

## Association of Tooth Loss and Oral Hygiene with Risk of Gastric Adenocarcinoma

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### Abstract

Poor oral health and tooth loss have been proposed as possible risk factors for some chronic diseases, including gastric cancer. However, a small number of studies have tested these associations. We conducted a case-control study in Golestan Province, Iran, that enrolled 309 cases diagnosed with gastric adenocarcinoma (118 noncardia, 161 cardia, and 30 mixed-locations) and 613 sex, age, and neighborhood matched controls. Data on oral health were obtained through physical examination and questionnaire including tooth loss, the number of decayed, missing, and filled teeth, and frequency of tooth brushing. ORs and 95% confidence intervals (95% CI) were obtained using conditional logistic regression models adjusted for potential confounders. Standard one degree-of-freedom linear trend test and a multiple degree-of-freedom global test of the effect of adding oral hygiene variables to the model were also calculated. Our results showed apparent associations between tooth loss and decayed, missing, filled teeth (DMFT) score with risk of gastric cancer, overall and at each anatomic subsite. However, these associations were not monotonic and were strongly confounded by age. The results also showed that subjects who brushed their teeth less than daily were at significantly higher risk for gastric cardia adenocarcinoma ORs (95% CI) of 5.6 (1.6–19.3). We found evidence for an association between oral health and gastric cancer, but the nonmonotonic association, the relatively strong effect of confounder adjustment, and inconsistent results across studies must temper the strength of any conclusions. *Cancer Prev Res*; 6(5); 477–82. ©2013 AACR.

### Introduction

Although gastric cancer is still the fourth most common cancer in the world by incidence, its rates have substantially declined over the past century (1). Declines in gastric cancer incidence have been attributed to changes in a number of environmental risk factors. A reduction in the prevalence of

*Helicobacter pylori* (*H. pylori*) infection (2–6) is probably the main factor in lower rates of gastric cancer, but dietary changes (7, 8) may also be contributing to this decline.

Poor oral health is another possible risk factor for gastric cancer. Some recent epidemiologic studies have shown an association between poor oral health or hygiene and cancers of different organs, including cancers of the oral cavity and oropharynx (9), esophagus (10–12), pancreas (13, 14), kidney (15), and lung (15), and also with other chronic diseases, such as cardiovascular disease (16) and diabetes (17). At least 2 previous studies have also examined the association between poor oral health and gastric cancer, overall and by its anatomic subtypes, that is, cardia and noncardia (11, 18). Although *H. pylori* in the stomach has not been shown to correlate with oral health, *H. pylori* infection in the mouth may act as a reservoir for stomach reinfection (19). If poor oral health is established as a risk factor for gastric cancer, it may explain part of the decline in rates over the past century, because oral health has improved through time in most populations with improved economic conditions.

Here, we use data from a case-control study in Golestan Province, in northeastern Iran, to investigate the association between oral health and oral hygiene and the risk of gastric cancer, overall and by its anatomic subtypes.

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## Materials and Methods

### Case and control selection

Case and control selection has been explained in detail elsewhere (20). Cases were recruited from December 2004 to December 2011 at Atrak Clinic, located in Gonbad City, in the eastern part of Golestan Province, Iran. Subjects with histologically proven gastric cancer who were referred or were diagnosed at Atrak clinic, the only specialized referral clinic for upper gastrointestinal problems in the area, were invited to enroll as cases in the study. Controls were selected from healthy subjects who enrolled in the Golestan Cohort Study (21). This cohort study recruited its participants from January 2004 to June 2008 in eastern Golestan Province. In total, 50,045 apparently healthy subjects, ages 40 to 75 years were enrolled. From this pool of cohort study participants, we randomly selected 2 controls matched to each case by age ( $\pm 5$  years), sex, and urban/rural residence status. We could not find matched controls for some of the cases; therefore these cases were excluded ( $N = 22$ ). For some cases, as the first set of controls did not have serum samples, we selected other controls while we also kept the previously selected controls. Three hundred and nine cases were selected from which 22 had one control assigned, 276 had 2 controls assigned, 5 had 3 controls assigned, and 6 had 4 controls assigned. By comparing our included subjects with the Golestan Cancer Registry, we found that we captured 60% of the gastric cancer cases in this geographic region. This study was approved by the Institutional Review Board of the Digestive Diseases Research Institute, Tehran University of Medical Sciences, Iran, and all participating individuals provided written informed consent.

### Questionnaires and physical examination

All participants completed a general lifestyle questionnaire, had a brief physical examination, and provided the blood samples. A general questionnaire was used to obtain detailed information on age, sex, ethnicity, place of residence, education, and ownership of property, cars, and appliances (as indicators of socioeconomic status), personal and family history of cancer, and lifelong history of opium and tobacco use. Height and weight were directly measured. All subjects also completed a food frequency questionnaire that was developed and validated for use in Golestan Province (22).

### Oral hygiene and dentition data

Data on oral health were obtained during the physical exam by dentist-trained health personnel. The number of decayed, missing, and filled teeth was recorded and we used the number of teeth lost or summed DMFT score as exposure variables. Interviewers also asked about the frequency of toothbrushing and use of dentures. Repeatability of DMFT counts were checked 2 months later in 130 subjects, with 88.3% agreement and a  $\kappa$  of 0.86 (23).

### *Helicobacter pylori* antibody assays

Serum and plasma samples from cases and controls, respectively, were used to conduct *Helicobacter pylori*

(*H. pylori*) antibody assays. A multiplex serology method was used to assay the serostatus of 15 antibodies against *H. pylori* proteins (24). *H. pylori* positivity in this analysis was defined on the basis of the result of the Cag A antibody from this assay.

### Statistical analysis

We used conditional logistic regression models to estimate unadjusted and adjusted ORs and 95% confidence intervals (CI). All models were conditioned on the matching factors, whereas adjusted models included variables for age, education, ethnicity, wealth score, total daily fruit intake, total daily vegetable intake, tobacco use, opium use, and denture use. We also tested adjustment for antibodies to *H. pylori* CagA antigen. *H. pylori* infection is very common in this population (25) and 84% of the cases and 82% of the controls in our study were positive for Cag A antibody. Adjustment for antibodies to *H. pylori* CagA antigen did not change the results, so it was not added in our final models. The wealth score was created using multiple correspondence analyses with data on ownership of automobiles, motorcycles, televisions, refrigerators, freezers, vacuums, and washing machines, as well as house ownership, house size, the presence on an indoor bath, and the occupation of the head of the family. The methods for creating this score and its association with cancer risk have been previously published (26). The regular use of opium and tobacco was defined as having these substances at least once a week for a minimum of 6 months. We categorized our primary exposures, tooth loss, and frequency of brushing, as previously described (10). We used 2 different overall tests of the hypothesis that the tooth loss or oral hygiene variables were associated with gastric cancer because the categorical risk estimates did not seem to show a linear trend. We used both a standard one degree-of-freedom linear trend test (assigning each category an ordinal number) and a multiple degree-of-freedom global test of the effect of adding oral hygiene variables to the model, which avoids an assumption of linearity.

### Results

Of the 309 gastric adenocarcinoma cases, 161 (52%) and 118 (38%) were cardia and noncardia cancer, respectively. For the other 30 cases, we could not define the origin of the tumor, so they were classified only as gastric adenocarcinomas. Table 1 presents a summary of the demographic and food variables, and the tobacco and opium use of the cases and controls. Cases and controls were well matched for gender and urban/rural residence. Controls were more likely to be of Turkmen ethnicity and to have some education than cases. The prevalence of opium use was higher in cases than in controls ( $P < 0.0001$ ).

The global and trend  $P$  values show some evidence for an association between tooth loss and DMFT score with the risk of gastric cancer, overall and at each anatomic subsite (Table 2). Comparing the unadjusted and adjusted models, the fully adjusted estimates showed several large changes. Age was the main confounding factor that caused these

**Table 1.** Summary of the demographic, nutrient, tobacco, and opium, and *H. pylori* status variables of the cases and controls

	All gastric adenocarcinoma (GA)		Gastric cardia adenocarcinoma (GCA)		Gastric noncardia adenocarcinoma (GNCA)	
	Matched controls (n = 613)	Cases (n = 309)	Matched controls (n = 323)	Cases (n = 161)	Matched controls (n = 231)	Cases (n = 118)
Age (y), mean (SD)	63.6 (9.1)	65.2 (10.7)	64.5 (8.9)	66.4 (10.9)	62.5 (9.5)	63.7 (10.6)
Female gender, N (%)	167 (27.2)	83 (26.9)	83 (25.7)	38 (23.6)	65 (28.1)	36 (30.5)
Urban residence, N (%)	192 (31.3)	100 (32.5)	96 (29.7)	52 (32.5)	73 (31.6)	38 (32.2)
Ethnicity, N (%)						
Turkmen	368 (60.0)	145 (46.9)	216 (66.8)	92 (57.1)	118 (51.1)	39 (33.1)
Fars	87 (14.2)	62 (20.1)	39 (12.1)	22 (13.7)	35 (15.2)	35 (29.7)
Turk	78 (12.8)	47 (15.2)	32 (9.9)	21 (13)	39 (16.9)	19 (16.1)
Sistani	57 (9.3)	33 (10.7)	30 (9.3)	18 (11.2)	24 (10.4)	13 (11)
Others	23 (3.7)	22 (7.1)	6 (1.9)	8 (5)	15 (6.5)	12 (10.1)
Education, N (%)						
Some education	164 (26.7)	55 (17.8)	88 (27.2)	27 (16.8)	60 (26.0)	21 (17.8)
No formal education	449 (73.3)	254 (82.2)	235 (72.8)	134 (83.2)	171 (74.0)	97 (82.2)
Total fruit consumption (g/day), mean (SD)	139.2 (116.5)	166.0 (155.5)	142.0 (115.5)	171.3 (174.0)	136.5 (122.9)	157.7 (133.2)
Total vegetable consumption (g/d), mean (SD)	185.7 (99.5)	176.7 (103.1)	184.4 (105.2)	174.4 (98.2)	184.8 (91.9)	172.9 (103.6)
Homeownership, N (%)	594 (96.9)	285 (92.2)	316 (97.8)	159 (94.4)	221 (95.7)	105 (89.7)
Home size (m <sup>2</sup> ), mean (SD)	105.9 (51.7)	100.5 (70.0)	107.8 (53.1)	101.2 (48.7)	103 (49.9)	99.7 (94.5)
Mean wealth score (SD)	50.7 (219.9)	28.7 (223.1)	42.3 (215.5)	1.8 (222.8)	55.1 (221.9)	42.8 (223.1)
Tobacco use						
Never	397 (64.8)	194 (62.8)	203 (62.8)	107 (66.5)	155 (67.1)	69 (58.5)
Ever	216 (35.2)	115 (37.2)	120 (27.2)	54 (33.5)	76 (32.9)	49 (41.5)
Opium use						
Never	482 (78.6)	200 (64.7)	256 (79.3)	110 (68.3)	180 (77.9)	72 (61.0)
Ever	131 (21.4)	109(35.3)	67 (20.7)	51 (31.7)	51 (22.1)	46 (39.0)

changes, whereas the other factors had minimal effect. We used 2 overall tests of association: a global test that assumes nonlinear effect and a linear trend test. These 2 tests did not always produce similar results.

Table 2 also shows the associations between frequency of tooth brushing and gastric cancer risk. There was a significant association only for gastric cardia cancer, for which subjects who brushed their teeth less than daily were at significantly higher risk. This association was apparent in the crude models and strengthened in the fully adjust models.

**Discussion**

We found that tooth loss and oral hygiene were associated with differing risks of gastric adenocarcinoma in this population. The nonlinear nature of the associations and the appreciable changes in ORs after adjusting for confounders suggest that these associations may be due to the residual confounding. The association between oral health, tooth loss, and gastric cancer has been investigated in a limited number of studies (11, 15, 18, 27–31). Two of these studies failed to find a significant effect of oral health on gastric

cancer risk (15, 27), whereas the others reported an increase in the risk of gastric cancer in subjects with poor oral hygiene. Among the previous studies, the strongest association was reported for noncardia gastric cancer, whereas in the same study, they found no association between tooth loss and gastric cardia adenocarcinoma (18). Recently 2 review articles have investigated the relationship between tooth loss, periodontal disease, and cancer in different organs (32, 33). Using available published data, neither of them could conclude the existence of an association between oral health parameters and gastric cancer. This lack of consistency among studies may be related to the methodologic differences in the criteria used to define periodontal disease and oral health, differences in study populations, difficulties in distinguishing gastric cardia and noncardia cancers, differences in risk factors in high and low incidence areas, or chance findings (type I error).

There are several mechanisms that have been proposed to explain the possible association between oral health and cancer. The association between periodontal disease and oral and upper gastrointestinal tract cancers may be related to the local activation of carcinogens in alcohol, tobacco, or

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**Table 2.** Adjusted ORs and 95% confidence intervals for tooth loss, oral hygiene variables, and gastric cancer

	All Gastric adenocarcinoma (GA)				Gastric cardia adenocarcinoma (GCA)				Gastric noncardia adenocarcinoma (GNCA)			
	Matched controls	GCA	OR (95%CI) for GA	Global P-value and Linear Trend P-value	Matched controls	GCA	OR (95%CI) for GCA	Global P-value and Linear Trend P-value	Matched controls	GNCA	OR (95%CI) for GNCA	Global P-value and Linear Trend P-value
	N (%)	N (%)			N (%)	N (%)			N (%)	N (%)		
<b>Tooth loss<sup>b</sup></b>												
Category 1 (≤12)	99 (16.2)	47 (15.2)	Reference	0.02	53 (16.4)	19 (11.8)	Reference	0.01	37 (16.0)	21 (17.8)	Reference	0.01
Category 2 (13–18)	105 (17.1)	24 (7.8)	0.4 (0.2–0.8)	0.01	57 (17.6)	12 (7.5)	0.6 (0.2–1.4)	0.02	39 (16.9)	10 (8.5)	0.4 (0.2–1.1)	0.07
Category 3 (19–24)	125 (20.4)	45 (14.5)	0.8 (0.5–1.4)	0.9 (0.4–1.7)	71 (22.0)	29 (18.0)	1.4 (0.6–3.1)	1.6 (0.6–4.35)	46 (19.9)	12 (10.2)	0.5 (0.2–1.3)	0.4 (0.1–1.3)
Category 4 (25–31)	105 (17.1)	68 (22.0)	1.6 (1.1–2.7)	1.6 (0.8–3.2)	53 (16.4)	39 (24.2)	2.9 (1.3–6.4)	3.5 (1.2–9.7)	36 (15.6)	25 (21.2)	1.4 (0.6–3.2)	1.7 (0.5–5.6)
Category 5 (32)	179 (29.2)	125 (40.5)	1.9 (1.1–3.1)	1.4 (0.6–3.0)	89 (27.6)	62 (38.5)	2.8 (1.3–6.1)	1.4 (0.4–4.5)	73 (31.6)	50 (42.3)	1.5 (0.6–3.2)	2.1 (0.6–6.9)
<b>DMFT<sup>c</sup></b>												
Category 1 (≤15)	60 (9.8)	34 (11.0)	Reference	0.08	31 (9.6)	15 (9.3)	Reference	0.02	26 (11.3)	14 (11.9)	Reference	0.3
Category 2 (16–22)	83 (13.5)	32 (10.4)	0.6 (0.3–1.2)	0.5 (0.2–1.1)	50 (15.5)	12 (7.5)	0.4 (0.1–1.2)	0.5 (0.1–1.8)	24 (10.4)	16 (13.6)	1.2 (0.4–3.2)	0.7 (0.1–2.6)
Category 3 (23–26)	69 (11.3)	30 (9.7)	0.7 (0.4–1.4)	0.8 (0.3–1.8)	50 (15.5)	20 (12.4)	1.0 (0.4–2.4)	1.7 (0.5–5.4)	18 (7.8)	7 (5.9)	0.6 (0.2–2.0)	0.4 (0.1–2.0)
Category 4 (27–31)	97 (15.8)	56 (18.1)	1.1 (0.5–1.8)	0.8 (0.3–1.7)	41 (12.7)	32 (19.9)	1.9 (0.8–4.7)	2.7 (0.8–9.0)	41 (17.7)	21 (17.8)	0.8 (0.3–2.1)	0.5 (0.1–2.0)
Category 5 (32)	304 (49.6)	157 (50.8)	0.8 (0.4–1.4)	0.4 (0.2–1.1)	151 (46.7)	82 (50.9)	1.3 (0.6–2.9)	1.1 (0.3–2.9)	122 (52.8)	60 (50.8)	0.6 (0.2–1.6)	0.3 (0.1–1.1)
<b>Frequency of tooth brushing</b>												
Daily	114 (18.6)	34 (11.0)	Reference	0.1	57 (17.6)	11 (6.8)	Reference	0.001	42 (18.2)	20 (16.9)	Reference	0.5
Less than daily	84 (13.7)	29 (9.4)	1.2 (0.6–2.2)	1.7 (0.8–3.6)	48 (14.9)	17 (10.6)	1.8 (0.7–4.5)	5.6 (1.6–19.3)	29 (12.5)	10 (8.5)	0.7 (0.3–1.9)	0.3
Never	415 (67.7)	246 (79.6)	2.2 (1.4–3.5)	1.8 (1.01–3.2)	218 (67.5)	133 (82.6)	3.6 (1.7–7.5)	5.1 (1.8–14.7)	160 (69.3)	88 (74.6)	1.2 (0.64–2.3)	0.6 (0.2–1.4)

NOTE: ORs were obtained from conditional logistic regression models.

<sup>a</sup>Adjusted for age, ethnicity, education fruit and vegetable use, socioeconomic status, ever opium or tobacco use, and denture use.

<sup>b</sup>Defined by number of lost teeth.

<sup>c</sup>Sum of decayed, missing, and filled teeth.

the diet, such as acetaldehyde (34) or nitrosamines (11). Poor oral health can increase the production of these products (35). The use of oral antiseptics (e.g., chlorhexidine) decreases salivary nitrosation (36) and may also reduce the production of other metabolites. A case-control study from China showed that regular tooth brushing reduced the risk of esophageal squamous cell carcinoma (ESCC; ref. 37). In another study from Iran, significant associations were found between the DMFT score and lack of daily tooth brushing and ESCC (10). Constant irritation of oral mucosa by improperly fitted dentures and irritation of the mucosa of the upper gastrointestinal tract by inappropriately chewed food, caused by tooth loss, have been proposed as other possible mechanisms (38). Alterations of dietary pattern, such as decreased fruits and vegetable intake secondary to tooth loss (39) may also predispose to oral and upper gastrointestinal cancers.

Alternatively, poor oral hygiene and altered oral microbiota may act on these or distant organs, like the stomach, pancreas, or cardiovascular system, via increased systemic inflammation (32). Systemic markers of cardiovascular disease and diabetes, like endothelial function (40) and glucose control (41), have been improved after successful treatment of periodontal disease.

Our study has several strengths and weaknesses. We captured more than half of the gastric cancer cases in this population and captured a wealth of information on potential confounders, allowing us to address the most likely sources of confounding. Potential limitations of this study included a lack of more detailed history of oral health and the lack of a direct periodontal examination, as tooth loss may be due to a variety of factors with different underlying disease processes.

In conclusion, we found some evidence for an association between oral health and gastric cancer, but the nonlinear association and relatively strong effect of confounder adjustment must temper the strengths of any conclusion. Our study adds to the relatively inconsistent literature on this topic and there is insufficient evidence for a clear pattern of association between oral health and the risk of gastric adenocarcinoma. Additional studies with more detailed oral health data and assessment of the oral microbiome (42) may provide more clarity.

#### Disclosure of Potential Conflict of Interest

P. Boffetta has expert testimony from Johnson & Johnson. No potential conflicts of interest were disclosed by the other authors.

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