Chronic Periodontitis and the Incidence of Head and Neck Squamous Cell Carcinoma

Mine Tezal,[1,2,3,5] Maureen A. Sullivan,[1,5] Andrew Hyland,[3,8] James R. Marshall,[3,8] Daniel Stoler,[9] Mary E. Reid,[8] Thom R. Loree,[6] Nestor R. Rigual,[4,6] Mihai Merzianu,[7] Linda Hauck,[10] Cheryl Lillis,[11] Jean Wactawski-Wende,[3] and Frank A. Scannapieco[2]

Departments of [1]Oral Diagnostic Sciences, [2]Oral Biology, [3]Social and Preventive Medicine, [4]Otolaryngology, The State University of New York, and Departments of [5]Dentistry and Maxillofacial Prosthetics, [6]Head and Neck Surgery, [7]Pathology and Anatomical Sciences, [8]Cancer Prevention and Population Sciences, [9]Cancer Genetics, [10]Health Information Management, and [11]Information Technology, Roswell Park Cancer Institute, Buffalo, New York

Abstract

Substantial evidence supports an association between chronic infections/inflammation, and cancer. The aim of this study was to assess the effect of chronic periodontitis on head and neck squamous cell carcinoma (HNSCC). The study population consisted of new patients at the Department of Dentistry and Maxillofacial Prosthetics, Roswell Park Cancer Institute between 1999 and 2005. Cases were patients diagnosed with primary HNSCC. Controls were all patients seen during the same time period but negative for malignancy. Patients age <21 years, edentulous, immunocompromised, and those with history of cancer were excluded. Periodontitis was measured by alveolar bone loss (ABL) from panoramic radiographs by one examiner blind to cancer status. A total of 473 patients (266 cases and 207 controls) were included in the study. Each millimeter of ABL was associated with >4-fold increased risk of HNSCC (odds ratio, 4.36; 95% confidence interval, 3.16-6.01) after adjustment for age, gender, race/ethnicity, marital status, smoking status, alcohol use, and missing teeth. The strength of the association was greatest in the oral cavity, followed by oropharynx and larynx. The association persisted in subjects who never used tobacco and alcohol. There was a significant interaction between smoking and ABL ($P = 0.03$). Patients with periodontitis were more likely to have poorly differentiated oral cavity SCC than those without periodontitis (32.8% versus 11.5%; $P = 0.038$). This study suggests that chronic periodontitis is an independent risk factor for HNSCC and smoking modifies this association. These results have implications for practical and safe strategies for prevention, diagnosis, and treatment of HNSCC. (Cancer Epidemiol Biomarkers Prev 2009; 18(9):2406–12)

Introduction

Smoking rates have declined over the past 40 years; yet, in many parts of the world, the incidences of the oral tongue, base of the tongue, and tonsil cancers have started to increase among younger people. Morbidity and mortality from head and neck squamous cell carcinoma (HNSCC) also remain high (1). It is estimated that ~$3.2 billion is spent in the United States each year on treatment of HNSCC. However, aggressive treatment, often associated with significant morbidity, does not radically reduce the mortality (2, 3). A better understanding of HNSCC etiology, interactions between risk factors, and new approaches to prevention and treatment are necessary to change the course of this disease.

The evidence supporting an association between chronic infections/inflammation and cancer has accumulated substantially (4, 5). Periodontitis is a chronic inflammatory disease associated with Gram-negative anaerobic bacteria in the dental biofilm. It leads to irreversible destruction of tissues supporting teeth, clinically detectable as periodontal pockets and alveolar bone loss (ABL; refs. 6, 7). Periodontitis results in a continuous release of bacterial and inflammatory markers into saliva and, to a lower degree, into blood (8). Furthermore, periodontal pathogens and inflammatory cytokines travel with saliva and blood from the affected tissues to distant sites and adversely affect systemic health (9-13). Most importantly, treatment of periodontal infections has been shown to prevent and reverse systemic adverse events (14, 15).

Previous studies from our group suggested that chronic periodontitis might be associated with oral premalignant lesions (16), tongue cancers (17), and tumor human papillomavirus (HPV) status in base of tongue cancers (18). We conducted the present study to assess the role of chronic periodontitis on overall HNSCC incidence as well as on individual incidences of the oral cavity, oropharyngeal and laryngeal SCC.

Materials and Methods

Study Population. We conducted a hospital-based case-control study consisting of new patients of the Department of Dentistry and Maxillofacial Prosthetics, Roswell Park Cancer Institute (RPCI), between June 15, 1999

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Requests for reprints: Mine Tezal, The State University of New York, NYS Center of Excellence in Bioinformatics and Life Sciences, 355 Squire Hall, Buffalo, New York 14214. Phone: 716-829-2241/716-881-7907; Fax: 716-829-3554. E-mail: mtezal@buffalo.edu

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and November 17, 2005. Located within the same physical area as the department of Head and Neck Surgery, the Department of Dentistry and Maxillofacial Prosthetics provides a complete range of dental services to cancer patients as well as to healthy patients with wide ranges of age and socioeconomic status. These services include routine dental care, dental implants, oral surgical procedures, maxillofacial prosthetics, and full-mouth rehabilitation. The majority of the RPCI patients are from the surrounding Erie, Niagara, and Chautauqua counties. This study was reviewed and approved by both the RPCI and the State University of New York Institutional Review Boards.

Exclusion Criteria. Patients younger than 21 y, edentulous, immunocompromised, and those with a history of cancer were excluded from both case and control groups. Immunocompromised subjects included patients with organ transplants, amyloidosis, myelofibrosis, myelodysplastic syndrome, HIV infection, and patients admitted with oral lesions related to autoimmune disorders such as lupus erythematosis, pemphigus vulgaris, cicatricial or bullous pemphigoid, dermatitis herpetiformis, linear IgA disease, and epidermolysis bullosa.

Definition of Cases. All patients newly diagnosed with primary HNSCC during the study period who met the inclusion criteria were included as cases. The diagnoses of the cancer cases were obtained from the RPCI Tumor Registry according to the International Classification of Diseases for Oncology, third edition (19). Tumor stage was assigned according to the American Joint Committee on Cancer staging criteria, sixth edition (20). The sites included were as follows: *oral cavity*: SCC of the oral tongue (C02.0-C02.9), gum (C03.0-C03.9), floor of the mouth (C04.0-C04.9), hard palate (C05.0), buccal mucosa (C06.0), vestibule (C06.1), retromolar area (C06.2), and overlapping lesion of other and unspecified parts of mouth (C06.8-C06.9); *oropharynx:* SCC of the base of tongue (C01.0), soft palate (C05.1), tonsil (C09.0-C09.9), and oropharynx (C10.0-C10.9); and *larynx:* SCC of the larynx (C32.0-C32.9). We excluded patients with other head and neck cancers such as cancers of the lip, salivary glands, nasopharynx, mandible, and maxilla to increase homogeneity of the study population.

Definition of Controls. All new patients seen at the Department of Dentistry and Maxillofacial Prosthetics during the same time period as the cases but not diagnosed with cancer and met the inclusion criteria were included as controls. These included general dentistry patients as well as those diagnosed with a broad spectrum of benign mucosal lesions including hyperplasia, fibroma, lipoma, wart, trauma, mucocele, cyst, abscess, pyogenic granuloma, frictional white lesion, and chemical burn. We excluded patients hospitalized with conditions associated with periodontitis. These included immunocompromised subjects as described above as well as those with congenital anomalies, trauma, gunshot, and motor vehicle accidents because these conditions may involve the periodontium. Employees were also excluded because they are a different population compared with the regular clinic patients. The diagnoses of controls were obtained from the RPCI Hospital Information System.

Assessment of Periodontitis. A cumulative history of periodontitis was assessed quantitatively by ABL from panoramic radiographs as described previously (17). Radiographs were taken at admission before the diagnosis of cancer and before therapy was initiated. ABL was measured in millimeters at the mesial and distal sites of all natural teeth using an operator-interactive program on digitized radiographic images by one trained periodontist blind to cancer status. ABL is an established measure of periodontitis and its accuracy and reliability have been previously established (21). We did duplicate ABL measurements on five study patients (207 sites) with a 3-d interval to establish intraexaminer reliability. The mean and SD of differences of duplicate measurements was 0.22 ± 0.41 mm.

Explanatory Variables. Information on explanatory variables, obtained at admission, was available through RPCI Electronic Medical Records. The following variables were available: age at diagnosis (years); gender (women, men); race (White, Black, Asian, Native American/Alaskan, Hawaiian/Pacific Islander, Other); ethnicity (Hispanic, non- Hispanic); marital status (married, single, divorced, widowed, separated); medical insurance (traditional, Medicare, Medicaid, uninsured); cigarette, cigar, or pipe smoking status (never, former, current); cigarette smoking (packs per day); and alcohol use (drinks per day; never, ever). We determined the number of missing teeth from panoramic radiographs.

Statistical Analysis. Means, SDs, frequencies, and proportions of available relevant variables were used to describe the study population. χ^2 for categorical variables and *t* tests for continuous variables were used to compare cases and controls for similarity. The independent associations of ABL and missing teeth with HNSCC were estimated from multiple logistic regression analyses including age at diagnosis, gender, race/ethnicity, marital status, smoking status, alcohol use, ABL, and number of missing teeth. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Statistical interactions of ABL and missing teeth with each of the explanatory variables were tested by including their interaction terms in the multiple regression models. We also stratified ABL-HNSCC and missing teeth-HNSCC associations by each explanatory variable. *P* values of <0.05 were considered statistically significant. SPSS software, version 15.0 (SPSS, Inc.) was used for data analyses.

Results

A total of 473 subjects (266 cases and 207 controls) met the inclusion criteria between June 15, 1999 and January 10, 2005. The cases were similar to the controls in respect to race/ethnicity and access to medical insurance but they were significantly older, smoked more cigarettes, drank more alcohol, had more missing teeth, and had greater ABL. In addition, cases were significantly more likely than controls to be men, smokers, alcohol users, and married. From 266 patients with HNSCC, 100 (37.6%) were diagnosed with oral cavity SCC, 115 (43.2%) with oropharyngeal SCC, and 51 (19.2%) with laryngeal SCC. Patients with oral cavity SCC had higher percentages of early-stage and well-differentiated tumors compared with patients with oropharyngeal and laryngeal SCC. Patients with oropharyngeal SCC were younger and the percentage of poorly differentiated tumors was higher among

these patients compared with patients with oral cavity and laryngeal SCC. Patients with laryngeal tumors were older, had more missing teeth, and consumed more tobacco and alcohol compared with patients with oral cavity and oropharyngeal SCC. Nearly all (50 of 51) patients with laryngeal SCC had a history of smoking (Table 1).

In both univariate and multivariate analyses, periodontitis was significantly associated with overall HNSCC, as well as with oral cavity, oropharyngeal, and laryngeal SCC. After adjustment for age at diagnosis, gender, race/ethnicity, marital status, smoking status, alcohol use, and number of missing teeth, each millimeter of ABL was associated with >4-fold increased risk of HNSCC (OR, 4.36; 95% CI, 3.16-6.01). When we stratified by specific head and neck sites, the strength of the association was slightly higher in the oral cavity (OR, 4.52; 95% CI, 3.03-6.75) than in the oropharynx (OR, 3.64; 95% CI, 2.54-5.22) and larynx (OR, 2.72; 95% CI, 1.78-4.16). Missing teeth was significantly associated with HNSCC in univariate analyses but its effect was attenuated and lost statistical significance with adjustment for periodontitis history and other explanatory variables (Table 2).

There was a significant interaction between smoking status and ABL ($P = 0.03$). The association between ABL and HNSCC was weaker in current smokers (OR, 2.85; 95% CI, 1.85-4.40) compared with former (OR, 7.59; 95% CI, 3.51-16.42) and never (OR, 5.96; 95% CI, 3.04-11.68) smokers. Alcohol use was not a significant effect modifier ($P = 0.474$). The strength of the ABL-HNSCC association was similar in drinkers (OR, 4.45; 95% CI, 2.70-7.34) and in nondrinkers (OR, 4.31; 95% CI, 2.82-6.58; Table 3).

Overall, periodontitis history was not significantly associated with tumor stage and differentiation. When we stratified these associations by tumor site, patients with history of periodontitis had a significantly higher percentage of poorly differentiated tumors compared with patients without periodontitis history (32.8% versus 11.5%; $P = 0.038$) in the oral cavity (Table 4).

Discussion

The results of this study provide the first evidence, to our knowledge, of an association between chronic periodontitis and HNSCC based on an objective and quantitative

Table 1. Description of the study population by disease status

	Patients with head and neck cancers*				Controls† ($n = 207$)	P‡
	Oral cavity ($n = 100$)	Oropharynx ($n = 105$)	Larynx ($n = 51$)	Total ($n = 266$)		
TNM stage						
Stage 0-II	44 (44.0)	20 (17.4)	16 (31.4)	80 (30.1)	—	—
Stage III-IV	54 (54.0)	92 (80.0)	34 (66.7)	180 (67.7)		
Unknown	2 (2.0)	3 (2.6)	1 (2.0)	6 (2.3)		
Tumor differentiation						
Well	29 (29.0)	9 (7.8)	5 (9.8)	43 (16.2)	—	—
Moderate	39 (39.0)	51 (44.3)	28 (54.9)	118 (44.4)		
Poor	25 (25.0)	50 (43.5)	17 (33.3)	92 (34.6)		
Unknown	7 (7.0)	5 (4.3)	1 (2)	13 (4.9)		
Age at diagnosis (y)	56.96 ± 14.27§	55.13 ± 9.11	60.73 ± 10.68	56.89 ± 11.73	54.00 ± 15.45	0.021
Gender						
Women	36 (36.0)‖	25 (21.7)	10 (19.6)	71 (26.7)	126 (60.9)	<0.001
Men	64 (64.0)	90 (78.3)	41 (80.4)	195 (73.3)	81 (39.1)	
Race/ethnicity						
White, non-Hispanic	87 (87.0)	101 (87.8)	42 (82.4)	230 (86.5)	170 (82.1)	0.431
Black, non-Hispanic	11 (11.0)	9 (7.8)	8 (15.7)	28 (10.5)	29 (14.0)	
Other	2 (2.0)	5 (4.3)	1 (2.0)	8 (3.0)	8 (3.9)	
Marital status						
Married	57 (57.0)	69 (60.0)	29 (56.9)	155 (58.3)	95 (45.9)	0.007
Other	43 (43.0)	46 (40.0)	22 (43.1)	111 (41.7)	112 (54.1)	
Medical insurance						
Traditional	49 (49.0)	75 (65.2)	26 (51.0)	150 (56.4)	113 (54.6)	
Medicare	36 (36.0)	20 (17.4)	19 (37.3)	75 (28.2)	61 (29.5)	0.400
Medicaid	13 (13.0)	12 (10.4)	5 (9.8)	30 (11.3)	18 (8.7)	
Uninsured	2 (2.0)	8 (7.0)	1 (2.0)	11 (4.1)	15 (7.2)	
Smoking Status						
Never	29 (29.0)	31 (27.0)	1 (2.0)	61 (22.9)	110 (53.1)	<0.001
Former	40 (40.0)	47 (40.9)	20 (39.2)	107 (40.2)	40 (19.3)	
Current	31 (31.0)	37 (32.2)	30 (58.8)	98 (36.8)	57 (27.5)	
Packs/d	0.60 ± 0.60	0.46 ± 0.58	0.84 ± 0.55	0.58 ± 0.59	0.29 ± 0.57	<0.001
Alcohol use						
Never	59 (59.0)	54 (47.0)	26 (51.0)	139 (52.3)	144 (69.6)	<0.001
Ever	41 (41.0)	61 (53.0)	25 (49.0)	127 (47.7)	63 (30.4)	
Drinks/d	0.75 ± 1.29	0.82 ± 2.09	1.27 ± 2.23	0.88 ± 1.87	0.32 ± 0.89	<0.001
ABL (mm)	4.13 ± 1.53	3.79 ± 1.38	4.09 ± 1.11	3.97 ± 1.40	2.44 ± 0.93	<0.001
Missing teeth	9.49 ± 7.82	7.60 ± 6.86	12.20 ± 7.45	9.19 ± 7.51	7.18 ± 6.80	0.003

Abbreviation: TNM, tumor-node-metastasis.
*Primary squamous cell carcinoma of the oral cavity, oropharynx, and larynx.
†Patients with no history of cancer.
‡P values were derived from t tests for continuous and χ^2 tests for categorical variables comparing cases and controls.
§Mean ± SD.
‖Frequency (percent).

Table 2. Association of HNSCC with periodontal variables stratified by tumor site

	Crude OR (95% CI)	Adjusted* OR (95% CI)
Total HNSCC		
ABL (per millimeter)	3.85 (2.96-5.01)	4.36 (3.16-6.01)
Missing teeth (per tooth)	1.04 (1.01-1.07)	1.02 (0.99-1.05)
Oral cavity SCC		
ABL (per millimeter)	3.26 (2.44-4.36)	4.52 (3.03-6.75)
Missing Teeth (per tooth)	1.04 (1.04-1.08)	1.03 (0.99-1.06)
Oropharynx SCC		
ABL (per millimeter)	3.06 (2.29-4.07)	3.64 (2.54-5.22)
Missing teeth (per tooth)	1.01 (0.98-1.04)	0.99 (0.95-1.03)
Larynx SCC		
ABL (per millimeter)	3.75 (2.60-5.41)	2.72 (1.78-4.16)
Missing Teeth (per tooth)	1.09 (1.05-1.13)	1.05 (0.99-1.10)

*ORs were derived from multiple logistic regression analysis including age at diagnosis, gender, race/ethnicity, marital status, smoking status, alcohol use, ABL, and missing teeth.

measure of periodontitis history. The strength of the association was greatest in the oral cavity, followed by oropharynx and larynx. The association persisted in patients who never used tobacco and alcohol but it was strongest in former smokers. Furthermore, this study suggests that periodontitis history is associated with poorly differentiated tumors in the oral cavity. These results support additional, confirmatory basic science, and prospective clinical studies.

Although both are called periodontal disease, gingivitis and periodontitis are distinct diseases. Gingivitis is a nondestructive reversible inflammation of the gums strongly associated with poor oral hygiene. On the other hand, only a small subset of the population with poor oral hygiene develops destructive periodontitis, leading to epithelial migration and bone loss (6, 7). Factors that initiate periodontitis are poorly understood. Smoking reduces gingivitis (22) but it is a strong risk factor for periodontitis (7). Gingivitis is mostly associated with Gram-positive facultative bacteria, whereas periodontitis with Gram-negative anaerobics (6). Accumulating evidence supports a role of viruses in the initiation and progression of periodontitis (23, 24). Our recent study also suggests a synergy between chronic periodontitis and oral HPV infection in base of tongue cancers (18). A link between poor oral hygiene and HNSCC has been suggested (25-30). It is possible that, among subjects with poor oral hygiene, those who develop periodontitis are at higher risk for HNSCC. Prospective clinical studies including both periodontitis patients and those with gingivitis without a periodontitis history will allow testing this hypothesis.

ABL associated with periodontal inflammation is a slow chronic process that is usually irreversible. The rate of bone loss ranges between 0.04 and 0.28 mm annually (31, 32). In our study, panoramic radiographs were taken at admission before the initial cancer diagnosis. Mean ABL of the cases was 3.97 mm at admission. At the maximum rate of bone loss, this represents >14 years before the cancer diagnosis. Thus, it is not likely that cancer preceded periodontitis. The biological mechanism of the association between chronic infection/inflammation and cancer has been described extensively (4, 5). However, well-designed longitudinal studies are required to prove the temporal relationship and the causality between chronic periodontitis and HNSCC.

The conventional periodontal treatment stops further bone loss but does not result in significant bone gain. Thus, ABL measurements represent the history of periodontitis quite accurately regardless of treatment (33). There are two alternative clinical measures of periodontitis. The first one, clinical attachment loss, is highly correlated with ABL (33, 34). The other one, probing depth, does not reflect history of periodontitis accurately because it can be reduced with treatment (33). Missing teeth is a surrogate measure and could be misleading because not all teeth are lost due to periodontal disease. Finally, biomarkers of periodontal disease are inflammatory markers that can only document current disease activity (8). They also do not differentiate gingivitis from periodontitis. There is a general consensus that although chronic infections/inflammation promote carcinogenesis, acute infections/inflammation counteract or have no association with it (4, 5). The periodontal measurement we used was ideal to test our hypothesis and is a strength of this study documenting long-standing periodontitis history before the diagnosis of cancer.

Our potential patient pool included 89 edentulous patients at admission and we collected the same data for them. They represented ~16% of all patients. However, we excluded them from the statistical analyses (at the

Table 3. Association of HNSCC with periodontal variables stratified by smoking status and alcohol use

	Crude OR (95% CI)	Adjusted* OR (95% CI)	Interaction term† (95% CI)
Smoking status			
Never			
ABL (per millimeter)	4.25 (2.55-7.09)	5.96 (3.04-11.68)	
Missing teeth (per tooth)	1.02 (0.97-1.07)	0.94 (0.86-1.02)	Smoking status* ABL 0.69 (0.49-0.96)‡
Former			
ABL (per millimeter)	4.77 (2.67-8.52)	7.59 (3.51-16.42)	
Missing teeth (per tooth)	1.02 (0.97-1.07)	0.94 (0.88-1.01)	Smoking status* missing teeth 0.98 (0.94-1.03)§
Current			
ABL (per millimeter)	2.78 (1.90-4.07)	2.85 (1.85-4.40)	
Missing teeth (per tooth)	1.03 (0.98-1.08)	0.93 (0.87-1.00)	
Alcohol use			
Never			
ABL (per millimeter)	4.00 (2.84-5.63)	4.31 (2.82-6.58)	Alcohol use* ABL 0.82 (0.47-1.43)‖
Missing teeth (per tooth)	1.06 (1.03-1.10)	0.97 (0.92-1.02)	
Ever			
ABL (per millimeter)	3.41 (2.26-5.14)	4.45 (2.70-7.34)	Alcohol use* missing teeth 0.95 (0.88-1.02)¶
Missing teeth (per tooth)	1.00 (0.96-1.04)	0.92 (0.86-0.97)	

*ORs were derived from multiple logistic regression analysis including age at diagnosis, gender, race/ethnicity, marital status, smoking status, alcohol use, and missing teeth.
†Multiplicative interaction was evaluated by including an interaction term in the multiple logistic regression model.
‡$P = 0.032$ for the interaction between smoking status and ABL.
§$P = 0.474$ for the interaction between smoking status and missing teeth.
‖$P = 0.491$ for the interaction between alcohol use and ABL.
¶$P = 0.124$ for the interaction between alcohol use and missing teeth.

Table 4. Association of periodontitis with tumor stage and differentiation

	Periodontitis*		$P^{\dagger}$
	No	Yes	
Total HNSCC			
Tumor differentiation			
Well/moderate	48 (69.6)[‡]	113 (61.4)	0.230
Poor	21 (30.4)	71 (38.6)	
TNM stage			
Stage 0-II	23 (32.4)	57 (30.2)	0.728
Stage III-IV	48 (67.6)	132 (69.8)	
Oral cavity SCC			
Tumor differentiation			
Well/moderate	23 (88.5)	45 (67.2)	0.038
Poor	3 (11.5)	22 (32.8)	
TNM stage			
Stage 0-II	12 (46.2)	32 (44.4)	0.881
Stage III-IV	14 (53.8)	40 (55.6)	
Oropharynx SCC			
Tumor differentiation			
Well/moderate	20 (57.1)	40 (53.3)	0.709
Poor	15 (42.9)	35 (46.7)	
TNM stage			
Stage 0-II	7 (18.9)	13 (17.3)	0.837
Stage III-IV	30 (81.1)	62 (82.7)	
Larynx SCC			
Tumor differentiation			
Well/moderate	5 (62.5)	28 (66.7)	0.820
Poor	3 (37.5)	14 (33.3)	
TNM stage			
Stage 0-II	4 (50.0)	12 (28.6)	0.234
Stage III-IV	4 (50.0)	30 (71.4)	

*Periodontitis is defined as ABL $\geq$ 3.07 mm (median).
†P values were derived from χ^2 tests.
‡Frequency (percent).

expense of smaller sample size), because their disease history (periodontitis or dental caries) was not known. This was an analysis of existing data collected between 1999 and 2005 and most patients were deceased at the time the data for this study were analyzed. A significant percentage of teeth are lost due to dental caries, which are different types of infections. Cariogenic bacteria, *Streptococci*, *Lactobacilli*, and *Actynomyces* are associated with periodontal health (35, 36). In addition, edentulous patients were significantly different from dentate patients in respect to several demographic and life-style variables. Therefore, the estimate of periodontitis-HNSCC association would have been biased if we had included edentulous subjects in the analyses.

Our results suggest that smoking modifies the periodontitis-HNSCC association. The strength of the association was lower in current smokers compared with former and never smokers. Similar to our results, three recent studies have observed that the associations between oral health variables with head and neck, esophageal, pancreatic, and upper gastrointestinal cancers were weaker in smokers compared with nonsmokers (37-39). Studies have also consistently shown that although smoking is a risk factor for oral leukoplakia, the risk of malignant transformation is significantly decreased in smokers (40, 41). These observations, seemingly paradoxical, are consistent with the biological effects of smoking. Smoking causes acute vasoconstriction and inhibits angiogenesis, proliferation, and production of inflammatory mediators in response to bacterial stimuli (42-44). However, these potent suppressive effects of smoking are reversible within a few hours of smoking cessation (43, 44). Our understanding of the mechanism and temporal sequence of smoking-related carcinogenesis is limited. Prospective studies assessing the time relationships between cessation of smoking and its relation to inflammation and carcinogenesis are needed. Although statistically significant, the estimate of the smoking-ABL interaction was relatively imprecise. There are probably other factors such as types of tobacco, duration, and patterns of use that are likely to be important modifiers. In addition, sample size was not very large. Larger studies with more comprehensive assessment of tobacco history are needed to confirm this interaction.

The recent increase in a subset of HNSCC has also been attributed to the increased rates of HPV infection. Epidemiologic studies have shown that nonsmokers are more likely than smokers to have HPV-related HNSCC (45, 46). It is reasonable to hypothesize that the increase in HPV-related HNSCC is also related to the declining rates of smoking. The interactions between these risk factors may be essential to understand carcinogenesis in the head and neck.

This study suggests an association between chronic periodontitis and poorly differentiated tumors in the oral cavity. Continuous stimulation of cellular proliferation by chronic inflammation may be responsible for this histologic type (4, 5). Rapid cell division gives rise to replication errors and aberrant DNA repair. Several studies have established the increase in cytokine levels in patients with increasing grade of cervical intraepithelial neoplasia (47). Grading is subjective with high interobserver variability and we only observed this association in the oral cavity. Therefore, this association may be due to chance and needs further exploration.

Our study had limitations. Not all variables we would have liked were available in the existing patient records, including diet, HPV status, and more comprehensive data on tobacco and alcohol history. On the other hand, reliable basic information on alcohol and tobacco use, age, gender, race, ethnicity, marital status, access to medical insurance, histologic confirmation of tumor diagnoses, and quantitative and objective measure of periodontitis history was available. In addition, using existing data has advantages such as allowing us to conduct a blind and objective study. Another limitation of our study was its hospital-based study population, differing from the general population in a number of ways. On the other hand, using the same source of population for both cases and controls increases the efficiency and reduces bias.

The choice of an appropriate control group is the most critical and difficult issue in case-control studies. The crucial requirement is that they be comparable with the source population of the cases and that any exclusions made in the identification of cases apply equally to the controls. Hospital controls are frequently used because they share the same selective processes by which the cases were identified. In addition, the same methods of data collection used for both cases and controls minimize bias. Patients hospitalized with conditions associated with the exposure of interest (in our study, periodontitis) should be excluded (48). We applied the same exclusion criteria for both cases and controls and excluded immunocompromised subjects from both groups. We also excluded those with congenital anomalies, trauma, gunshot, and motor vehicle accidents because these conditions may involve

the periodontium. In addition, Institute employees were excluded because they probably represent a different population compared with regular clinic patients. The prevalence of periodontitis in the general population ranges between 4.2% and 35% according to the latest three national surveys (49). In our study population, the prevalence of periodontitis in the control group was 19.3%, which is within the range of the general population suggesting that the selection bias in our study is minimal.

Evidence of a periodontitis-HNSCC association has practical implications for prevention, early diagnosis, and treatment. Chronic periodontitis may represent a clinical high-risk profile for HNSCC. Although validation through further prospective studies is essential, prevention of periodontitis may decrease the incidence of HNSCC, whereas periodontal treatment, as an adjunct to conventional oncologic management, may improve the prognosis of this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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