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Periodontal disease and mouthwash use are risk factors for head and neck squamous cell carcinoma

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Abstract

Purpose—The purpose of this study was to examine associations between oral hygiene, including history of periodontal disease and mouthwash use, and risk of head and neck squamous cell carcinoma (HNSCC).

Methods—We measured history of oral hygiene and dental care on 513 HNSCC cases and 567 controls from a population-based study of HNSCC. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CI).

Results—Periodontal disease was associated with a slightly elevated risk of HNSCC (OR = 1.09, 95% CI: 1.02, 1.16). Using any type of mouthwash at least once per day was associated with increased risk compared to never using mouthwash (OR = 1.11, 95% CI: 1.02, 1.20). HNSCC was associated with frequent use of nonalcoholic mouthwash compared to using any kind of mouthwash rarely or never (OR = 1.24, 95% CI: 1.05, 1.47).

Conclusions—Our results support an association between periodontal disease and HNSCC. Our data suggest that mouthwash use is associated with HNSCC, but we noted no difference between the effects of alcohol-containing and nonalcoholic mouthwashes.

Keywords

Periodontal disease; mouthwash use; oral hygiene; head and neck cancer

Introduction

Head and neck squamous cell carcinoma (HNSCC), the most common type of head and neck cancer, accounts for about 10% of incident cancer cases in the world [1] and for approximately 52,000 new cases annually in the United States [2]. The major risk factors for these cancers include tobacco smoking [3], alcohol use [4], and human papillomavirus (HPV) [5,6].

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Conflict of Interest Statement
The authors declare that they have no conflict of interest.

In recent years, researchers have additionally evaluated aspects of dental hygiene as risk factors for HNSCC. In particular, poor dental health, lack of regular dental care, and the development of periodontitis have been identified as possible risk factors for HNSCC, particularly in the oral cavity [7–9]. Periodontal disease involves a shift in bacterial flora in the gums, accompanied by a potentially pathogenic inflammatory response [10]. This inflammation may be associated with alterations of the immune system [11], leading to increased cellular proliferation and generation of potentially DNA-damaging free-radicals. It has also been hypothesized that poor dental health facilitates the conversion of ethanol to the mutagenic acetaldehyde through the metabolic activity of bacterial enzymes [12,13].

The possible effect of alcohol-containing mouthwashes on oral carcinogenesis also has been posited to contribute to oral cancer, but the epidemiologic data addressing this question have been inconsistent. Epidemiological and biological data suggest that long term use of alcohol-containing mouthwashes increases the risk of oral cancer [14]. Furthermore, it is thought that the use of alcohol-containing mouthwashes may affect oral health in a similar fashion as drinking alcohol. Previous studies on the association of dental hygiene and HNSCC have focused on cancers of the oral cavity and pharynx [15,16] and prior studies assessing mouthwash use primarily evaluated alcohol-containing mouthwash or did not distinguish by alcohol content [14]. However, although alcohol should not normally come into contact with the larynx, it is an accepted risk factor for laryngeal cancer [17,18], and we therefore have included subjects with cancers of the larynx in our analysis. Here we examine the association between dental insurance history, frequency of visits to a dental provider, periodontal disease, mouthwash and fluoride use, and the risk of HNSCC. In addition we examine whether alcohol content and quantity of mouthwash use modify cancer risk.

Methods

Study population

Incident cases of HNSCC diagnosed between October 2006 and June 2011 were recruited from 9 medical facilities in the Boston area, and controls were selected during over the same time frame using Massachusetts town lists, frequency-matched by sex, age (+/− 3 years), and town of residence from the same population. Subjects were eligible if they were 18 years of age or older, and cases had International Classification of Disease, Ninth Revision (ICD-9) diagnosis codes of 141–146, 148, 149, or 161. Cases were excluded if they were recurrent or were diagnosed more than six months prior to contact. A total of 513 cases and 567 controls were available for this analysis. All cases and controls in this study provided written informed consent as approved by the Institutional Review Boards of the participating institutions.

Cases and controls responded to an extensive questionnaire which collected information on demographics, family history of diseases, smoking and drinking habits, medical conditions, occupational history, dental insurance status, frequency of dental visits, history of periodontal disease, and mouthwash use, among other information. Cases were instructed to provide their pre-treatment information so to avoid confounding, for example, between chemotherapy and mouthwash use. Periodontal disease and mouthwash use were self-reported. Participants reported brand and frequency of mouthwash used and we approximated the percentage of alcohol in reported mouthwash.

Statistical analysis

Multiple imputation was performed to correct for missingness among covariates, specifically income, for which 12% of the data is missing. Data were imputed on age, gender, race, smoking, drinking, education and income. In addition to missing income data, education was

missing for four subjects (0.3%), drinking was missing for four subjects (0.3%), and race was missing for two subjects (0.2%). After imputing missing values, a total of 513 cases and 567 controls were available for analysis, including 148 oral cavity cases, 293 pharyngeal cases, and 68 laryngeal cases (4 cases were missing site). Case and control differences across baseline characteristics were assessed using t-tests for continuous variables and chi-square tests for categorical variables, controlling for sex and age. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated using unconditional logistic regression, controlling for age, race (White or non-White), sex, pack years smoked, average alcoholic drinks per week, education status (some college or more versus no college), and income level (above or below $50,000 per year). Models for mouthwash use, fluoride use, and dental insurance status were additionally adjusted for history of periodontal disease. Additional analyses were stratified by primary cancer site (oral, pharyngeal, laryngeal), smoking status (ever/never), and alcohol consumption status (non-drinker, ≤ 2 drinks/day, > 2 drinks/day). One drink was defined as 1.5 oz. liquor, 12 oz. beer, or 4 oz. wine. All analyses were performed using R (version 2.15) and multiple imputation was conducted using the R package *mi* [19–21].

Results

The distributions of demographics and HNSCC risk factors are provided by case-control status in Table 1. Cases were more likely than controls to be White ($p = 0.038$) and less likely to have a post-high school education ($p < 10^{-5}$). As expected, cases smoked more cigarettes ($p < 10^{-8}$) and drank more alcohol ($p < 10^{-7}$) than controls. The mean age was about 60 years with a 3:1 ratio of men to women for both cases and controls.

Having a history of periodontal disease was associated with a statistically significant increase in risk of HNSCC (OR = 1.09, 95% CI: 1.02, 1.16), which was similar for all tumor sites (Table 2). Using mouthwash at least once per day, compared to never using mouthwash, was associated with an 11% increase in risk of HNSCC (OR = 1.11, 95% CI: 1.02, 1.20); however, no association was observed for mouthwash and laryngeal cancer (Table 2). Additionally, HNSCC was associated with use of nonalcoholic mouthwash and marginally associated with use of alcoholic mouthwash, compared to using any kind of mouthwash rarely or never. Use of alcohol-containing mouthwash was associated with a 7% higher risk of pharyngeal cancer (OR = 1.07, 95% CI: 1.00, 1.13), but no associations were observed with other sites. Compared with using low alcohol or non-alcoholic mouthwash infrequently, subjects who used low or nonalcoholic mouthwash frequently were at significantly higher risk for HNSCC (OR = 1.24, 95% CI: 1.05, 1.47) and subjects who used high alcoholic mouthwash frequently were at a marginally elevated risk (OR = 1.07, 95% CI = 0.99, 1.16); estimates were similar for oral and pharyngeal cancer, although no association was observed with laryngeal cancer.

Subjects who reported having dental insurance for the majority of their lives were at significantly lower risk for oral cancer relative to those who did not (OR = 0.92, 95% CI = 0.86, 0.98); no association was observed between dental insurance status and pharyngeal or laryngeal cancer. There was no difference between cases and controls in fluoride use or frequency of dental visits.

We additionally explored possible interactions between dental factors and smoking and alcohol consumption, respectively. No interactions were observed for alcohol consumption (Table 3) or smoking status (Table 4).

Discussion

In this case-control study, a history of periodontitis was found to be a significant risk factor for HNSCC at all sites. Mouthwash use was a significant risk factor for oral cavity and pharyngeal but not for laryngeal cancer. The amount of alcohol in mouthwash was not associated with risk, and non-alcoholic mouthwash was also found to be a significant risk factor for HNSCC. Having dental insurance for the majority of life was associated with a lower risk of cancer of the oral cavity but not of the pharynx or larynx.

Our analysis supports findings in the existing literature that periodontal disease is a risk factor for HNSCC. Tezal et al. [9] studied the relationship between chronic periodontitis and the risk of HNSCC by performing radiographs on cases and controls to measure periodontitis as indicated by alveolar bone loss (ABL); each millimeter of ABL was associated with a more than four-fold increased risk of HNSCC. Periodontal pathogens initiate an inflammatory response around the gums and alveolar bone [11]. This inflammatory response may then lead to a systemic inflammatory condition that results in a breakdown of pathways in the immune system and can aid in tumor progression [8,22]. Fluoride use has been shown to reduce the accumulation of pathogenic oral bacteria [23], although we found no associated between fluoride use and risk of HNSCC in this study. In another case control study, no significant associations between periodontal disease and cancer of the oral cavity or pharynx were found [24].

Poor dental hygiene is highly associated with periodontal disease [25], and has also been found to be associated with the development of HNSCC, perhaps through the development of periodontitis. Moreno-Lopez et al. [26] found that subjects who reported brushing their teeth daily and subjects who visited a dentist at least once a year were at significantly reduced risk of developing oral cancer. Another case-control study [27] found that infrequent tooth brushing was associated with an increased risk of HNSCC at all three sites (oral, pharyngeal and laryngeal). Talamini et al. [5] found that visiting a dentist infrequently and brushing teeth less frequently than once per day were significant risk factors for oral but not pharyngeal cancer. Guha et al. [8] studied the effect of oral health on HNSCC at all three sites and found that infrequent dental visits was a risk factor for pharyngeal and laryngeal cancer but not oral cancer, while another case-control study [28] reported infrequent tooth brushing to be a significant risk factor for oral cancer.

One mechanism commonly suggested for the effect of alcohol on the risk of HNSCC is the conversion of ethanol into the mutagenic acetaldehyde [29,30]. A prior study found that subjects with intermediate or poor dental hygiene status had significantly higher levels of salivary acetaldehyde compared with subjects with good dental hygiene after adjusting for gender, age, smoking, and drinking [7]. However, despite the presumption that these differences stem from ingested alcohol that is converted into acetaldehyde, the study found that subjects who rarely or never drank alcohol had similar levels of salivary acetaldehyde to moderate or heavy drinkers. The authors note that some of the alcohol converted to acetaldehyde may come from mouthwash, although they caution that mouthwash use may be a reflection of overall oral health. A 2008 review [14] concluded that there is sufficient evidence linking alcohol-containing mouthwash to oral cancer and suggested the use of non-alcoholic mouthwashes; however, to date, no studies appear to have examined the effect of non-alcoholic mouthwashes on the development of HNSCC. In contrast, other studies have not found a significant link between alcohol-containing mouthwash use and HNSCC. A 2003 review [16] concluded that there was no significant evidence of association between alcohol-containing mouthwash and pharyngeal cancer. The authors speculated that mouthwash does not present a significant risk because it is only in the mouth for a short duration. Overall, findings to date are inconsistent.

Studies that looked at the effect of mouthwash on HNSCC usually restricted cases to oral cavity and pharyngeal. We included laryngeal subjects in this analysis because alcohol has been shown to be a significant risk factor for laryngeal cancer even though drinking does not normally expose the larynx to alcohol. Evidence from case-control studies indicates that alcohol consumption is a significant risk factor for laryngeal cancer [18,31].

Tobacco use, periodontal disease, and mouthwash use have been found to be associated with changes in the microbiome [31,11,32,10,33], which has in turn been shown to be associated with cancer [34,24,7,22], suggesting a possible mechanism for this observed association. Cetylpyridinium chloride (CPC), an active ingredient found in most mouthwashes (regardless of alcohol content), has been shown to alter oral flora. A double-blind study of the effect of mouthwash rinse containing .05% CPC found sustained decreases in gram-negative bacteria [35] but another study found no significant alterations to normal oral flora after 6 weeks of using CPC [36]. Yet another study [37] found temporary changes in oral bacteria resulting from the use of commercially available mouthwash, with bacterial levels returning to normal after thirty minutes to an hour. Active ingredients such as thymol and menthol are often used in lieu of CPC, but have been shown to have similar anti-bacterial properties [38]. Chlorhexidine gluconate, an active ingredient found in prescriptive mouthwash, has been shown to significantly alter normal oral flora [39]. Thus, it is possible that active antibacterial ingredients, rather than ethanol in mouthwash, contribute to risk by changing diversity of oral bacteria, potentially also altering the balance of immune tolerance which could further contribute to the genesis or promotion of cancers.

Our results support the prior findings that periodontal disease and mouthwash use are risk factors for HNSCC and additionally suggest that mouthwash may be important regardless of alcohol content. A major advantage of our study is that we used a large, well-characterized population-based cohort of head and neck cancer with detailed information on smoking, drinking, periodontitis, and mouthwash use. Our results showed that both alcohol-containing and non-alcoholic mouthwash are associated with increased risk in HNSCC. One limitation of our study is that very few subjects reported using nonalcoholic mouthwash, resulting in low power to test the effect of non-alcoholic mouthwash on HNSCC. Additionally, there may be some misclassification in the amount of alcohol in mouthwash. Participants reported brand used, which was converted into percent alcohol; if a participant reported using Scope we assumed this referred to the alcohol-containing type unless otherwise specified. It is also possible that cases may be more aware of periodontal disease status by virtue of a HNSCC diagnosis, resulting in an overestimate of the effect of periodontal disease on HNSCC. However, 70% of cases and 77% of controls reported visiting a dentist at least once a year, indicating that controls may be more aware of having periodontal disease. Adjusted for personal and sociodemographic factors, this difference was not significant. Finally, a small number of laryngeal cases limited our ability to examine this site, and although periodontal disease and mouthwash use were positively associated with risk of laryngeal cancer, associations were not statistically significant.

In conclusion, we observed that periodontal disease and mouthwash use are associated with an increased risk in HNSCC. The association between non-alcoholic mouthwash use and HNSCC suggests that the increased risk from mouthwash use may be unrelated to alcohol in mouthwash. One hypothesis is that the association is related to changes in oral bacteria, rather than the conversion of ethanol into the mutagenic acetaldehyde. Further research should be conducted to look at the effects of non-alcoholic mouthwash on HNSCC.

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Table 1

Descriptive statistics of head and neck squamous cell carcinoma cases and controls

Demographic Characteristic	Cases (n = 513)	Controls (n = 567)	P-value[a]
Age, years			
Mean (sd)	56.0 (11.3)	60.5 (10.8)	
Gender			
Male	377 (73.5%)	420 (75.0%)	
Female	136 (26.5%)	147 (25.0%)	
Race			
White	474 (92.6%)	504 (89.0%)	0.038
Non-White	38 (7.4%)	62 (11.0%)	
Education			
Up to high school diploma	186 (36.3%)	134 (23.8%)	$<10^{-5}$
Greater than high school diploma	326 (63.7%)	430 (76.2%)	
Income (per year)			
< $50,000	147 (33.4%)	171 (33.3%)	0.87
≥ $50,000	293 (66.6%)	343 (66.7%)	
Smoking			
Ever	129 (25.0%)	233 (41.3%)	$<10^{-8}$
Never	378 (75.0%)	331 (58.7%)	
Average alcoholic drinks per week			
None	50 (9.7%)	86 (15.2%)	$<10^{-7}$
≤14	261 (50.9%)	362 (63.8%)	
>14	201 (39.2%)	116 (20.5%)	

[a]Tests adjusted for age and sex. T-tests used to compute p-values for continuous variables and chi-square tests used to compute p-values for categorical variables.

Table 2

Results from logistic regression stratified by site

Risk Factors	Oral cavity			Pharyngeal			Laryngeal		
	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value
Periodontal disease[a]									
Never	97/417	Ref.		199/417	Ref.		43/417	Ref.	
Ever	51/150	1.07 (1.00, 1.13)	0.06	94/150	1.07 (1.00, 1.15)	0.04	25/150	1.05 (0.99, 1.10)	0.08
Mouthwash frequency[b]									
Never	24/134	Ref.		52/134	Ref.		15/134	Ref.	
Sometimes	62/255	1.05 (0.97, 1.13)	0.23	110/255	1.01 (0.93	0.80	30/255	1.01 (0.95, 1.07)	0.77
At least once per day	56/176	1.09 (1.01, 1.18)	0.03	115/176	1.11 (1.02	0.01	21/176	1.00 (0.94, 1.06)	0.96
Mouthwash use by alcohol content[b]									
Rarely or never	66/288	Ref.		116/288	Ref.		32/288	Ref.	
Non-alcoholic	8/15	1.17 (0.99, 1.38)	0.07	13/15	1.22 (1.03, 1.45)	0.02	3/15	1.06 (0.92, 1.22)	0.41
Alcoholic	69/264	1.02 (0.96, 1.08)	0.52	150/264	1.07 (1.00, 1.13)	0.05	31/264	1.00 (0.95, 1.04)	0.88
Mouthwash use by alcohol and frequency[b]									
Low or no alcohol infrequently	24/143	Ref.		51/143	Ref.		16/143	Ref.	
Low or no alcohol frequently	8/14	1.20 (1.01, 1.43)	0.04	12/14	1.22 (1.01, 1.47)	0.04	2/14	1.00 (0.86, 1.17)	0.96
High alcohol infrequently	40/161	1.06 (0.98, 1.14)	0.18	70/161	1.02 (0.94, 1.12)	0.59	20/161	1.01 (0.95, 1.08)	0.73
High alcohol frequently	51/201	1.05 (0.98, 1.13)	0.18	115/201	1.08 (0.99, 1.17)	0.08	22/201	0.99 (0.93, 1.05)	0.96
Fluoride use[b]									
No	144/455	Ref.		220/455	Ref.		49/455	Ref.	
Yes	30/111	1.02 (0.95, 1.10)	0.56	59/111	1.04 (0.96, 1.13)	0.30	17/111	1.03 (0.97, 1.09)	0.30
Dental insurance for the majority of life[b]									
No	82/242	Ref.		112/242	Ref.		30/242	Ref.	
Yes	61/321	0.92 (0.86, 0.98)	0.01	170/321	1.01 (0.95, 1.08)	0.74	36/321	0.99 (0.94, 1.04)	0.77

Risk Factors	Oral cavity			Pharyngeal			Laryngeal		
	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value
Dental visit frequency[b]									
Less than every year	42/131	Ref.		77/131	Ref.		28/131	Ref.	
At least once a year	102/433	0.98 (0.91, 1.05)	0.58	205/433	0.97 (0.90, 1.05)	0.50	38/433	0.95 (0.89, 1.00)	0.05

[a] Adjusted for age, sex, race, smoking, alcohol consumption, education and annual household income

[b] Adjusted for age, sex, race, smoking, alcohol consumption, education, annual household income, and history of periodontal disease

Table 3

Results from logistic regression stratified by alcohol consumption

Risk Factor	Non drinker			≤ two drinks per day			> two drinks per day		
	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value
Periodontal disease[a]									
Never	32/69	Ref.		160/260	Ref.		134/83	Ref.	
Ever	17/16	1.26 (1.04, 1.53)	0.02	90/100	1.09 (1.01, 1.19)	0.04	60/32	1.06 (0.94, 1.19)	0.34
Mouthwash frequency[b]									
Never	12/19	Ref.		47/82	Ref.		34/32	Ref.	
Sometimes	16/42	0.91 (0.74, 1.13)	0.40	108/171	1.02 (0.92, 1.13)	0.76	79/42	1.15 (0.99, 1.32)	0.06
At least once per day	20/25	1.08 (0.87, 1.34)	0.50	95/107	1.12 (1.01, 1.25)	0.04	78/42	1.14 (0.99, 1.32)	0.06
Mouthwash use by alcohol content[b]									
Rarely or never	24/45	Ref.		112/187	Ref.		81/55	Ref.	
Non-alcoholic	4/2	1.38 (0.92, 2.08)	0.11	11/12	1.12 (0.91, 1.38)	0.29	9/1	1.34 (0.99, 1.82)	0.06
Alcoholic	21/39	1.00 (0.84, 1.18)	0.97	127/163	1.07 (0.99, 1.16)	0.09	60/103	1.05 (0.95, 1.17)	0.33
Mouthwash use by alcohol and frequency[b]									
Low or no alcohol infrequently	11/21	Ref.		48/89	Ref.		33/32	Ref.	
Low or no alcohol frequently	3/2	1.32 (0.84, 2.06)	0.04	12/10	1.20 (0.96, 1.50)	0.10	7/2	1.27 (0.91, 1.77)	0.16
High alcohol infrequently	8/25	0.92 (0.73, 1.16)	0.18	70/108	1.04 (0.94, 1.16)	0.44	54/28	1.15 (0.98, 1.35)	0.08
High alcohol frequently	15/29	0.98 (0.79, 1.21)	0.18	92/123	1.07 (0.97, 1.19)	0.19	82/47	1.14 (0.99, 1.31)	0.07
Fluoride use[b]									
No	34/67	Ref.		195/295	Ref.		158/91	Ref.	
Yes	19/16	1.13 (0.94, 1.37)	0.19	54/66	1.07 (0.97, 1.18)	0.17	36/25	0.97 (0.85, 1.11)	0.70
Dental insurance for the majority of life[b]									
No	27/44	Ref.		105/149	Ref.		95/47	Ref.	
Yes	22/42	0.93 (0.78, 1.11)	0.42	146/211	0.97 (0.89, 1.06)	0.55	100/67	0.96 (0.86, 1.07)	0.48

Risk Factor	Non drinker			≤ two drinks per day			> two drinks per day		
	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value
Dental visit frequency[b]									
Less than every year	15/20	Ref.		53/80	Ref.		81/31	Ref.	
At least once a year	34/65	0.95 (0.77, 1.16)	0.61	199/281	1.02 (0.92, 1.13)	0.72	114/84	0.92 (0.81, 1.04)	0.17

[a]Adjusted for age, sex, race, smoking, alcohol consumption, education and annual household income

[b]Adjusted for age, sex, race, smoking, alcohol consumption, education, annual household income, and history of periodontal disease

Table 4

Results from logistic regression stratified by cigarette smoking

Risk Factor	Never smoker			Ever smoker		
	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value
Periodontal disease[a]						
Never	101/196	Ref.		225/218	Ref.	
Ever	42/66	1.05 (0.94, 1.17)	0.40	125/83	1.11 (1.03, 1.21)	0.01
Mouthwash frequency[b]						
Never	28/64	Ref.		65/70	Ref.	
Sometimes	63/121	1.03 (0.91, 1.16)	0.61	140/134	1.01 (0.89, 1.11)	0.84
At least once per day	50/79	1.10 (0.96, 1.25)	0.16	143/97	1.17 (1.01, 1.23)	0.04
Mouthwash use by alcohol content[b]						
Rarely or never	68/132	Ref.		149/156	Ref.	
Non-alcoholic	6/6	1.19 (0.90, 1.57)	0.23	18/9	1.24 (1.02, 1.50)	0.03
Alcoholic	68/127	1.01 (0.92, 1.11)	0.85	183/137	1.08 (1.00, 1.17)	0.05
Mouthwash use by alcohol and frequency[b]						
Low or no alcohol infrequently	27/69	Ref.		65/74	Ref.	
Low or no alcohol frequently	6/5	1.30 (0.96, 1.76)	0.09	16/9	1.21 (0.98, 1.49)	0.07
High alcohol infrequently	42/76	1.06 (0.93, 1.15)	0.34	90/85	1.03 (0.92, 1.14)	0.65
High alcohol frequently	51/90	1.08 (0.95, 1.22)	0.25	138/111	1.07 (0.97, 1.19)	0.18
Fluoride use[b]						
No	114/210	Ref.		273/245	Ref.	
Yes	29/55	1.02 (0.91, 1.15)	0.72	77/56	1.06 (0.97, 1.17)	0.19
Dental insurance for the majority of life[b]						
No	61/110	Ref.		166/132	Ref.	
Yes	85/152	0.99 (0.89, 1.09)	0.81	183/169	0.94 (0.87, 1.03)	0.17

Risk Factor	Never smoker			Ever smoker		
	No. cases/controls	OR (95% CI)	P-value	No. cases/controls	OR (95% CI)	P-value
Dental visit frequency[b]						
Less than every year	24/51	Ref.		125/80	Ref.	
At least once a year	122/212	1.03 (0.90, 1.17)	0.68	225/221	0.93 (0.85, 1.02)	0.11

[a]Adjusted for age, sex, race, smoking, alcohol consumption, education and annual household income

[b]Adjusted for age, sex, race, smoking, alcohol consumption, education, annual household income, and history of periodontal disease