Original Investigation

Dental Caries and Head and Neck Cancers

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IMPORTANCE Dental caries is the demineralization of tooth structures by lactic acid from fermentation of carbohydrates by commensal gram-positive bacteria. Cariogenic bacteria have been shown to elicit a potent Th1 cytokine polarization and a cell-mediated immune response.

OBJECTIVE To test the association between dental caries and head and neck squamous cell carcinoma (HNSCC).

DESIGN, SETTING, AND PARTICIPANTS Case-control study in a comprehensive cancer center including all patients with newly diagnosed primary HNSCC between 1999 and 2007 as cases and all patients without a cancer diagnosis as controls. Those with a history of cancer, dysplasia, or immunodeficiency or who were younger than 21 years were excluded.

EXPOSURES Dental caries, fillings, crowns, and endodontic treatments, measured by the number of affected teeth; missing teeth. We also computed an index variable: decayed, missing, and filled teeth (DMFT).

MAIN OUTCOMES AND MEASURES Incident HNSCC.

RESULTS We included 620 participants (399 cases and 221 controls). Cases had a significantly lower mean (SD) number of teeth with caries (1.58 [2.52] vs 2.04 [2.15]; $P = .03$), crowns (1.27 [2.65] vs 2.10 [3.57]; $P = .01$), endodontic treatments (0.56 [1.24] vs 1.01 [2.04]; $P = .01$), and fillings (5.39 [4.31] vs 6.17 [4.51]; $P = .04$) but more missing teeth (13.71 [10.27] vs 8.50 [8.32]; $P < .001$) than controls. There was no significant difference in mean DMFT. After adjustment for age at diagnosis, sex, marital status, smoking status, and alcohol use, those in the upper tertiles of caries (odds ratio [OR], 0.32 [95% CI, 0.19-0.55]; P for trend = .001), crowns (OR, 0.46 [95% CI, 0.26-0.84]; P for trend = .03), and endodontic treatments (OR, 0.55 [95% CI, 0.30-1.01]; P for trend = .15) were less likely to have HNSCC than those in the lower tertiles. Missing teeth was no longer associated with HNSCC after adjustment for confounding.

CONCLUSIONS AND RELEVANCE There is an inverse association between HNSCC and dental caries. This study provides insights for future studies to assess potential beneficial effects of lactic acid bacteria and the associated immune response on HNSCC.

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The American Cancer Society predicted an estimated 53 640 new cases of head and neck squamous cell carcinoma (HNSCC) and 11 520 deaths in 2013 in the United States.[1] A steady increase in the incidence of oropharyngeal cancers has been observed over the past 3 decades despite a substantial decline in tobacco consumption.[2] This increase has been attributed mainly to oral infection with human papillomavirus (HPV) type 16, which was shown to be a causal factor.[2] Whereas bacterial colonizations on oral mucosa also differ between healthy individuals and patients with cancer, a causal association between an oral bacterial infection and HNSCC has not been established.[3]

Dental caries (or decay) and periodontitis are major oral bacterial infections associated with dental plaque.[4,5] Although these 2 oral diseases are often combined in a single category as indicators of poor oral health, they are distinct in terms of both etiology and outcome. Periodontitis is a chronic inflammation of structures around the teeth associated with gram-negative anaerobic bacteria leading to alveolar bone loss (ABL).[5] It is characterized by Th2 and Th17 polarized immune responses.[5] In contrast, dental caries results from demineralization of teeth by lactic acid produced from the fermentation of carbohydrates by gram-positive facultative bacteria.[4] Cariogenic bacteria are associated with periodontal health, and decreased levels of these commensal bacteria have been shown to be associated with increased periodontal inflammation and destruction.[6-8] Multiple studies have shown that dental caries and associated bacteria elicit a potent Th1 immune response in peripheral blood mononuclear cells promoting $CD8^+$ T-cell response.[9-11]

Whereas Th2 and Th17 cell responses have been generally associated with increased risk of cancer, Th1 cell response has been consistently associated with decreased risk of cancer.[12]

We previously observed that periodontitis was associated with increased risk of oral potentially malignant disorders[13] and HNSCC.[14] The purpose of the present study was to test the association between dental caries and HNSCC.

Methods

Study Design and Population

We conducted a case-control study of newly presenting patients of the Department of Dentistry and Maxillofacial Prosthetics at Roswell Park Cancer Institute (RPCI). All patients seen between June 15, 1999, and September 14, 2007, except those who had a history of cancer, dysplasia, or immunodeficiency or were younger than 21 years were included. The RPCI patients come mainly from the surrounding Erie, Niagara, and Chautauqua counties and have a wide range of socioeconomic status. This study was reviewed and approved by institutional review boards of the RPCI and the State University of New York at Buffalo.

Cases

All patients with newly diagnosed primary HNSCC during the study period who met the inclusion criteria were included as cases. The following sites, identified from the RPCI Tumor Registry according to the *International Classification of Diseases for Oncology*, Third Edition,[15] were included: oral cavity, including 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 other parts of the mouth (C06.8-C06.9); oropharynx, including base of tongue (C01.0), soft palate (C05.1), tonsil (C09.0-C09.9), and oropharynx (C10.0-C10.9); and larynx (C32.0-C32.9).

Controls

All new patients seen at the department during the same time period as the cases but who did not have a diagnosis of cancer or dysplasia and met the inclusion criteria were included as controls. These included general dentistry patients, as well as those with a diagnosis of benign mucosal lesions such as fibroma, lipoma, wart, traumatic lesion, mucocele, cyst, abscess, pyogenic granuloma, frictional keratosis, and chemical burn. Employees of RPCI were excluded because they represent a different referent population from the one that the cases came from. The diagnoses of controls were obtained from the RPCI Hospital Information System.

Assessment of Oral Variables

The numbers of teeth with caries, fillings, crowns, and endodontic treatments, as well as the severity of periodontitis and missing teeth, were assessed from panoramic radiographs taken at admission before treatment. Severity of periodontitis was assessed according to extent of ABL in millimeters as described previously.[14] One examiner blind to cancer status performed all dental measurements. To establish intraexaminer reliability, duplicate measurements were made on 5 randomly selected patients (110 teeth/207 sites). The κ statistics for the numbers of teeth with caries, fillings, crowns, and endodontic treatments and missing teeth were 0.91, 0.96, 1.00, 1.00, and 1.00, respectively. The mean (SD) differences of duplicate ABL measurements were 0.22 (0.41) mm.

Explanatory Variables

Information on the following variables, obtained at the time of diagnosis, was available in patient records: age at diagnosis, sex, race (white, black, Asian, or other), ethnicity (Hispanic or non-Hispanic), marital status (married, single, divorced, widowed, or separated), medical insurance (traditional, Medicare, Medicaid, or uninsured), smoking status (never, former, or current; packs per day), alcohol use (no or yes; drinks per day), tumor stage (I-IV), and tumor differentiation (poor, moderate, well).

Statistical Analysis

Demographic, lifestyle, and clinical characteristics of the study population were summarized by frequency distributions for categorical variables and means with standard deviation for continuous variables. We computed decayed, missing, and filled teeth (DMFT), a widely used measure of caries history.[16] To estimate the unadjusted association of HNSCC with dental caries and other exposure variables, crude odds ratios (ORs) and their 95% confidence intervals were calculated from cross-tabulations. Tertiles in the control group were used to categorize exposure variables. The independent association of each exposure variable with HNSCC was estimated from multiple logistic regression analysis. Because of colinearity, each dental variable was evaluated in a separate model. For variable selection, we assessed change in OR when the covariate was added individually to the model. Potential effect modification in the association of dental caries with HNSCC by each covariate was evaluated in stratified analyses and by including multiplicative interaction terms in regression models. A 2-sided $P \leq .05$ was considered statistically significant. SPSS Statistics, version 20.0 (IBM), was used for all data analyses.

Results

A total of 620 participants (399 cases and 221 controls) were included. Of the 399 patients with HNSCC, 146 (36.6%) had a diagnosis of oral cavity squamous cell carcinoma (SCC), 151 (37.8%) of oropharyngeal SCC, and 102 (25.6%) of laryngeal SCC. The prevalences of men ($P < .001$), smokers ($P < .001$), alcohol users ($P < .001$), and married participants ($P = .01$) were significantly higher among cases compared with controls. The cases were significantly older (mean age, 58.62 vs 54.35 years; $P < .001$), smoked more cigarettes (mean, 0.69 vs 0.30 packs/d; $P < .001$), and consumed more alcohol (mean, 0.88 vs 0.31 drinks/d; $P < .001$) compared with controls. The mean numbers of teeth with caries (1.58 vs 2.04; $P = .03$), endodontic treatments (0.56 vs 1.01; $P = .005$), crowns (1.27 vs 2.10; $P = .004$), and fillings (5.39 vs 6.17; $P = .04$) were significantly lower among cases compared with controls. Conversely, the sever-

Table 1. Description of the Study Population

Characteristic	Patients, No. (%)		P Value[c]
	Cases (n = 399)[a]	Controls (n = 221)[b]	
Age at diagnosis, mean (SD), y	58.62 (11.43)	54.35 (15.57)	<.001
Sex, No. (%)			
Female	118 (29.6)	134 (60.6)	<.001
Male	281 (70.4)	87 (39.4)	
Race/ethnicity, No. (%)			
White, non-Hispanic	345 (86.5)	183 (82.8)	.45
Black, non-Hispanic	44 (11.0)	30 (13.6)	
Other	10 (2.5)	8 (3.6)	
Marital status, No. (%)			
Married	222 (55.6)	100 (45.2)	.01
Other	177 (44.4)	121 (54.8)	
Medical insurance, No. (%)			
Traditional	201 (50.4)	118 (53.4)	.10
Medicare	139 (34.8)	70 (31.7)	
Medicaid	46 (11.5)	18 (8.1)	
Uninsured	13 (3.3)	15 (6.8)	
Smoking			
Status, No. (%)			
Never	71 (17.8)	116 (52.5)	<.001
Former	168 (42.1)	42 (19.0)	
Current	160 (40.1)	63 (28.5)	
Consumption, mean (SD), packs/d	0.69 (0.59)	0.30 (0.57)	<.001
Alcohol use[d]			
No, No. (%)	197 (55.0)	154 (70.3)	<.001
Yes, No. (%)	161 (45.0)	65 (29.7)	
Consumption, mean (SD), drinks/d	0.88 (1.84)	0.31 (0.87)	<.001
Dental variables, mean (SD), teeth, No.			
Dental caries	1.58 (2.52)	2.04 (2.15)	.03
Crowns	1.27 (2.65)	2.10 (3.57)	.004
Endodontic treatments	0.56 (1.24)	1.01 (2.04)	.005
Fillings	5.39 (4.31)	6.17 (4.51)	.04
Missing teeth	13.71 (10.27)	8.50 (8.32)	<.001
DMFT	16.40 (6.79)	15.39 (6.31)	.09
Alveolar bone loss, mean (SD), mm	4.03 (1.33)	2.44 (0.93)	<.001

Abbreviation: DMFT, decayed, missing, and filled teeth.

[a] Patients with incident primary squamous cell carcinoma of the oral cavity, oropharynx, or larynx.

[b] Patients with no history of cancer.

[c] *P* values were derived from *t* tests for continuous variables and from χ^2 tests for categorical variables comparing cases and controls.

[d] Alcohol use data were missing for some participants.

ity of ABL (mean, 4.03 vs 2.44 mm; $P < .001$) and the mean numbers of missing teeth (13.71 vs 8.50; $P < .001$) were significantly higher among cases compared with controls. The cases were not significantly different from controls with respect to race and ethnicity, access to medical insurance, and DMFT (**Table 1**).

In univariate analyses, participants in the upper tertiles of caries (OR, 0.37 [95% CI, 0.24-0.58]; *P* for trend <.001), crowns (OR, 0.46 [95% CI, 0.29-0.75]; *P* for trend = .01), and endodontic treatments (OR, 0.46 [95% CI, 0.28-0.77]; *P* for trend = .01) were significantly less likely to have HNSCC compared with those in the lower tertiles. Conversely, participants in the upper tertiles of missing teeth (OR, 2.58 [95% CI, 1.73-3.85]; *P* for trend <.001) and DMFT (OR, 1.58 [95% CI, 1.02-2.44]; *P* for trend = .06) were significantly more likely to have HNSCC. After adjustment for age at diagnosis, sex, marital status, smoking status, and alcohol use, participants in the upper tertiles of caries (OR, 0.32 [95% CI, 0.19-0.55]; *P* for trend = .001), crowns (OR, 0.46 [95% CI, 0.26-0.84]; *P* for trend = .03), and endodontic treatments (OR, 0.55 [95% CI, 0.30-1.01]; *P* for trend = .15) were less likely to have HNSCC compared with those in the lower tertiles. Missing teeth and DMFT were no longer associated with HNSCC after adjustment for confounding (**Table 2**).

Stratified analysis by tumor site has shown that dental caries was associated with HNSCC among patients with oral cavity SCC (OR, 0.30 [95% CI, 0.16-0.57]; *P* for trend <.001) and oropharyngeal SCC (OR, 0.27 [95% CI, 0.13-0.56]; *P* for trend <.001) but not among those with laryngeal SCC (OR, 0.89 [95% CI, 0.36-2.23]; *P* for trend = .67) (**Table 3**).

There were no significant interactions between dental caries and any of the other exposure variables. The association between dental caries and HNSCC remained statistically significant among never smokers (OR, 0.27 [95% CI, 0.09-0.79];

Table 2. Association of Head and Neck Squamous Cell Carcinoma With Dental Caries and Their Treatments

Characteristic, Teeth, No.[a]	Patients, No. (%)		Unadjusted Odds Ratio (95% CI)	Adjusted[b] Odds Ratio (95% CI)
	Cases	Controls		
Caries				
0	148 (48.2)	60 (29.0)	1 [Ref]	1 [Ref]
1-2	96 (31.3)	78 (37.7)	0.50 (0.33-0.76)	0.49 (0.30-0.80)
≥3	63 (20.5)	69 (33.3)	0.37 (0.24-0.58)	0.32 (0.19-0.55)
P value for trend			<.001	<.001
Crowns				
0	203 (66.1)	116 (56.0)	1 [Ref]	1 [Ref]
1-3	66 (21.5)	44 (21.3)	0.86 (0.55-1.34)	1.00 (0.60-1.69)
≥4	38 (12.4)	47 (22.7)	0.46 (0.29-0.75)	0.46 (0.26-0.84)
P value for trend			.01	.03
Endodontic treatments				
0	218 (71.0)	125 (60.4)	1 [Ref]	1 [Ref]
1	56 (18.2)	41 (19.8)	0.78 (0.50-1.24)	0.95 (0.57-1.61)
≥2	33 (10.7)	41 (19.8)	0.46 (0.28-0.77)	0.55 (0.30-1.01)
P value for trend			.01	.15
Fillings				
≤3	123 (40.1)	63 (30.4)	1 [Ref]	1 [Ref]
4-7	86 (28.0)	74 (35.7)	0.60 (0.39-0.92)	0.73 (0.44-1.21)
≥8	98 (31.9)	70 (33.8)	0.72 (0.47-1.10)	1.19 (0.72-1.97)
P value for trend			.06	.17
DMFT				
≤12	88 (28.7)	70 (33.8)	1 [Ref]	1 [Ref]
13-18	94 (30.6)	74 (35.7)	1.01 (0.65-1.57)	0.97 (0.58-1.63)
≥19	125 (40.7)	63 (30.4)	1.58 (1.02-2.44)	1.23 (0.72-2.10)
P value for trend			.06	.61
Missing teeth				
≤3	90 (22.6)	77 (34.8)	1 [Ref]	1 [Ref]
4-9	86 (21.6)	70 (31.7)	1.05 (0.68-1.63)	0.94 (0.57-1.56)
≥10	223 (55.9)	74 (33.5)	2.58 (1.73-3.85)	1.57 (0.95-1.58)
P value for trend			<.001	.08

Abbreviations: DMFT, decayed, missing, or filled teeth; ref, reference.

[a] Numbers of teeth are categorized by tertiles.

[b] Adjusted odds ratios were derived from multiple logistic regression models including age at diagnosis, sex, marital status, alcohol use, and smoking status.

P for trend = .05) and never drinkers (OR, 0.35 [95% CI, 0.19-0.67]; *P* for trend = .04).

Discussion

We observed an inverse association between dental caries and HNSCC, which persisted among never smokers and never drinkers. This association remained significant among patients with oral cavity and oropharyngeal SCC but not among those with laryngeal SCC. Besides untreated caries, 2 other objective measures of long-standing caries history (endodontic treatments and crowns) were also inversely associated with HNSCC with similar effect sizes. This supports the validity of the association between dental caries and HNSCC, suggesting that it is not likely a chance finding. Missing teeth was associated with increased risk of HNSCC in univariate analyses, but after adjustment for potential confounders, its effect was attenuated and was no longer statistically significant.

An increased risk of HNSCC among subjects with periodontitis was reported previously.[13,14] To our knowledge, the present study suggests, for the first time, an independent association between dental caries and HNSCC. An inverse association was an unexpected finding because dental caries has been considered a sign of poor oral health. A limited number of previous studies all used composite indices combining dental caries with other oral variables.[17-19] Graham et al[17] formed a "dentition index" combining decayed, missing, and septic teeth with oral hygiene and condition of prostheses. After adjustment for smoking and alcohol use, inadequate dentition was associated with an increased risk of oral cavity cancer (Mantel-Haenszel relative risk, 3.15; *P* < .001). Talamini et al[18] defined "general oral condition" as a composite index of decayed teeth, tartar, and mucosal irritation. A poor general oral condition was associated with an increased risk of oral cavity and oropharyngeal cancers (OR, 4.5 [95% CI, 1.8-10.9]) after adjustment for age, sex, fruit and vegetable intake, smoking, and alcohol use. In an international study, Guha et al[19] defined "general oral health" by the presence of decaying teeth, tartar, gingival bleeding, and mucosal irritation. Poor oral health was associated with an increased risk of HNSCC (oral cavity, pharynx, and larynx) in both central Europe (OR, 2.89 [95% CI, 1.74-4.81]) and Latin America (OR, 1.89 [95% CI, 1.47-2.42]). Because poor oral hygiene, periodontal disease, and missing teeth

Table 3. Association of Head and Neck Squamous Cell Carcinoma With Dental Caries by Tumor Site

Tumor Site, Caries, No.	Patients, No. (%)		Crude Odds Ratio (95% CI)	Adjusted[a] Odds Ratio (95% CI)
	Cases	Controls		
Oral Cavity				
0	63 (54.3)	60 (29.0)	1 [Ref]	1 [Ref]
1-2	30 (25.9)	78 (37.7)	0.37 (0.21-0.63)	0.38 (0.20-0.70)
≥3	23 (19.8)	69 (33.3)	0.32 (0.18-0.57)	0.30 (0.16-0.57)
P value for trend			<.001	<.001
Oropharynx				
0	68 (56.2)	60 (29.0)	1 [Ref]	1 [Ref]
1-2	33 (27.3)	78 (37.7)	0.37 (0.22-0.64)	0.49 (0.27-0.90)
≥3	20 (16.5)	69 (33.3)	0.26 (0.14-0.47)	0.27 (0.13-0.56)
P value for trend			<.001	<.001
Larynx				
0	17 (24.3)	60 (29.0)	1 [Ref]	1 [Ref]
1-2	33 (47.1)	78 (37.7)	1.49 (0.76-2.93)	1.28 (0.55-3.03)
≥3	20 (28.6)	69 (33.3)	1.02 (0.49-2.13)	0.89 (0.36-2.23)
P value for trend			.38	.67

Abbreviation: ref, reference.

[a] Odds ratios and their 95% CIs at each head and neck site were derived from multiple logistic regression analysis after adjustment for age at diagnosis, sex, marital status, smoking status, and alcohol use.

are all associated with increased risk of HNSCC, an index variable combining these conditions with dental caries will have an apparent positive association with HNSCC, masking the true individual associations.

Mutans streptococci have been suggested as the major cariogenic bacteria, although other acidogenic and aciduric bacterial species including non-mutans streptococci, lactobacilli, actinomycetes, bifidobacteria, and veillonellae also play important roles in the caries process.[4] The potential mechanisms by which these commensal bacteria may protect the host from cancer include (1) production of antitumorigenic and antimutagenic compounds; (2) regulation of the cytokine production profile of host cells, promoting cell-mediated response with interferon γ, interleukin 2, interleukin 12, and lymphotoxin α as the prototypic cytokines; (3) production of antimicrobial substances; (4) clearance, inhibition of growth, and downregulation of fimbrial expression of gram-negative bacteria that are potent stimulators of inflammation; (5) production of surfactants; (6) competition with pathogens for adhesion receptors and nutrients; and (7) stabilization of a low pH.[20] Interactions between the commensal flora and the host are important for stimulating local mucosal and systemic immunity, tolerance and fine-tuning of T-cell receptor function, epithelial turnover, mucosal vascularity, and lymphoid tissue mass. Dysregulation of such interactions might tip the balance from protective-adaptive to an inflammatory response and result in loss of antitumor effects.[20]

Supporting our results, a recent study has shown that the prevalence of streptococci in the normal esophagus was significantly higher than that in esophagitis and Barrett esophagus.[21] A type 1 microbiome dominated by the genus *Streptococcus* concentrated in the normal esophagus, and a type 2 microbiome, characterized by gram-negative anaerobes, was associated with esophagitis and Barrett esophagus. The shift from type 1 to type 2 microbiome was significantly correlated with decreasing levels of streptococci. It has also been shown that patients receiving chemotherapy experience a shift in the oral flora from largely oral streptococci to a more pathogenic gram-negative anaerobic flora that contributes to oral mucositis.[22]

Whereas caries are localized to tooth surfaces, the commensal cariogenic bacteria are extensively present in saliva and on aerodigestive mucosa. Spread of oral commensals and pathogens to distant body sites by saliva, aspiration, or blood has been demonstrated by many studies.[23] Saliva plays an important role in field cancerization by providing a means of transport from 1 surface to another, as well as a means of interaction between different carcinogens.[24] In a previous study with the same source population, we had observed that periodontitis, a chronic inflammatory disease, was associated with oral cavity, oropharyngeal, and laryngeal cancers.[14] In the present study, dental caries was associated with HNSCC among patients with oral cavity and oropharyngeal cancers but not among those with laryngeal cancers. Almost all patients with laryngeal cancer (98%) had a history of smoking, compared with 76% and 78% of patients with oral cavity and oropharyngeal cancers. They also consumed significantly greater amounts of tobacco and alcohol, were older, and had more missing teeth.

The number of missing teeth was associated with increased HNSCC risk in univariate analysis, but its effect size was attenuated and lost statistical significance after adjustment for explanatory variables. Whereas few previous studies reported a positive association between tooth loss and HNSCC,[25-27] most studies, similar to ours, reported a nonsignificant association after adjustment for confounding.[18,19,28,29] Missing teeth can be misleading as a surrogate measure for caries or periodontitis when their relationships with HNSCC are assessed because the etiologies, as well as the outcomes, of these 2 diseases are very different. Because periodontitis is associated with an increased risk of HNSCC, the risk will increase proportional to the number of affected teeth. Conversely, if dental caries is inversely associated with HNSCC, the risk will decrease proportional to the number of affected teeth. Therefore, the association between missing teeth and HNSCC

depends on the reason for tooth loss. The number of DMFT was also not associated with HNSCC in the present study, which was not a surprise. The number of DMFT is a measure of dental caries with a long record of use in the literature and is widely accepted around the world.[16] However, it is a composite index combining untreated dental caries with missing teeth and fillings, and for the reasons discussed here, it does not represent dental caries history accurately.

Missing teeth is a difficult issue to deal with especially in retrospective studies when the reason for tooth loss is unknown. In our initial analyses, we assessed the effect of missing teeth as a potential confounder and an effect modifier. Dental caries was not significantly correlated with missing teeth ($r = -0.012$). When missing teeth was added as a covariate to the model, the change in the main effect estimate (OR) was only 0.02, suggesting that missing teeth was not a significant confounder. In addition, potential effect modification by missing teeth was evaluated in stratified analyses and by including an interaction term in the multiple logistic regression. There was no significant interaction between missing teeth and caries ($P = .77$). The association between dental caries and HNSCC remained significant in subjects with low, moderate, and high numbers of missing teeth (categorized by tertiles) with similar effect sizes in all strata.

The present study analyzed existing data, and the information on certain potential confounders, including socioeconomic status (SES), diet, and HPV status was not available. The SES variables are highly correlated with each other, with higher education usually leading to higher income, better residence, and better health insurance.[30,31] Therefore, surrogate variables of SES, such as zip code or medical or dental insurance, may be used when data on traditional SES variables such as education and income are not available. In the present study, the only standard SES variable available for all study participants was medical insurance, and 51.5% had employer-sponsored insurance, 33.7% had Medicare, 10.3% had Medicaid, and 4.5% were uninsured. According to the Census Bureau's 2011 Current Population Survey, 55.3% of the US general population is covered by employer-sponsored insurance, 14.5% by Medicare, 15.9% by Medicaid, and 16.3% is uninsured.[31] Although the proportions of employer-sponsored insurance and Medicaid in our study population were similar to those of the general US population, the proportion of subjects with Medicare was higher and the proportion of uninsured subjects was lower. This is expected because our study population is hospital-based and older.

Frequent consumption of sugar is an important factor in the etiology of dental caries.[4] On the other hand, an inverse association between fruit and vegetable intake and the risk of HNSCC is well established.[17,20] It is likely that sugar and acid in fruits contributed to the higher frequency of dental caries in controls while lowering their risk of HNSCC. Therefore, the role of diet in the association between dental caries and HNSCC needs to be assessed in future studies.

Data regarding HPV status were available for a subset of patients with cancer. Among 125 patients with known HPV status, the mean numbers of teeth with dental caries (1.37 vs 1.86; $P = .37$), fillings (5.25 vs 5.40; $P = .86$), endodontic treatments (0.46 vs 0.57; $P = .63$), and crowns (0.90 vs 0.93; $P = .95$) were not significantly different in patients with HPV-negative and HPV-positive tumors, suggesting that HPV is not likely to influence the effect estimate. In addition, there is no known association between dental caries and oral HPV infection.

Another limitation of the study is that detailed data on dental caries, including their depth and location, were not available. It is known that radiographs underestimate the frequency and extent of dental caries, especially in early stages.[32] However, because the same methods were used for cases and controls and all measurements were performed by 1 examiner blind to cancer status, the measurement bias is not likely to be significant and would only lead to underestimation of the true effect.[33] The radiographs from which dental caries was assessed were obtained at the time of diagnosis before cancer treatment was initiated. Dental caries is a chronic disease, which starts and progresses slowly, and detectable dental caries on radiographs reflects preexisting disease history. Therefore, despite the case-control design of the present study, existing data provide evidence of temporality that dental caries preceded cancer diagnosis.

An important strength of the present study is that the cases and controls were selected from the same source population, the same way. All case and control patients with new diagnoses who met the inclusion criteria during the study period were included without knowledge of their dental status. Therefore, the selection bias in this study is also not likely to be significant.[33]

Although the importance of the local environment for carcinogenesis is widely accepted, research evaluating the role of oral factors in the natural history of HNSCC is lacking. If confirmed by other studies, the findings of this study have important implications for the management of HNSCC, as well as oral infections. It is important to remember that the majority of commensal bacteria are beneficial to the host, and streptococci are the most abundant genus in the oral cavity (52%).[34] Cariogenic bacteria are part of the commensal oral flora, and their presence is not sufficient to cause dental caries in the absence of the other risk factors, such as dental plaque, frequent consumption of a carbohydrate-rich diet, and reduced saliva production.[4] Caries is a dental plaque–related disease. Lactic acid bacteria cause demineralization (caries) only when they are in dental plaque in immediate contact with the tooth surface. The presence of these otherwise beneficial bacteria in saliva or on mucosal surfaces may protect the host against chronic inflammatory diseases and HNSCC. We could think of dental caries as a form of *collateral damage* and develop strategies to reduce its risk while preserving the beneficial effects of the lactic acid bacteria. For example, antimicrobial treatment, vaccination, or gene therapy against cariogenic bacteria may lead to more harm than benefit in the long run, including a shift in microbial ecology toward gram-negative bacteria and increased risks of chronic inflammatory diseases and cancer. Instead, strategies preserving microbial ecology beneficial to the host such as mechanical plaque control, preservation of saliva, and use of fluoride, as well as control of diet and other risk factors, might be wiser. Future studies assessing the potential effects of the oral microbiome and associated immune responses on HNSCC will help elucidate the biological mechanism of the clinical association that we have observed in this study.

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