Chronic Periodontitis and the Risk of Tongue Cancer

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Objective: To assess the association between the history of chronic periodontitis and the risk of tongue cancer.

Design: Case-control study using preexisting data from patients admitted between June 15, 1999, and November 17, 2005.

Setting: Department of Dentistry and Maxillofacial Prosthetics at Roswell Park Cancer Institute (RPCI), Buffalo, NY.

Patients: The cases comprised 51 non-Hispanic white men newly diagnosed as having primary squamous cell carcinoma of the tongue, and the controls, 54 non-Hispanic white men evaluated during the same period but with negative results for malignancy. Children (aged <21 years), edentulous or immunocompromised patients, and those with history of any cancer were excluded. History of periodontitis was assessed by alveolar bone loss measured from panoramic radiographs by 1 examiner blind to cancer status.

Main Outcome Measure: Incidence of tongue cancer obtained from the RPCI Tumor Registry.

Results: After adjusting for the effects of age at diagnosis, smoking status, and number of teeth, each millimeter of alveolar bone loss was associated with a 5.23-fold increase in the risk of tongue cancer (odds ratio, 5.23; 95% confidence interval, 2.64-10.35).

Conclusions: This study suggests an association between chronic periodontitis and the risk of tongue cancer in men, independent of smoking status, age, race, ethnicity, and number of teeth. This association needs to be confirmed by larger studies using quantitative assessment of lifetime tobacco exposure. If this association is confirmed, it has a potential impact on understanding the etiology of oral cancer as well as on its prevention and control.

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initiation and progression of periodontitis. Periodontal bacteria and viruses may act synergistically to cause periodontitis. More interestingly, studies suggest that periodontal pockets act as reservoirs for human papilloma virus (HPV), cytomegalovirus, and Epstein-Barr virus, suspected agents associated with oral cancer. Periodontitis, characterized by epithelial proliferation and migration, results in chronic release of inflammatory cytokines, chemokines, prostaglandins, growth factors, and enzymes, all of which are also closely associated with carcinogenesis.

In summary, substantial evidence supports an association between chronic infections and increased risk of cancer. A specific association between chronic periodontitis and oral cancer is plausible and needs to be explored. The aim of this study was to assess the association between the history of periodontitis and the risk for tongue cancer.

METHODS

STUDY DESIGN AND POPULATION

A case-control study design was used. The study population consisted of patients seen in the Department of Dentistry and Maxillofacial Prosthetics at Roswell Park Cancer Institute (RPCI), Buffalo, NY, between June 15, 1999, and November 17, 2005. The department provides a complete range of dental services including routine prophylaxis, restorative care, full-mouth rehabilitation, dental implants, oral surgical procedures, and maxillofacial prosthetics to cancer as well as healthy patients with a wide range of age and socioeconomic status. Institutional review board approval for existing data review and waiver of Health Insurance Portability and Accountability Act authorization for use and disclosure of protected health information in research were obtained to access the medical records at RPCI.

For the present analyses, we restricted the study population to non-Hispanic white men. Children (aged <21 years), edentulous patients, and those with a history of any type of cancer, cancer therapy, oral dysplasia, immunodeficiency, and autoimmune disorders were excluded.

DEFINITION OF CASES AND CONTROLS

All non-Hispanic white males with primary squamous cell carcinoma of the tongue (International Classification of Diseases for Oncology [ICD-O] codes C01.0-C02.9), diagnosed between June 15, 1999, and November 17, 2005, were included as cases. The diagnoses of cancer cases were obtained from the RPCI Tumor Registry.

All non-Hispanic white men seen in the department during the same period as cases but not diagnosed with any cancer or oral dysplasia were included as controls. The diagnoses of the controls were obtained from the RPCI Hospital Information System.

ASSESSMENT AND DEFINITION OF PERIODONTITIS

History of periodontitis was assessed by the severity of alveolar bone loss (ABL) from panoramic radiographs. These were taken with a software-controlled orthopantomograph (OP100; Instrumentarium Imaging, Tuusula, Finland) using standard exposure time (17.6 seconds) and settings (70 kV [peak] and 12 mA). Patient positioning was standardized with the help of positioning lights, head, temple and chin supports, occlusion adjustment keys, and a bite fork. The films were developed with an automatic film processor.

Alveolar bone loss, an established measure of periodontitis history, quantifies cumulative vertical bone loss. Alveolar bone loss was measured on the mesial and distal sites of all teeth using an operator-interactive program. The program allows measurement of the distance from the cementoenamel junction to the bone crest in a line parallel to the long axis of the tooth (Figure). Radiographic images are captured by a digital imaging system. A millimetric grid is used to convert image measurements from pixel to millimeter. Typically, ABL of less than 2 mm is considered as normal or healthy periodontium.

Accuracy and reliability of the ABL measurements using this technique have been previously established. In the present study, all ABL measurements were performed by 1 trained periodontist. The examiner was blind to the patients' cancer status. Duplicate ABL measurements were performed on 5 study subjects with a 3-day interval to establish intra-examiner reliability. The mean ± SD of differences of duplicate measurements was 0.22 ± 0.41 mm.

COVARIATES

For the selection and definition of covariates, we were limited to information available in existing patient records. Information on cigarette, pipe, or cigar smoking status (never, former, current), age at diagnosis (years), sex (men and women), race (white, black, Asian, Native American/Alaskan, Hawaiian/Pacific Islander, and other), and ethnicity (Hispanic and non-Hispanic) was available electronically from the RPCI Hospital Information System. Information on the number of natural teeth present (continuous), number of teeth with cavities (continuous), fillings (continuous), crowns (continuous), and endodontic treatments (continuous) was obtained from radiographs.

STATISTICAL ANALYSES

Means, standard deviations, frequencies, and proportions of available relevant variables were used to describe the study population. To compare cancer cases and controls for similarity, χ² and t tests (unpaired and 2-tailed) were used. The independent effect of ABL on the risk of tongue cancer was estimated from multiple logistic regression analyses after adjusting the effects of confounders. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. SPSS statistical software, version 12.0 (SPSS Inc, Chicago, Ill) was used for data analyses.
Table 1. Description of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls* (n = 54)</th>
<th>Cases† (n = 51)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y§</td>
<td>53.06 ± 14.40 (25-87)</td>
<td>53.37 ± 9.65 (30-73)</td>
<td>.89</td>
</tr>
<tr>
<td>Smoking§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>22 (40.7)</td>
<td>16 (31.4)</td>
<td>.17</td>
</tr>
<tr>
<td>Former</td>
<td>12 (22.2)</td>
<td>20 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>20 (37.0)</td>
<td>15 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Alveolar bone loss, mm§</td>
<td>2.74 ± 1.08 (1.53-7.49)</td>
<td>4.21 ± 1.52 (1.77-8.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Missing teeth, No.§</td>
<td>9.52 ± 7.85 (0-26)</td>
<td>7.49 ± 7.24 (0-23)</td>
<td>.17</td>
</tr>
<tr>
<td>Decayed teeth, No.§</td>
<td>1.56 ± 2.25 (0-12)</td>
<td>1.80 ± 2.88 (0-16)</td>
<td>.62</td>
</tr>
<tr>
<td>Filled teeth, No.§</td>
<td>4.33 ± 4.18 (0-17)</td>
<td>5.73 ± 4.27 (0-15)</td>
<td>.09</td>
</tr>
<tr>
<td>Crowns, No.§</td>
<td>2.46 ± 4.42 (0-16)</td>
<td>1.51 ± 2.82 (0-11)</td>
<td>.19</td>
</tr>
<tr>
<td>Root canal treatments, No.§</td>
<td>1.26 ± 2.57 (0-12)</td>
<td>0.75 ± 1.69 (0-9)</td>
<td>.23</td>
</tr>
</tbody>
</table>

*Subjects without cancer. †Subjects with squamous cell carcinoma of tongue (International Classification of Diseases for Oncology codes C01.0-C02.9). ‡P values were derived from χ² tests for categorical or t tests for continuous data. §Mean ± SD (range). ¶Frequency (percentage).

Table 2. Adjusted Odds Ratios of Oral Variables for the Risk of Tongue Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio* (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar bone loss, per mm</td>
<td>5.23 (2.64-10.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Decayed teeth, per tooth</td>
<td>1.03 (0.88-1.21)</td>
<td>.70</td>
</tr>
<tr>
<td>Filled teeth, per tooth</td>
<td>1.06 (0.94-1.19)</td>
<td>.34</td>
</tr>
<tr>
<td>Crowns, per tooth</td>
<td>0.89 (0.78-1.01)</td>
<td>.07</td>
</tr>
<tr>
<td>Root canal treatments, per tooth</td>
<td>0.86 (0.70-1.06)</td>
<td>.15</td>
</tr>
<tr>
<td>Missing teeth, per tooth</td>
<td>0.95 (0.90-1.01)</td>
<td>.09</td>
</tr>
</tbody>
</table>

*Odds ratios were adjusted for age at diagnosis, smoking status, and number of teeth.

Table 3. Alveolar Bone Loss in Cases and Controls Stratified by Smoking Status*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls†</th>
<th>Cases‡</th>
<th>P Value (t Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar Bone Loss, mm</td>
<td>2.74 ± 1.08</td>
<td>4.22 ± 1.52</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Entire study population</td>
<td>2.33 ± 0.89</td>
<td>3.31 ± 0.96</td>
<td>.003</td>
</tr>
<tr>
<td>Never smokers</td>
<td>2.58 ± 0.77</td>
<td>4.12 ± 1.12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Former smokers</td>
<td>3.29 ± 1.24</td>
<td>5.32 ± 1.83</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise specified. †Subjects without cancer. ‡Subjects with squamous cell carcinoma of tongue (International Classification of Diseases for Oncology codes C01.0-C02.9).

RESULTS

Table 1 describes the study population. The age and smoking status of cases and controls were not significantly different. The mean ABL was significantly higher in cancer cases compared with controls (4.21 vs 2.74 mm; P < .001). The remaining oral variables were not significantly different between cases and controls.

After adjusting for the effects of age, smoking status, and the number of teeth, each millimeter of ABL was significantly associated with a 5.23-fold increase in the risk of tongue cancer (OR, 5.23; 95% CI, 2.64-10.35). Other oral variables (the number of dental decays, fillings, crowns, and root canal treatments) were not significantly associated with the risk for tongue cancer (Table 2).

Table 3 describes the mean ABL in cases and controls stratified by smoking status. The association between ABL and tongue cancer remained significant independent of smoking status. Alveolar bone loss was consistently higher in cancer cases compared with controls among never (3.31 vs 2.33 mm; P = .003), former (4.12 vs 2.58 mm; P < .001), and current (5.32 vs 3.29 mm; P < .001) smokers.

This study presents, to our knowledge, the first evidence of a possible association between the history of chronic periodontitis and tongue cancer independent of smoking. Considering the results of previous studies linking chronic infections and inflammation to cancer risk in several other organs, we expected to see a trend in this study. However, we did not expect to see such a clear association with a relatively small sample size. Therefore, the results of this preliminary study encourage larger studies with more comprehensive assessments of confounding to confirm this association.

Periodontitis is a chronic disease; it starts and progresses very slowly. Alveolar bone loss, an outcome of periodontitis, is irreversible and cumulative. Detectable ABL on radiographs reflects preexisting chronic periodontitis of usually decades in older populations such as ours. This provides evidence of temporality that periodontitis history preceded the cancer diagnosis.

Besides chronic periodontitis, the effects of dental cavities, fillings, crowns, and root canal treatments were also assessed, and the results suggest that periodontitis was the only oral variable that was significantly associated with...
oral cancer. However, the small sample size as well as the fact that the diagnoses were made from radiographs limit our ability to draw conclusions. The diagnoses of dental cavities are underestimated, and only relatively advanced lesions can be detected from radiographs.\textsuperscript{16} Future studies with more sensitive clinical diagnoses will provide better answers.

A disadvantage of secondary data analyses is that they depend on the availability of data in adequate detail from preexisting records. In this study also, limited information was available on exposure variables that could confound the periodontitis–oral cancer association. For example, data on alcohol use, smokeless tobacco, and diet were not available. In addition, smoking history was not quantitative and no information on time since quitting smoking was available. However, basic information on age, sex, race, ethnicity, smoking status, histologic confirmation of cancer diagnoses, and quantitative and objective measure of periodontitis history with evidence of temporality allowed us to test our hypothesis. In addition, the observed association in never smokers suggests that this association is independent of smoking.

The question of how infection and inflammation can influence carcinogenesis has interested scientists for over one and a half centuries, but only now are the general principles and the complexity of this association emerging.\textsuperscript{20} Chronic infections, such as periodontitis, can play a direct or indirect role in carcinogenesis:

1. Direct toxic effect of microorganisms: Microorganisms and their products such as endotoxins (lipo-polysaccharides), enzymes (proteases, collagenases, fibrinolysin, and phospholipase A), and metabolic by-products (hydrogen sulfide, ammonia, and fatty acids) are toxic to surrounding cells and may directly induce mutations in tumor suppressor genes and proto-oncogenes or alter signaling pathways that affect cell proliferation and/or survival of epithelial cells.

2. Indirect effect through inflammation: Chronic infection may stimulate the formation of epithelial-derived tumors through an indirect mechanism involving activation of surrounding inflammatory cells. Inflammation exposes epithelial cells to substances with mutagenic potential. Microorganisms and their products activate host cells such as neutrophils, macrophages, monocytes, lymphocytes, fibroblasts, and epithelial cells to (a) generate reactive oxygen species (hydrogen peroxide and oxygen radicals), reactive nitrogen species (nitric oxides), reactive lipids and metabolites (malondialdehyde and 4-hydroxy-2-nonenal), and matrix metalloproteases, which can induce DNA damage in epithelial cells and (b) produce cytokines, chemokines, growth factors, and other signals that provide an environment for cell survival, proliferation, migration, angiogenesis, and inhibition of apoptosis. This environment may help epithelial cells to accumulate mutations and drive these mutant epithelial cells to proliferate, migrate, and give them a growth advantage.

In summary, substantial evidence from previous studies supports an association between chronic infections and increased risk of cancer. Therefore, a specific association between chronic periodontitis and oral cancer is plausible and needs to be explored. We have presented preliminary data suggesting an independent association between history of periodontitis and the risk of tongue cancer. This association needs to be confirmed by larger studies that include other oral cancer sites, women, and subjects of other races with a more comprehensive assessment of confounding. If this association is confirmed, it has a potential impact on understanding the etiology of oral cancer as well as on its prevention and control.

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Author Contributions: Dr Tezal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tezal, Reid, Marshall, and Scannapieco. Acquisition of data: Tezal, Sullivan, Loree, Lillis, and Hauck. Analysis and interpretation of data: Tezal, Reid, Marshall, Hyland, Wactawski-Wende, and Scannapieco. Drafting of the manuscript: Tezal. Critical revision of the manuscript for important intellectual content: Reid, Marshall, Hyland, Loree, Wactawski-Wende, and Scannapieco. Administrative, technical, and material support: Tezal, Sullivan, Marshall, Loree, Lillis, Hauck, and Scannapieco. Study supervision: Tezal, Reid, Wactawski-Wende, and Scannapieco.

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REFERENCES


