Tooth Loss and Lack of Regular Oral Hygiene Are Associated with Higher Risk of Esophageal Squamous Cell Carcinoma

Christian C. Abnet,[1] Farin Kamangar,[1] Farhad Islami,[2,3] Dariush Nasrollahzadeh,[3] Paul Brennan,[3] Karim Aghcheli,[2] Shahin Merat,[2] Akram Pourshams,[2] Haj Amin Marjani,[2] Abdolhakim Ebadati,[2] Masoud Sotoudeh,[2] Paolo Boffetta,[3] Reza Malekzadeh,[2] and Sanford M. Dawsey[1]

[1]Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland; [2]IARC, Lyon, France; and [3]Digestive Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract

We tested the association between tooth loss and oral hygiene and the risk of esophageal squamous cell carcinoma (ESCC) in people living in a high-risk area of Iran. We used a case-control study of pathologically confirmed ESCC cases (n = 283) and controls (n = 560) matched on sex, age, and neighborhood. Subjects with ESCC had significantly more decayed, missing, or filled teeth (DMFT) with a median (interquartile range) of 31 (23-32) compared with controls 28 (16-32; P = 0.0045). Subjects with ESCC were significantly more likely than controls to fail to practice regular oral hygiene (78% versus 58%). In multivariate-adjusted conditional logistic regression models, having 32 DMFT compared with ≤15 conferred an odds ratio (95% confidence interval) of 2.10 (1.19-3.70). Compared with daily tooth brushing, practicing no regular oral hygiene conferred an odds ratio (95% confidence interval) of 2.37 (1.42-3.97). Restricting the analysis to subjects that had never smoked tobacco did not materially alter these results. We found significant associations between two markers of poor oral hygiene, a larger number of DMFT and lack of daily tooth brushing, and risk of ESCC in a population at high risk for ESCC where many cases occur in never smokers. Our results are consistent with several previous analyses in other high-risk populations. (Cancer Epidemiol Biomarkers Prev 2008;17(11):3062–8)

Introduction

Esophageal cancer causes over 380,000 deaths per year and ranks as the sixth leading cause of cancer death worldwide, just after breast cancer (1). Two primary cell types, squamous cell carcinoma and adenocarcinoma, account for most cases. Although the rates of esophageal adenocarcinoma have risen rapidly in the United States (2) and elsewhere, esophageal squamous cell carcinoma (ESCC) still accounts for 80% of all esophageal cancer cases. Many of these cases occur in high-risk areas with sharp geographic boundaries within China, Iran, some parts of central Asia, South Africa, Kenya, and a small region spanning several countries in South America. In some areas, ESCC can cause more than 1 in 10 deaths in a population. Studies of ESSC in economically developed countries, such as the United States, point to smoking tobacco, heavy alcohol drinking, poor diets deficient in fresh fruits and vegetables, and low socioeconomic status as the main etiologic factors (3). Smoking tobacco and heavy alcohol consumption do not explain the incidence rates in the high-risk regions because these habits are less common and less intensely practiced in these high-risk areas compared with the low-risk areas (4, 5). Also, in high-risk areas, the incidence rates are similar in men and women despite differences in the rates of tobacco smoking and alcohol drinking (5, 6). Therefore, it is important to consider a wide range of etiologic factors to explain the high rates of cancer in these populations.

Epidemiologic studies have associated tooth loss and/or periodontal disease with higher risk of cancer at several sites including the oral cavity (7), stomach (8-10), pancreas (11, 12), and lung (13, 14). Studies from China in the 1970s led to the hypothesis that higher risk of ESCC could also result from poor oral health, poor oral hygiene practices, or tooth loss (15). Several recent studies found significant associations between tooth loss and ESCC in populations with varying rates of this tumor from China (8, 9), Latin America (16), eastern Europe (16), and Japan (17), whereas one other study found no significant association (10). Furthermore, two studies (18, 19) have shown a significant association between tooth loss and esophageal squamous dysplasia, the precursor lesion for ESCC (20). Regular oral hygiene, which may prevent caries, periodontal disease, and tooth loss, conferred lower risk of ESCC in one published study (7) but not another (16). Confounding from tobacco smoking (13) is an important concern, but several biological mechanisms have been suggested to explain these associations including the production of carcinogenic byproducts by oral pathogens.

Received 6/17/08; revised 7/31/08; accepted 8/6/08.

Grant support: Digestive Disease Research Center of Tehran University of Medical Sciences grant 82-603 and National Cancer Institute, NIH intramural funds.

Requests for reprints: Christian C. Abnet, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Executive Plaza South, Room 320, 6120 Executive Boulevard, MSC 7232, Rockville, MD 20852. Phone: 301-594-1511; Fax: 301-496-6829; E-mail: abnetc@mail.nih.gov

doi:10.1158/1055-9965.EPI-08-0558

The population of Golestan Province in Iran has high rates of ESCC (21, 22) and low rates of tobacco smoking (23). Tobacco smoking is not an important risk factor for ESCC in the population (5, 24), which makes it a good place to study the association between tooth loss and ESCC with little concern for confounding by tobacco smoking. We undertook just such an analysis in a case-control study of ESCC conducted in Golestan Province.

Materials and Methods

Case and Control Selection. The study area included five counties in eastern Golestan Province. Cases were recruited at Atrak Clinic, which is located in Gonbad City and is the only specialized clinic for upper gastrointestinal tract cancers in this area. Physicians in the study catchment area were asked to refer their patients suspected of having upper gastrointestinal tract cancers to Atrak Clinic. Cases were recruited from December 2003 to June 2007. Other eligibility criteria included being aged ≥18 years, residing in the study area at the time of registration, and having no history of concurrent cancer in other organs or history of previous cancer in any organ. All the patients underwent video esophagogastroduodenoscopy at Atrak Clinic, and fixed biopsy samples were sent to the Tehran University Digestive Disease Research Center in Tehran, where they were examined by experienced pathologists. All cases were histopathologically confirmed as invasive ESCC. By comparing our recruitment to a newly established cancer registry, we estimate that ~70% of all incident ESCC cases in this the catchment area were referred to Atrak Clinic, all of whom participated in this study. For each case subject, we attempted to select two population-based control subjects, individually matched to the case for neighborhood of residence, age (±2 years), and gender, using the annually updated family health census that is conducted by the Iranian Primary Health Care System. For rural patients, in each village, our interview group identified all of the potentially eligible controls and randomly selected one to interview. If the first person could not be interviewed for any reason, the second person on the list was invited, and so forth. In urban areas, a list of the eligible controls was ordered by geographic proximity to the case's residence, with the list starting from the eligible person living closest to the case's residence. If the first person was repeatedly not available for interview, then the second closest person was invited, and so forth. Seventy-seven percent of the controls enrolled in this study were the first randomly selected person, and 11% and 3%, respectively, were the second and third choices. For nearly all controls, the reason for not participating in the study was the absence of the selected potential control subject from the home at the time of each attempted contact. In total, we collected 300 ESCC cases and 571 matched controls, but due to missing data for our main exposures, we here analyze 283 cases and 560 controls.

The study was reviewed and approved by the institutional review boards of the Digestive Disease Research Center of Tehran University of Medical Sciences and the U.S. National Cancer Institute.

Physical Exam and Questionnaire. Two trained interviewers, a nurse and a physician, administered a structured questionnaire. Face-to-face interviews were conducted for all cases and controls and no proxies were used. Each case subject was interviewed on the day of diagnostic endoscopy at the Atrak Clinic. Rural control subjects were interviewed in the village health houses. Urban control subjects were interviewed in urban health centers, except those selected from Gonbad City, who were interviewed at a Digestive Disease Research Center research facility.

The questionnaires collected detailed information on age, sex, education, ethnicity, place of residence, number of appliances (an indicator of socioeconomic status), and other potential confounders of interest. Dietary data were collected using a food frequency questionnaire specifically designed for this population (25).The questionnaire included questions on lifelong history of tobacco use. Ever cigarette smokers were those who had smoked at least weekly for a period of ≥6 months. Ever tobacco users were individuals who had smoked cigarettes or used nass, hookah, or a pipe at least weekly for at least 6 months. The questionnaire also included questions on opium use. Opium users were defined as subjects who had consumed opium at least once per week for a minimum of 6 months. Overall, the reliability of the questionnaire and the validity of the questions on opium are very good (26), including the reliability for tooth counts that had a percent agreement of 88.3% and a κ of 0.86 for repeated examinations of 130 subjects 2 months apart (23).

Oral Health Variable Construction. The trained medical personnel counted each patient's teeth, recorded the number of decayed, missing, or filled teeth (the sum of which was the DMFT score), and recorded the age of first adult tooth loss, oral hygiene habits (tooth brushing or rinsing the teeth with salt water), and denture use. Tooth loss, DMFT, and age of first tooth loss all had multiple modes, and categories were created that split these variables into approximately equal groups. The results of the analysis were not sensitive to choice of cutoff points for these categories. All oral hygiene practices other than at least daily brushing were lumped into a single category due to small numbers.

Statistical Methods. We tested for differences between cases and controls in the distributions of covariates using Pearson χ^2 tests for dichotomous variables, Mantel-Haenszel χ^2 tests for trend if there were more than two categories, and Wilcoxon rank-sum tests for continuous variables. Multivariate linear regression was used to test for predictors of tooth loss. Qualitatively similar results were produced when we substituted the category of tooth loss for the actual number of teeth retained in the linear regression. Conditional logistic regression models were used to calculate unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95% CI). By design, case and control subjects were matched for age, sex, and place of residence. Models were further adjusted for use of tobacco, opium, or both, alcohol drinking, vegetable intake, number of appliances owned and education (as markers of socioeconomic status), and ethnicity (Turkmen versus non-Turkmen). P values for trend were obtained by assigning ordinal values to each category. Two-sided P values < 0.05 were considered

Table 1. Subject characteristics by case status in the GEMINI case-control study of ESCC

Variables	ESCC cases	Controls	P*
n	283	560	
Age (y), median (IQR) †	65 (56-73)	65 (57-72)	0.81
Sex, *n* (%)			
Males	142 (50)	273 (49)	0.70
Females	141 (50)	287 (51)	
Place of residence, *n* (%)			
Rural	206 (73)	413 (74)	0.77
Urban	77 (27)	147 (26)	
Turkmen ethnic group, yes, *n* (%)	160 (57)	307 (55)	0.64
Ever use alcohol, yes, *n* (%)	7 (2)	15 (3)	0.86
Ever use tobacco or opium, *n* (%)			
Neither	156 (55)	392 (70)	0.0002
Ever use tobacco	41 (14)	64 (11)	
Ever use opium	29 (10)	34 (6)	
Ever use tobacco and opium	57 (20)	70 (13)	

*P values come from χ^2 tests for categorical variables ($\chi 2$ for trend in variables with more than two categories) and Wilcoxon rank-sum tests for continuous variables.
†Interquartile range.

significant. All statistical analyses were done using SAS software version 9.1.

Results

Table 1 presents the subject characteristics by case status. The study design matched case and control subjects on sex, age, and neighborhood, which induced a degree of matching on ethnic group, so we saw no differences in these factors. We found a significant difference between ESCC cases compared with controls in that a higher percentage of cases reported ever using tobacco and/or opium.

We fit a linear regression model using only the control subjects to assess what confounders we should consider when building our multivariate models for tooth loss and the results are given in Table 2. As expected, age had the strongest association with number of teeth and the model predicted that, for every 3 years after age 65 years, the subject would lose another tooth. This model had only two other significant predictors of tooth loss, sex, and alcohol drinking. It predicted that women would have lost 1.69 more teeth than men and that alcohol drinkers would have lost 4.84 more teeth on average compared with never drinkers. Because only 2% of cases and 3% of controls reported alcohol consumption, the β coefficient for alcohol had wide 95% CI. The total model r^2 was 18%, little more than the 15% found when using age alone in the model, so the model had low explanatory power.

Table 3 presents the differences in oral health variable distributions by case status. The median number of teeth lost in subjects diagnosed with ESCC differed significantly from the median number in controls, 29 in cases and 25 in controls (P = 0.0045), and there was a significant trend across categories of tooth loss. We calculated the DMFT score and found that this median differed significantly as well, 31 in cases and 28 in controls. The age of first adult tooth loss also differed significantly when tested as a trend across categories, but the medians did not differ significantly, ages 27 versus 30 years in cases and controls, respectively. We found a significant difference in oral hygiene habits, with 78% of cases and 58% of controls reporting no regular oral hygiene practices such as tooth brushing or rinsing with salt water. We found no difference in the percent of subjects using dentures, 34% of both cases and controls.

Table 4 presents age- and sex-adjusted and multivariate-adjusted models for the association between tooth loss and ESCC. Increasing tooth loss led to increasing risk of ESCC, and edentulous subjects had an OR (95% CI) of 1.90 (1.12-3.23) compared with subjects that had lost fewer than 13 teeth. Because we found few predictors of tooth loss (Table 2), the multivariate-adjusted models were quite similar to the crude models, and for edentulous subjects, the OR (95% CI) changed only to 1.79 (1.03-3.13). Using DMFT produced similar results and the ORs became smoothly monotonic across categories, with ORs of 1.31, 1.62, 1.89, and 2.10 and a P of 0.0058 for the trend test.

We also estimated the effects of age of first adult tooth loss. We only present OR (95% CI) adjusted for all considered factors, including the number of teeth, because the age of first tooth loss strongly correlates with the number of teeth lost. We found increasing risk of cancer with lower age of first tooth loss up to the

Table 2. Predictors of the number of teeth lost using a linear regression model in controls from the GEMINI case-control study of ESCC

Variable	β	P
Intercept*	17.95	<0.0001
Age, † 1 y	0.36	<0.0001
Sex, female	1.69	0.04
Place of residence, rural	1.33	0.14
Ethnicity, Turkmen	0.92	0.22
Ever use alcohol	4.84	0.042
Never use tobacco nor opium	Reference	—
Ever user tobacco	0.15	0.90
Ever use opium	1.08	0.48
Ever use tobacco and opium	1.59	0.20
Education level, no formal school	Reference	—
Education level, any formal school	-0.51	0.65
No. appliances	0.03	0.69
Fruit and vegetable intake, 100 g/d	0.10	0.28

*Total r^2 for this model is 18%.
†Age was modeled relative to age 65 y, the baseline median.

Table 3. Oral health variables by case status in the GEMINI case-control study of ESCC

	ESCC cases	Controls	P^*
No. subjects	283	560	
No. adult teeth lost, median (IQR)	29 (18-32)	25 (16-32)	0.0064
Tooth loss, *n* (%)			
Category 1 (≤ 12)	39 (14)	93 (17)	0.026
Category 2 (13-18)	34 (12)	88 (16)	
Category 3 (19-24)	44 (16)	90 (16)	
Category 4 (25-31)	48 (17)	99 (18)	
Category 5 (32)	118 (42)	190 (34)	
No. decayed teeth, median (IQR)	0 (0-3)	0 (0-3)	0.70
No. filled teeth, median (IQR)†	0 (0-0)	0 (0-0)	0.60
DMFT, median (IQR)	31 (23-32)	28 (2-32)	0.0045
DMFT, *n* (%)			
Category 1 (≤15)	33 (12)	102 (18)	0.0034
Category 2 (16-22)	35 (12)	85 (15)	
Category 3 (23-26)	31 (11)	69 (12)	
Category 4 (26-31)	55 (19)	82 (15)	
Category 5 (32)	129 (46)	222 (40)	
Age of first adult tooth loss, median (IQR)	27 (20-35)	30 (20-40)	0.056
Age at first loss, *n* (%)			
Category 1 (≥40)	54 (19)	143 (26)	0.041
Category 2 (31-39)	26 (9)	65 (12)	
Category 3 (26-30)	67 (24)	115 (21)	
Category 4 (20-25)	94 (15)	152 (27)	
Category 5 (<20)	42 (15)	85 (15)	
Frequency of tooth brushing, *n* (%)			
Daily	37(13)	117 (21)	<0.0001
Less than daily	24 (8)	119 (21)	
Never	222 (78)	324 (58)	
Any denture use, yes, *n* (%)	97 (34)	192 (34)	1.00

*P values come from χ^2 tests for categorical variables (χ^2 for trend in variables with more than two categories) and Wilcoxon rank-sum tests for continuous variable.
†Only 13 controls and 5 cases had any filled teeth.

second lowest category, ages 20 to 25 years, with an OR (95% CI) of 1.57 (1.02-2.43). The category that included subjects who began losing adult teeth below age 20 years showed no significant association with ESCC risk, with an OR (95% CI) of 1.27 (0.73-2.19).

Compared with daily tooth brushing, subjects who did not practice any oral hygiene had significantly increased risk of having ESCC, with an OR (95% CI) of 2.37 (1.42-3.97). Subjects who brushed less than daily or who used other oral hygiene methods (rinsing with salt water, etc.) did not differ in their risk of ESCC from those who brushed daily.

As shown in Table 2, tobacco use had no significant association with tooth loss in our population, but to further remove the potential for confounding by tobacco use, we recalculated each of our models after excluding subjects that reported ever using tobacco. This reduced the power of our tests, but we found no meaningful changes in our results (Table 4). Alcohol use was uncommon and not associated with ESCC in this population and we found no meaningful changes to our results after removing subjects that reported ever consuming alcohol (Table 4).

Finally, we fit a single model that included DMFT category, age of first adult tooth loss, and oral hygiene practices and found that each of these three exposures retained independent associations with risk of ESCC. Compared with those in the lowest category, subject with a DMFT of 32 had an OR (95% CI) of 2.15 (1.19-3.91) and those never performing regular oral hygiene had an OR (95% CI) of 2.31 (1.38-3.89), but the OR (95% CI) for an age of first loss of 20 to 25 dropped to 1.36 (0.86-2.14).

Discussion

We used a case-control study conducted in Golestan Province in Iran, a high-risk area for ESCC, to test for an association between tooth loss or oral hygiene practices and ESCC. We found that increasing numbers of teeth lost led to a progressively higher predicted risk of ESCC. Subjects with no teeth had nearly a 2-fold higher risk of having ESCC compared with subjects who lost fewer than 13 teeth. This pattern held true and became monotonic when using the number of DMFT instead of simply missing teeth as our measure of exposure. Compared with people who reached age 40 years before losing any adult teeth, those losing teeth earlier had a higher risk of ESCC, but this association was not significant in a complete model using all oral health indicators in a single model. We also found that failure to use any routine oral hygiene practices led to a >2-fold higher risk of ESCC compared with people who brushed their teeth daily. All of these findings were retested and found to be materially unchanged in subjects who reported never having used any tobacco products or any alcoholic beverages. Furthermore, the associations between tooth loss, DMFT, or oral hygiene and ESCC were stronger than the association between ever using tobacco and ESCC [OR (95% CI), 1.47 (0.98-2.21; ref. 24)]. Thus, no level of correlation between tobacco use and the tooth loss or oral hygiene exposures could explain the associations between the latter variables and ESCC, because any association due to confounding by tobacco use would have to be of lower magnitude than the primary association between tobacco use and ESCC.

At least five studies (8, 16, 17, 19, 27) have reported significant associations between tooth loss and ESCC or its precursor lesion, and the only published study that did not show a significant association had low power, with only 49 cases (10). These results have come from studies conducted in different ethnic groups and different cultures with different underlying rates of ESCC and different primary risk factors for the disease. Our results are consistent with these previous reports.

Smoking tobacco can cause periodontal disease and subsequent tooth loss (28) and ESCC as well as lung and other cancers. As noted in several previous studies (13, 14), confounding by tobacco smoking could create the appearance of an association between tooth loss and ESCC that has no other basis. Hujoel et al. published a detailed analysis of this possibility in the case of lung cancer and suggested that the association between tooth loss and lung cancer was not present in never tobacco smokers, and any association in tobacco smokers could be due to insufficient control for confounding by smoking (13). Another recent analysis found that periodontal disease conferred nonsignificantly increased risk of lung cancer in never tobacco smokers but was still associated with a 21% increased risk of total cancer (14). The potential for confounding by tobacco smoking remains an important concern, but we should judge its relevance within the context of each individual study. We did not see a strong association between tobacco and tooth loss in Golestan Province, so confounding by tobacco smoking cannot explain our findings. We also adjusted for other important potential confounders, such as opium use (24) and socioeconomic status. Despite these arguments, we acknowledge that all findings from observational studies can result from unmeasured or poorly controlled confounders.

We have previously described several hypotheses to explain the association between tooth loss and ESCC (9, 16). As noted above, confounding by other behavioral risk factors can never be totally ruled out in a case-control study and neither can confounding by genetics. For example, a genetic profile that predisposes an individual to react poorly to inflammation induced by oral pathogens and thus lose teeth may also lead to a poor reaction to other inflammatory stimuli and thus

Table 4. OR (95% CI) for the association between tooth variables and ESCC in the GEMINI case-control study

No. teeth lost	≤12	13-18	19-24	25-31	32	P_{trend}
No. cases/controls	39/93	34/88	44/90	48/99	118/190	
	Reference	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Sex and age adjusted	1.0	1.08 (0.61-1.90)	1.51 (0.86-2.66)	1.32 (0.75-2.34)	1.90 (1.12-3.23)	0.011
Fully adjusted*	1.0	1.08 (0.59-1.98)	1.46 (0.81-2.65)	1.02 (0.56-1.87)	1.79 (1.03-3.13)	0.044
Never tobacco users, fully adjusted	1.0	0.94 (0.49-1.79)	1.38 (0.72-2.62)	0.95 (0.48-1.86)	1.50 (0.84-2.65)	0.14
Never alcoholic beverage drinkers, fully adjusted	1.0	0.89 (0.51-1.58)	1.24 (0.71-2.15)	1.09 (0.63-1.90)	1.59 (0.97-2.59)	0.027
DMFT	≤15	16-22	23-26	26-31	32	
No. cases/controls	33/102	35/85	31/69	55/82	129/222	
	Reference	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	P_{trend}
Sex and age adjusted	1.0	1.41 (0.77-2.57)	1.62 (0.88-2.99)	2.29 (1.29-4.06)	2.22 (1.30-3.79)	0.0012
Fully adjusted*	1.0	1.31 (0.70-2.46)	1.62 (0.85-3.09)	1.89 (1.03-3.46)	2.10 (1.19-3.70)	0.0058
Never tobacco users, fully adjusted	1.0	1.17 (0.60-2.28)	1.40 (0.69-2.87)	2.14 (1.09-4.19)	1.78 (1.01-3.14)	0.019
Never alcoholic beverage drinkers, fully adjusted	1.0	1.27 (0.71-2.27)	1.60 (0.87-2.96)	2.22 (1.25-3.95)	1.95 (1.18-3.22)	0.0035
Age at first adult tooth loss	≥40 †	31-39	26-30	20-25	<20	P_{trend}
No. cases/controls	54/143	26/65	67/115	94/152	42/85	
	Reference	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Fully adjusted*	1.0	0.96 (0.52-1.76)	1.62 (1.01-2.60)	1.57 (1.02-2.43)	1.27 (0.73-2.19)	0.057
Never tobacco users, fully adjusted	1.0	0.97 (0.48-1.98)	1.49 (0.85-2.61)	1.81 (1.07-3.07)	1.68 (0.88-3.21)	0.015
Never alcoholic beverage drinkers, fully adjusted	1.0	1.00 (0.56-1.78)	1.48 (0.94-2.34)	1.64 (1.06-2.54)	1.31 (0.77-2.23)	0.046

Frequency of tooth brushing	Daily	Less than daily ‡	Never	
No. cases/controls	37/117	24/119	222/324	
	Reference	OR (95% CI)	OR (95% CI)	P_{trend}
Sex and age adjusted	1.0	0.66 (0.35-1.22)	2.49 (1.58-3.95)	<0.0001
Fully adjusted*	1.0	0.60 (0.32-1.16)	2.37 (1.42-3.97)	<0.0001
Never tobacco users, fully adjusted	1.0	0.71 (0.36-1.44)	2.53 (0.47-4.36)	<0.0001
Never alcoholic beverage drinkers, fully adjusted	1.0	0.58 (0.32-1.07)	2.15 (1.36-3.39)	<0.0001

*Adjusted for age, sex, place of residence, ethnicity, alcohol drinking, use of tobacco, opium, or both, education in two categories, number of appliances, and fruit and vegetable intake.
†Includes subjects who have not lost any adult teeth.
‡Includes subjects who described different types of tooth washing (e.g., rinsing with salt water) without brushing.

increase risk of cancer. In this case, no mechanistic connection between tooth loss and ESCC would exist; these conditions would just be two independent sequelae of the same underlying genetic predisposition. Poor diet leading to both tooth loss and ESCC or poor chewing ability leading to swallowing of large, irritating boluses of food are other possible but less likely explanations for the association between tooth loss and ESCC (9). A last alternative, which we favor, is that the some oral pathogens may cause periodontal disease and some may produce carcinogens or carcinogen precursors that affect the esophagus. For example, previous studies have shown that oral bacteria can convert ethanol or dietary sugars into acetaldehyde (29, 30), a known carcinogen. In addition, some bacteria can reduce nitrate to nitrite (31), which can then combine spontaneously with other dietary components to form nitrosamines, and some nitrosamines are esophageal-specific carcinogens (32).

Our study also evaluated another related exposure, oral hygiene practices, which has been examined in only a few previous studies (7, 16). Lack of regular oral hygiene practices conferred a >2-fold increased risk of ESCC. This is notable for three reasons. First, oral hygiene showed no association with tobacco or opium consumption, so this exposure is not susceptible to confounding by tobacco or opium use. Second, it is consistent with our proposed mechanism that oral pathogens produce carcinogenic products that directly affect the esophageal mucosa. Third, it suggests that a simple intervention, teaching routine oral hygiene, may lead to lower risk of ESCC in addition to being unambiguously beneficial in its own right.

Our study has several strengths. We used trained medical personnel to conduct interviews and count the number of teeth present and the number of DMFT. We collected extensive information on potential confounders. We had sufficient power to examine the questions of interest. On the other hand, our examination of tooth loss predictors suggests that there are many causes of tooth loss that we did not assess, and one of these undefined factors may be an important unmeasured confounder.

We found that higher numbers of teeth lost or damaged, as represented by the number of DMFT (the DMFT score) and lack of regular oral hygiene practices, had independent associations with higher risk of ESCC. These findings concur with similar results in other independent studies. These consistent results suggest that studies are warranted to evaluate the underlying mechanism of this association. They also suggest that teaching the practice of regular oral hygiene should be a priority for public health campaigns in high-risk areas for ESCC, because it would be directly beneficial to people now and may reduce the risk of developing ESCC in the future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide, version 2.0. IARC CancerBase No. 5. Lyon: IARC Press. http://www-depdb.iarc.fr/globocan2002.htm.
2. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin N Am 2002;11:235–56.
3. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 2003;95:1404–13.
4. Tran GD, Sun XD, Abnet CC, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer 2004;113:176–81.
5. Islami F, Kamangar F, Aghcheli K, et al. Epidemiologic features of upper gastrointestinal tract cancers in northeastern Iran. Br J Cancer 2004;90:1402–6.
6. Ke L. Mortality and incidence trends from esophagus cancer in selected geographic areas of China circa 1970-90. Int J Cancer 2002;102:271–4.
7. Zheng TZ, Boyle P, Hu HF, et al. Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. Cancer Causes Control 1990;1:235–41.
8. Abnet CC, Qiao Y-L, Mark SD, et al. Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes Control 2001;12:847–54.
9. Abnet CC, Qiao YL, Dawsey SM, et al. Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort. Int J Epidemiol 2005;34:467–74.
10. Abnet CC, Kamangar F, Dawsey SM, et al. Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. Scand J Gastroenterol 2005;40:681–7.
11. Michaud DS, Joshipura K, Giovannucci E, Fuchs CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst 2007;99:171–5.
12. Stolzenberg-Solomon RZ, Dodd KW, Blaser MJ, et al. Tooth loss, pancreatic cancer, and *Helicobacter pylori*. Am J Clin Nutr 2003;78:176–81.
13. Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. Ann Epidemiol 2003;13:312–6.
14. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. Lancet Oncol 2008;9:550–8.
15. Yang CS. Research on esophageal cancer in China: a review. Cancer Res 1980;40:2633–44.
16. Guha N, Boffetta P, Wunsch FV, et al. Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case-control studies. Am J Epidemiol 2007;166:1159–73.
17. Hiraki A, Matsuo K, Suzuki T, Kawase T, Tajima K. Teeth loss and risk of cancer at 14 common sites in Japanese. Cancer Epidemiol Biomarkers Prev 2008;17:1222–7.
18. Sepehr A, Kamangar F, Fahimi S, et al. Poor oral health as a risk factor for esophageal squamous dysplasia in northeastern Iran. Anticancer Res 2005;25:543–6.
19. Wei W-Q, Abnet CC, Lu N, et al. Risk factors for oesophageal squamous dysplasia in adult inhabitants of a high risk region of China. Gut 2005;54:759–63.
20. Wang GQ, Abnet CC, Shen Q, et al. Histological precursors of oesophageal squamous cell carcinoma: results from a 13 year prospective follow up study in a high risk population. Gut 2005;54:187–92.
21. Kamangar F, Malekzadeh R, Dawsey SM, Saidi F. Esophageal cancer in northeastern Iran: a review. Arch Iran Med 2007;10:70–82.
22. Semnani S, Sadjadi A, Fahimi S, et al. Declining incidence of esophageal cancer in the Turkmen Plain, eastern part of the Caspian Littoral of Iran: a retrospective cancer surveillance. Cancer Detect Prev 2006;30:14–9.
23. Pourshams A, Saadatian-Elahi M, Nouraie M, et al. Golestan cohort study of oesophageal cancer: feasibility and first results. Br J Cancer 2004;92:176–81.
24. Nasrollahzadeh D, Kamangar F, Aghcheli K, et al. Opium, tobacco and alcohol use in relation to esophageal squamous cell carcinoma in a high-risk area of Iran. Br J Cancer 2008;98:1857–63.
25. Malekshah AF, Kimiagar M, Saadatian-Elahi M, et al. Validity and reliability of a new food frequency questionnaire compared to 24 h recalls and biochemical measurements: pilot phase of

Golestan cohort study of esophageal cancer. Eur J Clin Nutr 2006;60:971–7.
26. Abnet CC, Saadatian-Elahi M, Pourshams A, et al. Reliability and validity of opiate use self-report in a population at high risk for esophageal cancer in Golestan, Iran. Cancer Epidemiol Biomarkers Prev 2004;13:1068–70.
27. Sepehr A, Kamangar F, Fahimi S, et al. Poor oral health as a risk factor for esophageal squamous dysplasia in northeastern Iran. Anticancer Research 2005;25:543–6.
28. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366:1809–20.
29. Salaspuro MP. Acetaldehyde, microbes, and cancer of the digestive tract. Crit Rev Clin Lab Sci 2003;40:183–208.
30. Salaspuro MP. Alcohol consumption and cancer of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2003;17:679–94.
31. Shapiro KB, Hotchkiss JH, Roe DA. Quantitative relationship between oral nitrate-reducing activity and the endogenous formation of *N*-nitrosoamino acids in humans. Food Chem Toxicol 1991;29:751–5.
32. Mirvish SS. Role of *N*-nitroso compounds (NOC) and *N*-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. Cancer Lett 1995;93:17–48.