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Association between Chronic Periodontitis and Oral/ Oropharyngeal Cancer

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The aim of this case control study was to assess the association between the extent and severity of chronic periodontitis and oral cavity and/or oropharyngeal cancer. The case group comprised 35 patients (mean age 56.1±8.4), diagnosed for oral and/or oropharyngeal cancer. The control group comprised 40 individuals (mean age 55.4±9.4) without diagnostic of cancer. All individuals were subjected to a periodontal examination, including bleeding on probing, plaque index, gingival index, probing pocket depth (PPD), clinical attachment loss (CAL), and decayed, extracted and filled teeth index (DMFT). The case group had significantly more sites with plaque. GI and BOP had similar values in both groups. The median PPD and CAL values were significantly higher for the case group. Chronic generalized periodontitis was predominant in 80% of patients with oral and/or oropharyngeal cancer. Eighty nine percent of the patients in the case group presented severe chronic periodontitis. There was no significant difference between groups for median values of DMFT. The extent and severity of chronic periodontitis remained as risk indicators for oral cavity and/or oropharyngeal cancer even after the adjustments for traditional confound factors, i.e. smoking and alcohol consumption.

Key Words: oral cancer, periodontitis, risk indicator.

Introduction

Chronic inflammation has been associated with carcinogenesis since the 19th century when Virchow hypothesized that the origin of cancer was chronic inflammation. The characteristics relating cancer to inflammation include presence of inflammatory cells and inflammatory mediators (e.g. cytokines and prostaglandins) in tumor tissue, tissue remodeling and angiogenesis that are similar to those observed in chronic inflammatory response and tissue repair (1). Other findings may link cancer and inflammation: 1) non-steroidal anti-inflammatory drugs reduce the risk of developing certain types of cancers (such as colon and breast) and reduce the mortality rates of these types of cancers; 2) signaling pathways involved in inflammation operate downstream of oncogenic mutations (such as mutations in the genes encoding RAS, MYC and RET); 3) adoptive transfer of inflammatory cells or over-expression of inflammatory cytokines produces development of tumors; and 4) inflammatory diseases increase the risk of developing certain types of cancer (including bladder, cervical, gastric, intestinal, esophageal, ovarian, prostate and thyroid cancer) (2).

Chronic inflammation caused by infection has been suggested as one of the major preventable causes of cancer in general. It is estimated that 15 to 20% of all human tumors are initiated by infection/inflammation (3). Since evidence supports an association between chronic infection/inflammation and cancer, a link between chronic periodontitis and oral/oropharyngeal cancer seems acceptable.

The major risk factors for oral cavity and oropharyngeal cancers are tobacco and excessive alcohol consumption (4). These factors may act separately or synergistically, increasing the risk of cancer by up to 32 times (5). However, these factors are not related to all cases and may not explain the recent increased incidence of new cases, where patients had very little or no exposure to known major risk factors (6). Recent studies have focused on non-conventional etiologic factors, such as human papilloma virus (HPV) (7) and chronic inflammation/infection (2).

Recent evidence also suggests that periodontal pockets may be considered as reservoirs for HPV, cytomegalovirus and Epstein-Barr virus, which are agents that are supposedly associated with oral cancer (8). Moreover, chronic periodontal lesions are known to harbor important inflammatory mediators such as IL1-ß and TNF-α (9), previously associated with carcinogenesis (2). Therefore, the aim of this study was to assess the association between the extent and severity of chronic periodontitis and oral cavity and/or oropharyngeal cancer.

Material and Methods

Patients

Seventy-five individuals were included in this case-

control study. The case group included first-time patients of the National Institute of Cancer (INCA), Rio de Janeiro, Brazil, who did not previously undergo any kind of treatment for cancer. Thirty-five patients (32 men and 3 women) aged between 39 and 76 years (mean 56.1±8.4), diagnosed with oral/oropharyngeal cancer, during their first appointment at the head and neck surgery outpatient service were examined within a 10-month period. The control group comprised patients and/or accompanying persons at the National Institute of Traumatology and Orthopedics (INTO) Rio de Janeiro, Brazil, who did not have diagnosis of any type of cancer. Forty subjects were evaluated (36 men and 4 women), aged between 36 and 78 years (mean 55.4±9.4). The study was approved by the INCA Research Ethics Committee. All patients involved in this study were individually informed about the aims of the study and signed an informed consent statement.

The inclusion criteria were: 1) histological diagnosis of oral/oropharyngeal cancer (case group), 2) presence of at least six teeth and 3) no previous periodontal treatment in the previous six months. The exclusion criteria were 1) patients with lip cancer, 2) patients with the human immunodeficiency virus (HIV), immune disorders and chronic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, Crohn's disease) and 3) those who used anti-inflammatory medication on a daily basis.

Demographic, socioeconomic data and medical history were obtained by an interview conducted by a single experienced investigator (RM). Marital status was dichotomized as married and unmarried and race was determined by the examiner and qualified as white or nonwhite. Family income was classified as below or above 6 Brazilian minimum monthly wages (approximately U$ 2000.00 at the time of the study). Educational level was classified as no school, elementary school, high school, graduate and post-graduate degrees. In addition, patients were also asked about previous periodontal treatment, history of cardiovascular disease (acute myocardial infarction and hypertension), diabetes, chronic inflammatory diseases, use of medications, dietary habits, history of physical activity, smoking habits, alcohol consumption and family history of oral/oropharyngeal cancer. The family history for cancer was considered only for previous cases in parents, grandparents, uncles and brothers. The weight (kg) and height (m) were measured and used to calculate the body mass index (BMI). BMI was calculated as weight in kilograms divided by squared height in meters (kg/m^2).

Tobacco and Alcohol

The smoking habits were stratified into nonsmokers, smokers and former smokers. Individuals who stopped smoking for more than 3 months were classified as former smokers. Alcohol consumption was determined by the weekly intake. In this study, alcohol was defined as a risk factor when its consumption exceeded 14 drinks per week for men and 7 drinks per week for women. A drink was defined as a glass of wine (150 mL), a dose of distillate (45 mL) or 300 mL of beer (10).

Exercises and Dietary Habits

Individuals were considered practitioners of physical activity when they exercised for at least 1 year prior to the date of the examination. The exercises were categorized into aerobic (running, walking, cycling, surfing and football playing) and anaerobic (weightlifting and gymnastics). The intensity was defined as mild, moderate and strong. The amount of exercise practiced per week was calculated by multiplying the number of minutes of daily activity by the average of days practiced weekly. Consumption of fruit, red meat and vegetables was determined by the number of days per week they were consumed.

Oral Health Analysis

Periodontal examination was performed by a single experienced and calibrated examiner (RM). Intra-examiner level agreement at calibration was 97.5% for PPD and CAL, considering a ±1 mm margin of error. Periodontal parameters included: probing pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI) and gingival index (GI). Clinical parameters were evaluated in all teeth, excluding third molars. PI and GI were recorded at four sites, while PPD and CAL were measured at six sites per tooth (buccal, mesiobuccal, distobuccal, lingual, mesiolingual, distolingual). PI and GI were considered as present or absent. BOP was observed by the presence or absence of bleeding 10 s after probing. All measurements were performed using a calibrated millimeter periodontal probe (PCP15; Hu-Friedy®, Chicago, IL, USA) and the values were rounded up to the nearest millimeter. Severe chronic periodontitis was defined as the presence of at least 2 sites with CAL ≥6 mm and PPD ≥7 mm at proximal sites of two different teeth (11), while generalized chronic periodontitis was defined as the presence of at least 30% of the measured sites with CAL ≥4 mm (12). The teeth were examined according to the DMFT using the World Health Organization (WHO) criteria.

Tumor Analysis

Tumor type was determined by histological examination of biopsy confirmed by INCA's pathologists. The location of each tumor was defined according to the International Classification of Diseases for Oncology 3rd edition

(ICD-O-3) and tumor stage was determined according to the classification of Tumor, Nodes, Metastases (TNM). Both the location and tumor stage were established by an experienced physician who performed the first examination.

Statistical Analysis

The sample size calculation indicated that for a 25% frequency of chronic periodontitis in the control group and 60% in the case group, a sample of 35 patients in each group would be needed for values of ß=20% and α=5%. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess whether variables were normally distributed. Normally distributed variables were reported as mean (±SD), while medians (interquartile range) were used to describe non-normally distributed data. The Chi-square test was used to assess differences in frequencies, while the Mann-Whitney test was used to assess differences in continuous data. Logistic regression analysis for risk factor indicators for oral and/or oropharingeal cancer was calculated, including severity and extension of chronic periodontitis, consumption of alcohol and smoking. All statistical analyses were carried out by a statistics program (IBM SPSS 19.0 – SPSS Inc., Chicago, IL, USA) with a significance level of 5%.

Results

The study population was comprised predominantly by male, white, married individuals who had elementary school education and family income of up to 6 times the minimum Brazilian wage. There were no significant differences in the frequency of patients practicing aerobic and moderate intensity exercise, the consumption of fruit, vegetables and read meat (p>0.05) although the median BMI values were significantly lower in the case group (p<0.05). The number of smokers was significantly higher in the case group, while nonsmokers and former smokers prevailed in the control group (p<0.05). Alcohol consumption was significantly higher in the case group. The description of the population is shown in Table 1.

Malignant tumors in the case group were diagnosed as squamous cell carcinoma. Table 2 shows the location and stage of the tumors. Thirty-nine percent of the studied population presented tumors located in the oral cavity and 78% of these lesions were advanced stage at levels III and IV.

Table 3 presents the data from the oral assessment of patients. There was no significant difference between groups for median values of DMFT. The case group had significantly more sites with plaque. GI and the BOP had similar values in both groups. The median PPD and CAL values were significantly higher for the case group. The prevalence of generalized chronic periodontitis was 80% in the case group, while the corresponding value in the control group was 25%. Severe chronic periodontitis was diagnosed in 88.6% of the individuals in the case group and in 32.5% of the control group (p<0.05).

Logistic regression analysis for risk factor indicators for oral and/or oropharyngeal cancer, presented in Table 4, showed that the severity and extent of chronic periodontitis remained statistically significant even after adjusting for smoking and alcohol. Smoking remained as an independent risk factor indicator in both models although excessive consumption of alcohol was not a significant relative risk

Table 1. Demographic and economic characteristics of the study population

	Case	Control
Age	56.1±8.4	55.4±9.4
Male gender (%)	91	90
Non-white race (%)	43	45
Married	54	75
Educational level (%)		
No school attended	5.7	2.5
Elementary school	57.1	60
High school	34.3	32.5
Graduate and post-graduate	2.9	5
Income up to 6 minimum wages (%)	100	90
BMI †	22.0 (4.2) *	27.9 (4.8)
Physical activity (yes) (%)	34	58
Minutes practiced per week †	0 (180)	75 (280)
Type of physical activity (%)		
Aerobic	23	53
Anaerobic	11	5
Intensity (%)		
Mild / Moderate	26	45
Strong	9	13
Dietary habits (days/week)†		
Fruit	3 (6)	6 (4)
Vegetables and vegetable	7 (4)	6 (4)
Red meat	5 (5)	3 (4)
Smoking habits (%)		
Non-smoker	17*	55
Smoker	74*	3
Ex-Smoker	9*	43
Risk/alcohol (%)	66*	25
Family history of cancer (yes) (%)	40	40

BMI: body mass index. †Median (interquartile range),*(p<0.05).

in any of the tested models.

Discussion

The aim of this case control study was to determine the association between the extent and severity of chronic periodontitis and oral cavity and/or oropharyngeal cancer. The study outcomes showed that generalized and severe chronic periodontitis were frequent among patients with oral and/or oropharyngeal cancer. Both the severity and the extent of chronic periodontitis may be considered potential risk indicators for oropharyngeal cancer even after adjustments for tobacco and alcohol. The results are consistent with the findings of Tezal et al. (13-15). In a cross-sectional study with 13.798 participants, alcohol was included in a multivariate analysis and had no significant association with oral lesions either. CAL was significantly associated with the presence of the tumor only in smoking patients (OR .67, 95% CI=2.25, 9.30) (13). Tezal et al. (14,15) reported that alveolar bone loss measured by radiographs remained as an independent risk factor for oral and oropharyngeal cancer even in patients who never used tobacco or alcohol.

Some studies (16-20) have suggested a positive association between periodontal disease and oral and oropharyngeal cancer. Nonetheless, diversity in study designs, in the studied population and especially different measurements to define periodontal disease makes it difficult to establish a link between periodontitis and cancer. Studies used tooth loss (18), periodontal partial indexes such as CPITN (19) or even self-reported periodontal evaluation (20) as diagnostic criteria to define periodontitis. Tooth loss may not be related to periodontal disease, and partial indexes and self-assessment questionnaires may underestimate the prevalence of periodontitis. In the present study, full mouth examination was used, providing more reliable results of the periodontal status (21).

According to the obtained results, squamous cell carcinoma was the predominant histological type and the prevalence of oropharyngeal lesions was higher than the one observed in mouth lesions. Oropharyngeal lesions are more aggressive and therefore require more radical

Table 2. Tumor localization and stage in case group (n=35)

	Frequency
Localization	
Mouth floor	12%
Base of tongue	15%
Tonsils	3%
Epiglottis	3%
Gingival border	3%
Palate	3%
Lateral border of tongue	21%
Oropharyngeal	40%
Stage	
IV	44%
III	34%
II	19%
I	3%

Table 3. Median (interquartile range) of periodontal data and frequency of generalized and severe chronic periodontitis

	Case (n=35)	Control (n=40)
Generalized chronic periodontitis (%)	80*	25
Severe chronic periodontitis (%)	88.6*	32.5
Number of present teeth	13.2 (5.9)*	18.2 (6.4)
DMFT	18.1 (5.5)	16.1 (5.9)
Plaque index (%)	34.7 (21.7)*	23.1 (19.5)
Gingival index (%)	11.9 (14.1)	15.1 (16.9)
Bleeding on probing	25.9 (18.9)	18.6 (16.6)
% sites with PPD 4-5 mm	34.4 (13.6)*	10.6 (11.8)
% sites with PPD ≥ 6 mm	7.6 (11.1)*	4.5 (12.7)
% sites with CAL 4-5 mm	44.4 (16.5)*	16.1 (13.5)
% sites with CAL ≥ 6 mm	29.0 (22.5)*	9.4 (20.2)
PPD for all sites (mm)	3.5 (0.8)*	2.9 (0.9)
CAL for all sites (mm)	4.8 (1.2)*	3.4 (1.4)

DMFT: decayed, missing and filled teeth, PPD: probing pocket depth, CAL: clinical attachment level. *($p<0.05$).

Table 4. Logistic regression analysis for risk factor indicators of oral and/or oropharyngeal cancer - Models 1 and 2

Risk factors indicators	Odds ratio	CI 95%	p value
Model 1			
Severity	10.9	(1.9–61.2)	0.006
Tobacco	63.9	(6.1–665.3)	0.001
Alcohol	1.85	(0.34–9.9)	0.476
Model 2			
Extension	12.5	(2.3–67.6)	0.003
Tobacco	97.5	(8.6–1009.4)	0.000
Alcohol	1.5	(0.28–8.3)	0.63

CI: confidence interval.

treatments. There is controversy regarding the classification of tongue base lesions, which sometimes belong to the oral cavity and sometimes to the oropharynx. This fact directly affects the proportion of mouth tumors in relation to the oropharynx. According to the INCA manual of internal routines, the anatomical regions of the oral cavity are: lips, anterior 2/3 of the tongue, buccal mucosa, floor of the mouth, upper and lower gums, hard palate and retromolar area.

The literature suggests an association between increased cancer risk and individuals with a family history of the disease. In a study conducted by Negri et al. (22), a family history of head and neck cancer was reported by 305 (3.6%) cases and 238 (1.8%) controls, and significantly increased the risk of head and neck cancer (OR=1.68, 95% CI 1.23–2.29). However, the present findings showed that 60% of the examined patients had no close relatives like parents, siblings, uncles or grandparents who had suffered from the disease.

Conway et al. (23) reported that low socioeconomic status is significantly associated with an increased risk of oral cancer both in developed and developing countries. In this study, all patients in the case group earned less than 6 Brazilian minimum wages per month (approximately U$ 2.000 at the time of the study) and 63% studied only until primary education (up to 9th grade). The socioeconomic status may be associated with both an increased risk of oral cancer and periodontal disease. However, the relatively small number of patients evaluated in the present study prevents verifying whether the socioeconomic status influenced the prevalence of cancer.

Alcohol consumption increases nine-fold the risk for oral and oropharyngeal cancer. Although patients in the case group had a significantly higher alcohol intake than those in the control group, alcohol was not a significant risk indicator factor for cancer after multivariate analysis. Tezal et al. (13,15) also did not find association between alcohol intake and increased risk for oral cancer.

While the consumption of fruit and vegetables is related to protection against the risk of cancer, the consumption of red meat over five times a week seems to be associated with an increased risk of oral and oropharyngeal cancer (24). In the present study, the control patients had healthier eating habits with a more frequent intake of fruit and vegetables than the patients in the case group. The frequency of red meat intake was lower in the control group. However, there were no statistically significant differences in any of the dietary habits between the groups.

Individuals who practice moderate to vigorous physical activity for at least 45 min five or more days a week, may achieve the optimal levels of activity required to reduce the risk of developing some types of cancer (25). The recommendation on physical activity for lowering the risk of cancer, according to the INCA report on food, nutrition, physical activity and cancer prevention is that individuals perform moderate physical activity, equivalent to a brisk walk, for at least 30 min every day. In this study, the control group practiced more exercise. However, the median amount of physical activity was below the recommendation for both groups.

Periodontitis is a chronic inflammatory disease, highly prevalent in humans. Histologically, exposure of connective tissue after epithelial disruption may be observed. It may release the same inflammatory substances found in the first phase of carcinogenesis, such as TNF-α and IL1-ß (2,9). The biological explanation for the association between periodontitis and carcinogenesis includes chronic inflammation, presence of bacteria and a reservoir for possible carcinogenic agents (e.g. HPV). According to Mantovani et al. (2) the non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of developing certain types of cancer while reducing the mortality caused by these cancers. Furthermore, inflammatory cells, cytokines and chemokines are present in the microenvironment of all tumors in experimental animal models and in humans from the early stages of tumor development and overexpression of inflammatory cytokines may promote tumor development.

The association between periodontal disease and oral and/or oropharyngeal cancer may have implications for public health in preventive measures and for the patients who might experience major improvements in the complications of cancer and its treatment. This might reduce morbidity and mortality. An association between periodontal disease and cancer may lead us to consider patients with periodontitis as population at risk for developing oral/oropharyngeal cancer.

Resumo

O objetivo deste estudo caso controle foi determinar a associação entre extensão e severidade da periodontite crônica e câncer da cavidade oral e/ou orofaringe. O grupo caso consistiu de 35 pacientes (idade média 56,1±8,4), diagnosticados para câncer oral e/ou de orofaringe. O grupo controle foi composto por 40 pacientes (idade média 55,4±9,4) sem diagnóstico de câncer. Todos os pacientes foram submetidos a exame periodontal, incluindo sangramento à sondagem, índice de placa, índice gengival, profundidade de sondagem e nível de inserção clínica, além do índice de dentes cariados, perdidos e obturados (CPOD). O grupo caso tinha significativamente mais sítios com placa. Índice gengival e sangramento à sondagem mostraram valores similares em ambos os grupos. A mediana dos valores de profundidade de bolsa à sondagem e nível de inserção clínica foram significativamente maiores para o grupo caso. A prevalência de periodontite crônica generalizada foi de 80% em pacientes com câncer oral e/ou de orofaringe. Oitenta e nove por cento dos pacientes no grupo de caso apresentaram periodontite crônica severa. Não houve diferença significante entre os grupos para os valores medianos de CPOD. A extensão e severidade da periodontite crônica permaneceram como indicadores de risco para câncer oral e/ou de orofaringe mesmo após o ajuste para fatores de confundimento tradicional, isto é, fumo e consumo de álcool.

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