescoço* (GENCAPO), in English Environmental, Clinical, Histopathological, and Molecular Factors Associated with the Development and Prognosis of Head and Neck Squamous Cell Carcinomas (GENCAPO), which sought volunteers with histopathological confirmation of cancer from 5 Brazilian hospitals: Hospital das Clínicas da Faculdade de Medicina da USP, Hospital Heliópolis, Instituto do Câncer Arnaldo Vieira de Carvalho, Hospital de Ensino Padre Anchieta da Faculdade de Medicina do ABC, and Hospital do Câncer de Barretos Fundação Pio XII. The controls were recruited from the same hospitals but from different departments, as per dermatology, orthopedics, general clinics, and also prevention departments.

This investigation is in accordance with the international and national parameters of ethical investigation with human beings; the investigation protocol was submitted and approved by the Ethics Committee of the School of Dentistry of Universidade de São Paulo (FOUSP) (CAAE: 59663516.0.0000.0075; approval number: 1.731.007).

The data were stored in a database developed for GENCAPO II and can be viewed on the website <http://www.gencapo2.fsp.usp.br/>. The data used were collected between 2010 and 2015. The study population comprised patients with head and neck cancer whose lesions were qualified by the international classification of oncological diseases (ICD-O 3rd Edition) and showed in (Supplement Material 1)¹⁴. This led to a case-control study in which participants were electronically paired using a tool developed by the GENCAPO technical team (available at <http://www.gencapo.famerp.br/gencapo3/pareamento/index.php>) in patient/control pairs by gender and age (five-year intervals).

Specially trained interviewers collected information on sociodemographic factors, lifestyle, and family history of cancer prior to treatment. Oral hygiene habits were collected through questionnaires with several alternatives. Brushing teeth data are presented as brushing once a day and twice a day, since we wanted to analyze whether the differences in brushing frequency could bring different results.

Conditional logistic regression was performed with bivariate analysis and with multiple analysis, standardized by the brushing frequency.

To enable statistical analysis, the STATA 13.0[®] software was used to evaluate *p*-values, odds ratios (OR), and confidence intervals (95%CI), with bivariate and multiple logistic regression tests; all cases were analyzed and sequentially separated into the oral cavity and other cancers.

RESULTS

The study included 899 cases and 899 controls, paired by gender and age. Men represented 80% of the sample. The most predominant education level in both groups was incomplete primary education, 56.0% of cases and 47.0% of controls; 4.0% of cases and 11.0% of controls completed higher education. White skin color was self-reported for more than half of the cases and the controls, 58.0 and 68.0%, respectively. The distribution of other ethnic groups was also balanced, and the group that self-reported brown skin color was the second most frequent, 29.5 and 24.2% for cases and controls, respectively. The most common malignant neoplasm sites were: tongue edge (11.4%), tongue base (10.9%), and anterior floor (5.9%). Other topographic locations (50 classifications) did not reach 5.0% of the sample and they were presented in the supplementary material (Supplement Material 1). Table 1 shows the sample characterization by gender, age and the most important risk factors — consumption of tobacco and alcohol.

The statistical tests of conditional logistic regression were performed with bivariate analysis adjusted by brushing — once or twice — presented in Table 2, which found statistical significance for flossing (OR = 0.16; 95%CI 0.08 – 0.33), regular visits to the dentist (OR = 0.59; 95%CI 0.37 – 0.93), and good hygiene (OR = 0.59; 95%CI 0.38 – 0.90) showing them as a protective factor, while bleeding (OR = 3.90; 95%CI 1.40 – 11.73) and six or more missing teeth (OR = 3.86; 95%CI 2.67 – 5.58) were shown to be risk factors.

The multivariate analysis was presented in Table 3. Among cases of head and neck without oral cavity, protective factors were brushing twice (OR = 0.40; 95%CI 0.21 – 0.72), flossing (OR = 0.53; 95%CI 0.38 – 0.73), and good hygiene (OR = 0.24; 95%CI 0.10 – 0.58), while high number of missing teeth (OR = 3.21; 95%CI 1.75 – 5.89) figured as a risk factor. When analyzing the cases of oral cavity, we found significance in the same groups, except for the variable 'brushing twice' (OR = 0.67; 95%CI 0.36 – 1.26).

Table 1. Cases and controls distribution.

	Cases		Controls		p
	N	%	N	%	
Patients	899	50.0	899	50.0	1.00**
Mean age (yrs)	899	59.3	899	57.9	0.01*
Male	728	80.9	728	80.9	1.00**
Female	181	20.2	181	20.2	1.00**
Smoker	602	66.9	145	16.1	0.01**
Former smoker	220	24.5	336	37.4	0.01**
Alcohol consumer	446	49.6	426	47.4	0.89**
Former alcohol consumer	339	37.7	216	24.0	0.01**

*Student's test; ** χ^2 .

Table 2. Bivariate analysis of the variables with all patients in the sample.

		Head and neck cancer (including oral cavity)					
		Bivariate		Brushing once		Brushing twice	
		OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Brushing once	no	1.00		-	-	-	-
	yes	0.33 (0.25 – 0.44)	< 0.001	-	-	-	-
Brushing twice	no	1.00		-	-	-	-
	yes	0.42 (0.35 – 0.52)	< 0.001	-	-	-	-
Flossing always	no	1.00		1.00		1.00	
	yes	0.19 (0.13 – 0.27)	< 0.001	0.16 (0.09 – 0.30)	< 0.001	0.16 (0.80 – 0.26)	< 0.001
Flossing sometimes	yes	1.00		-	-	-	-
	no	0.19 (0.15 – 0.24)	< 0.001	-	-	-	-
Bleeding	yes	1.0		1.0		1.00	
	no	2.40 (1.40 – 4.09)	0.001	4.12 (1.47 – 13.00)	0.015	3.90 (1.40 – 11.73)	0.017
Mouthwash	yes	1.0		-	-	-	-
	no	1.42 (1.08 – 1.85)	0.010	-	-	-	-
Removable partial prosthesis	yes	1.00		-	-	-	-
	no	1.17 (0.97 – 1.42)	0.096	-	-	-	-
Prosthesis	yes	1.00		1.00		1.00	
	no	1.99 (1.54 – 2.56)	< 0.001	1.36 (0.90 – 1.96)	0.144	1.28 (0.88 – 1.86)	0.190
Visiting the dentist	no	1.00		1.00		1.00	
	yes	0.29 (0.22 – 0.37)	< 0.001	0.58 (0.38 – 0.88)	0.024	0.59 (0.374 – 0.93)	0.024
Good hygiene	no	1.00		1.00		1.00	
	yes	0.21 (0.17 – 0.27)	< 0.001	0.58 (0.38 – 0.90)	0.010	0.59 (0.38 – 0.90)	0.015
Regular hygiene	no	1.00		-	-	-	-
	yes	0.20 (0.16 – 0.25)	< 0.001	-	-	-	-
Number of missing teeth (6 or more)	no	1.00				1.00	
	yes	3.30 (2.67 – 4.08)	< 0.001	3.86 (2.64 – 5.50)	< 0.001	3.86 (2.66 – 5.58)	0.001

OR: odds ratio; 95%CI: 95% interval of confidence.

Table 3. Multivariable analysis of the variables separating cancers from the oral cavity of the other locations.

		Head and neck (without oral cavity)		Oral cavity only	
		OR (95%CI)**	p-value	OR (95%CI)**	p-value
Brushing twice	no	1.00		1.00	
	yes	0.40 (0.21 – 0.72)	0.002	0.67 (0.36 – 1.26)	0.217
Flossing always	no	1.00		1.00	
	yes	0.53 (0.38 – 0.73)	< 0.001	0.53 (0.36 – 0.78)	0.002
Bleeding	yes	1.0		-	
	no	3.14 (0.67 – 14.88)	0.147	-	-
Prosthesis	yes	1.00		1.00	
	no	0.79 (0.43 – 1.46)	0.462	1.25 (0.64 – 2.47)	0.508
Visiting the dentist	no	1.00		1.00	
	yes	1.02 (0.49 – 2.11)	0.951	0.45 (0.19 – 1.05)	0.064
Good hygiene	no	1.00		1.00	
	yes	0.24 (0.10 – 0.58)	0.002	0.43 (0.20 – 0.94)	0.035
Number of missing teeth (6 or more)	no	1.00		1.00	
	yes	3.21 (1.75 – 5.89)	< 0.001	4.36 (2.26 – 8.41)	< 0.001

*Collinear variables were automatically excluded from the model; **adjusted as per age; OR: *odds ratio*; 95%CI: 95% interval of confidence.

DISCUSSION

This study brings pooled data from 5 reference hospitals, and not as per hospital, since there were differences in the number of patients treated in each unit; they are reference hospitals in which socioeconomic conditions of the patients are similar. The *Hospital da Clínicas da Faculdade de Medicina* of USP accounted for most of the cases (41.60%) and the *Hospital do Câncer de Barretos Fundação Pio XII*, with 4.89%.

Brushing teeth was a protective measure for head and neck cancer. Patients who brushed at least once a day were less affected, and the relationship was even stronger for patients who brushed their teeth twice or more a day. In the literature search, we found controversial results with respect to the brushing frequency and its potential to prevent oral lesions¹⁰. Based on this information, we decided to maintain the variables “brush once” and “brush twice” and all analyses. Neoplasms in other organs are also associated with poor hygiene; for example, penile cancer has similarities to mouth cancer, e.g., mostly squamous cell

carcinomas, more prevalent in developing countries, and a predominance in more vulnerable social classes, and poor local hygiene as a risk factor¹⁵. Cervical carcinoma, whose main risk factor is HPV, is also correlated with poor hygiene¹⁶.

As the oral cavity connects the external environment to the gastrointestinal system, the association between oral hygiene and pancreatic cancer and the presence of bacteria from the oral cavity in the pancreas was confirmed¹⁷. As oral hygiene is correlated with various types of cancer, microbiota dysregulation, and inflammation may be important and plausible factors in carcinogenesis. Furthermore, people with poor oral hygiene have higher formation of endogenous nitrosamine, a known carcinogen¹⁸. Thus, this set of factors may contribute to the complex mechanism of cancer. Another sustainable hypothesis is that a specific bacterium or a group of bacteria may have the ability to evade the host's response and impair innate immunity, making the environment favorable to excessive bacterial growth, promoting the conversion of the symbiotic state into the dysbiotic one¹⁹, generating a favorable environment through cascade events for the initiation and promotion of neoplasm²⁰.

Comparing the findings of this study with those for other populations, a risk factor attributable only to the population of hospitals included in the GENCAPO project is not expressed. A Chinese study that used the same indicators, only for those who did not smoke and did not present with alcoholism, indicated that cancer patients had worse oral hygiene²¹. A study with a similar design, conducted in India, found that poor oral hygiene increased the risk of mouth cancer by 7 times (95%CI 3.7 – 13.0). In this study, gingival bleeding increased the risk of mouth cancer four-fold (95%CI 2.5 – 6.2), and dentist visits motivated only by pain were also correlated (OR = 3.8; 95% CI 2.4 – 6.2); this interaction seemed to be more harmful when associated with smoking and/or chewing tobacco²². The INHANCE Consortium collected data through a multicenter project with the participation of centers in the United States, Japan, Latin America, and Europe, concluding that good hygiene is associated with a lower risk of cancer¹³. The American study Carolina Head and Neck Cancer Epidemiologic (CHANCE) showed that poor hygiene affected head and neck survival²³.

Multicenter studies with wide population coverage have possible limitations; even though they provide primary databases, they may have some degree of inconsistency. For example, a project interviewer's manual may advise that toothless patients do not respond to questions regarding brushing frequency, use of floss, and gingival bleeding, making the number of respondents vary in these categories. Another factor that alters sample groups is that patients can choose not to answer a question.

It is expected that these patients avoid brushing, due both to the fear of manipulating an altered region and the psychological aspects inherent to the diagnosis. However, tooth loss is not a specific problem, nor does it occur abruptly²⁴, except in cases of aggressive periodontitis, which is a rare disease in the population studied²⁵. In addition to being more present in vulnerable populations, its decline is not consistent around the world²⁶. Dental loss can then be considered a more reliable measure than hygiene, once that the brushing frequency can change as well as the brushing quality.

This study showed interesting data about tooth loss that was an important factor associated to head and neck cancer, regardless of the analysis performed. Patients with many dental losses were 3 or 4 times more likely to present these neoplasms, reinforcing the theoretical model of the distribution of mouth and head and neck cancer that affects more patients in the poorest sections of society (which have limited access to dental services). It is still necessary to clarify whether there is a causal enhancement between oral diseases and cancer or only the similarity of exposure factors.

Another relevant finding was that the variables of good hygiene were used as a protective factor for head and neck cancer, even without cases of mouth, which opens the possibility for further studies to verify the cause of this correlation is in fact caused by poor hygiene deregulation of the microbites producing acetaldehyde as in chronic alcohol users or if there are other reasons such as bacterial migration²⁷.

The biological plausibility of the relationship between oral hygiene and oral cancer can be explained by the fact that bacterial dysregulation and *Candida albicans* produce acetaldehyde, a known carcinogen in animal experiments and in vitro, due to their mutagenic effect, in clinically relevant amounts, which is why we present separate results with regard to the oral cavity and other locations; then, we could try to understand if the proximity to the source of infection could have a greater causal relationship¹⁰.

These data showed that, in the studied population, indicators of good hygiene such as brushing teeth and flossing were protective factors for mouth and head and neck cancer, while bleeding and many missing teeth were risk factors.

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contributed to the study design and interpretation of the data. EMC and MGHB completed the data analyses. MGHB and NFP were responsible for drafting the article. NFP, RML, TNT, RDC, CKS, EMC, and MGHB critically revised the article for intellectual content. NFP, RML, TNT, RDC, CKS, EMC, and MGHB issued the final approval of this version to be published and agreed to be guarantors of the work.

