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Association between oral health and gastric precancerous lesions

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Although recent studies have suggested that tooth loss is positively related to the risk of gastric non-cardia cancer, the underlying oral health conditions potentially responsible for the association remain unknown. We investigated whether clinical and behavioral measures of oral health are associated with the risk of gastric precancerous lesions. We conducted a cross-sectional study of 131 patients undergoing upper gastrointestinal endoscopy. Cases were defined as those with gastric precancerous lesions including intestinal metaplasia or chronic atrophic gastritis on the basis of standard biopsy review. A validated structured questionnaire was administered to obtain information on oral health behaviors. A comprehensive clinical oral health examination was performed on a subset of 91 patients to evaluate for periodontal disease and dental caries experience. A total of 41 (31%) cases of gastric precancerous lesions were identified. Compared with non-cases, cases were significantly more likely to not floss their teeth [odds ratio (OR) = 2.89, 95% confidence interval (CI): 1.09–7.64], adjusting for age, sex, race, body mass index, smoking status, educational attainment and *Helicobacter pylori* status in serum. Among participants who completed the oral examination, cases (n = 28) were more likely to have a higher percentage of sites with gingival bleeding than non-cases [OR = 2.63, 95% CI: 1.37–5.05 for a standard deviation increase in bleeding sites (equivalent to 19.7%)], independent of potential confounders. Our findings demonstrate that specific oral health conditions and behaviors such as gingival bleeding and tooth flossing are associated with gastric precancerous lesions.

Introduction

Gastric cancer is the second most common malignancy worldwide (1). Although major risk factors including *Helicobacter pylori* colonization, tobacco smoking and increased intake of salt and meats have been identified, gaps remain in our understanding of the factors that contribute to its etiology.

The majority (95%) of gastric cancers are adenocarcinomas. The two histological classes for gastric adenocarcinomas, developed by Lauren's classification (2), are intestinal and diffuse. The intestinal subtype accounts for ~70% of gastric cancer cases (3) and is characterized as having a preneoplastic sequence spanning from chronic superficial gastritis to atrophic gastritis, intestinal metaplasia, dysplasia and ultimately malignancy (4,5). Several case–control studies of gastric precancerous lesions, predominantly atrophic gastritis and intestinal metaplasia, have identified common risk factors for gastric cancer such as cigarette smoking, old age and low levels of fruit or vitamin C intake (6,7,8,9,10,11). Studies of gastric precancerous lesions may improve our understanding of the biologic basis of carcinogenesis and the natural history of gastric cancer.

Several prospective epidemiologic studies (12,13,14,15) reported a positive association between tooth loss and the risk of gastric non-cardia adenocarcinoma. However, specific oral health conditions that may be responsible for this association remain unknown. Most of the studies that measured tooth loss were based on self-report information (12,14,15). Although self-reported tooth loss may represent a cumulative measure of lifetime exposure to periodontal disease or caries, tooth loss itself is not a direct measure of either condition. The validity of self-reported information on tooth loss in these studies is also unknown. It has been hypothesized that periodontal disease increases the risk of gastric non-cardia adenocarcinoma through alterations in the oral bacterial flora and subsequent chronic systemic inflammation (12,13). However, to our knowledge, no previous study has objectively evaluated the role of periodontal disease in gastric cancer or precancerous lesions. Studies with direct clinical measurement of periodontal disease and caries may provide insights into the role of oral health in the development of gastric cancer. We conducted an endoscopic population-based cross-sectional study to evaluate the association between clinical and behavioral measures of oral health and gastric precancerous lesions.

Abbreviations: CI, confidence interval; OR, odds ratio.

Materials and methods

Patient population

All potential study participants were scheduled for upper endoscopy at Bellevue Hospital Center in New York City for clinically indicated reasons. Given the known epidemiologic trend for average age of gastric cancer development (16), subjects ≥40 years old were asked to participate in this study. Exclusion criteria were (i) prior gastric surgery, (ii) use of antimicrobial agents within the prior 2 weeks, (iii) current use of anticoagulants, (iv) active gastrointestinal bleeding and (v) having had or suspected to have esophageal varices. Information on demographic and lifestyle factors was collected using structured questionnaires administered by a trained interviewer before the endoscopic procedure. For non-English participants, the interview was conducted with the assistance of Team/Technology Enhanced Medical Interpreting System, a simultaneous translation service that has been implemented successfully at Bellevue Hospital Center. Participants also filled out a modified version of the Block food frequency questionnaire in their preferred language (English, Spanish or Chinese); the food frequency questionnaire has been validated for these populations (17,18,19). All procedures involving human subjects were approved by the Institutional Review Boards of New York University School of Medicine and Bellevue Hospital Center. We obtained written informed consent from all subjects at time of enrollment. Overall, 283 eligible participants were approached, and 162 (57%) were recruited between April 2009 and April 2011. Among those who refused (n = 121), 80% refused due to not having time for the oral exam, not interested in the research and not wanting to participate in research studies in general. As of April 2011, complete data for case status were available for 131 subjects. Participants and non-participants were similar with respect to race/ethnicity, gender and age. Roughly two-thirds of non-participants were of Asian or Hispanic race/ethnicity, 60% were female and their average age was 58 years.

Endoscopy and pathology review

Endoscopic evaluation was performed using Olympus GIF-XQ140 or GIFQ-160 video-endoscopes following existing protocol (20). To assess histology, a total of eight biopsies of ~2 × 2 × 2 mm in dimension were obtained from the stomach, with four from the antrum and two each from the corpus and fundus. Biopsy specimens were processed according to preestablished standardized protocols and reviewed by three experienced gastrointestinal histopathologists (B.W., H.H. and Z.P.) designated to the study. The

histopathologic review was conducted blind to questionnaire data and results of the oral examination. Parameters evaluated for gastric biopsies included (i) degree of acute inflammation, (ii) atrophy and (iii) intestinal metaplasia. The degree of gastritis was scored using the updated Sydney System (21). Participants were categorized according to the most advanced lesion found. Participants were classified as cases if they were diagnosed with chronic atrophic gastritis, intestinal metaplasia or dysplasia on biopsy review. Non-cases included those who were not found to have gastric precancerous lesions, of which some may have had superficial gastritis.

Helicobacter pylori *serology*

Serum samples were collected at the time of endoscopy and were tested for *H.pylori* using enzyme-linked immunosorbent assay for immunoglobulin G antibodies to *H.pylori* whole-cell antigens in duplicate and in parallel with known positive controls (the cutoff for positivity was optical density ratio >1.0) (22). Immunoglobulin G antibodies to *cagA* were measured by enzyme-linked immunosorbent assay (the cutoff for positivity was an optical density ratio >0.35) (23).

Oral examination

Within 1–4 weeks following the upper endoscopy, an experienced faculty member (R.H.) performed a comprehensive oral examination on participants, blinded to their endoscopy biopsy results. Absence of antibiotic use was confirmed at this time. The caries and periodontal clinical assessments were standardized in a calibration session against two experienced dentists (G.C. and R.C.), following the National Institute of Dental and Craniofacial Research diagnostic criteria for the Oral Health Survey of United States Adults (24).

The dental caries examination was performed on all teeth except third molars; excluding third molars avoids misclassification if they are missing due to reasons other than caries. Missing teeth were recorded separately. Past and present caries experience was assessed in terms of the number of decayed, missing and filled teeth and tooth surfaces. Restorations that were placed as a result of trauma or for aesthetic purposes were not counted as filled.

The periodontal examination involved measurements at six sites (mesiobuccal, buccal, distobuccal, distolingual, lingual and mesiolingual) of all retained teeth using a manual North Carolina 15 periodontal probe (25). Levels of clinical attachment loss, defined as the distance from the cementoenamel junction to the free gingival margin in millimeters, and periodontal pocket depth (PD), defined as the distance from the free gingival margin to the bottom of the pocket to the nearest whole millimeter, were recorded for each of the six tooth surfaces assessed. Bleeding on probing was recorded dichotomously for each tooth surface and deemed positive if it occurred within 15 s of probing.

Although all the study participants agreed to participate to an oral examination, results are available for a subsample of 91 participants (70%). The major reason (90%) for not completing the oral examination was lack of time availability.

Statistical analyses

In the overall study population ($n = 131$), we first conducted descriptive analyses comparing participants with gastric precancerous lesions and those without gastric precancerous lesions in terms of sociodemographic and lifestyle characteristics. We estimated odds ratios (ORs) for gastric precancerous lesions in relation to self-reported oral health conditions and behaviors, including tooth health, gum health, frequency of brushing and flossing. To assess the level of potential confounding, among non-cases, descriptive analyses were also conducted to evaluate correlates of oral health behaviors and selected oral health conditions (Supplementary Appendix III is available at *Carcinogenesis* Online). ORs were adjusted for (i) age and sex and (ii) age, sex, ethnic background, smoking status, body mass index, *H.pylori* status and educational attainment. Additional control for average daily intakes of meats, vegetables and fruits did not change the results appreciably (data not shown) and therefore the final models did not include these variables.

Among the 91 participants who completed oral examination, we compared differences in oral health indices between cases and non-cases. We first computed least square means of clinical oral health indices according to case status using linear regression, adjusting for age and sex. Then, we estimated ORs for gastric precancerous lesions in relation to oral health indices by entering each measure as a continuous variable in serially adjusted models. All estimates were scaled according to the standard deviations of oral health indices in the overall study population to facilitate interpretation (Supplementary Appendix I is available at *Carcinogenesis* Online).

Exploratory analyses were conducted to evaluate whether the associations of oral health behaviors and oral health indices with gastric precancerous lesions differ appreciably by sex, smoking status, *H.pylori* status and race/ethnicity. We performed all statistical analyses using SAS 9.2 (SAS Institute, Cary, NC). All tests were two sided and $P < 0.05$ was considered significant.

Results

Of the 41 cases with gastric precancerous lesions, a total of 27 (65.9%) had intestinal metaplasia and 14 (34.1%) had chronic atrophic gastritis. Participants with gastric precancerous lesions were more likely to have ever smoked and to be infected with *H.pylori*, particularly the *cagA*-positive strain, compared with those without gastric precancerous lesions (P values all <0.05) (Table I). There were no significant differences with case status in terms of age; sex; educational attainment; consumption of alcohol, tea and coffee; body mass index and race/ethnic background, although there was a higher percentage of Asians among cases ($P = 0.23$).

There were no significant differences between participants who completed oral examination ($n = 91$) and those who did not ($n = 40$) in terms of socioeconomic and lifestyle characteristics (Supplementary Appendix II is available at *Carcinogenesis* Online), although participants who underwent the oral examination were slightly older. There was also no difference in case status between those who agreed to the oral examination compared with those who did not ($P = 0.84$) (Supplementary Appendix II is available at *Carcinogenesis* Online). Cases were less likely to floss their teeth regularly ($P = 0.01$) (Table II). There were no significant differences by case status in terms of brushing frequency and self-reported tooth health and

Table I. Distributions of participant characteristics by status of gastric precancerous lesions

Patient characteristics	Gastric precancerous lesions		P value[a]
	Cases ($N = 41$)	Non-cases ($N = 90$)	
Sex, %			0.60
Men	41.5	36.7	
Women	58.5	63.3	
Age, years			0.64
Mean (SD)	57.0 (9.0)	56.1 (9.9)	
Education, %			0.90
Less than high school	37.5	33.7	
High school	37.5	38.2	
Some college or graduate	25.0	28.1	
Race, %			0.23
Asian/Pacific Islander	42.5	28.1	
Hispanic/African-American	47.5	55.1	
White/others	10.0	16.9	
BMI, kg/m^2			0.53
Mean (SD)	27.1 (7.2)	26.3 (6.1)	
Smoking status, %			0.003
Ever	47.4	21.4	
Never	52.6	78.7	
Alcohol consumption, %			0.58
Ever	28.6	33.7	
Never	71.4	66.3	
Tea consumption, %			0.21
Yes	63.9	75.0	
Coffee consumption, %			0.47
Yes	70.3	63.6	
Place of birth, %			0.34[b]
Foreign born	94.4	87.6	
Helicobacter pylori status (in serum), %			0.004
Negative	23.1	55.0	
Positive			
cagA negative	12.8	8.8	
cagA positive	64.1	36.3	

BMI, body mass index; SD, standard deviation.
[a]P value by chi-square test.
[b]P value by two-sided fisher exact test.

gingival health. These associations remained similar in multivariable logistic models. The OR for having gastric precancerous lesions was 2.89 [95% confidence interval (CI) = 1.09–7.64], comparing participants who did not floss regularly with those who did, after adjustment for age, sex, race, education attainment, body mass index, smoking status and *H.pylori* status. This pattern of association was similar when we considered frequency of flossing. Compared with flossing once per day or more, the ORs for gastric precursor lesions were 1.66 (95% CI = 0.41–6.78) and 3.40 (95% CI = 1.14–10.1) for individuals who flossed every few days or weeks and those who did not floss (*P* value for trend = 0.08), respectively. The association did not differ appreciably by sex, smoking status, *H.pylori* status (data not shown) or race/ethnicity, although the sample size is limited for testing interactions. When restricted to *H.pylori*-positive subjects ($n = 73$), this association remained (Supplementary Appendix IV is available at *Carcinogenesis* Online).

Nearly all (94.5%) the subjects had one or more decayed, missing or filled teeth. Table III shows the age- and sex-adjusted means of caries and periodontal indices among cases and non-cases. Cases had a lower average decayed, missing and filled teeth than non-cases ($P = 0.07$), likely driven largely by a lower number of filled teeth ($P = 0.05$). However, there were no significant associations between any of the caries indices and gastric precursor lesions in final multivariable logistic models.

Compared with non-cases, cases had higher average periodontal pocketing and percentage of sites with ≥3 mm of periodontal pocket depth; however, these differences were not statistically significant (Table III). A significantly higher number of bleeding sites were present among cases than non-cases after controlling for age and sex (35.4 versus 23.7%, $P = 0.006$), and the association remained significant in final multivariable logistic models. The OR for gastric precursor lesions was 2.63 (95% CI = 1.37–5.05) in relation to every standard deviation increase in the average percentage of gingival sites with bleeding on probing (equivalent to 19.7%).

Discussion

In this cross-sectional study of oral health and gastric precancerous lesions, we observed that participants with gastric precancerous lesions were significantly less likely to floss their teeth and more likely to have a higher percentage of gingival sites with bleeding. To the best of our knowledge, the present study is the first to report these associations.

Table II. Adjusted ORs for gastric precancerous lesions in relation to oral health behaviors

Oral health behaviors	Gastric precancerous lesions		Model 1	Model 2
	Cases *n* (%)	Non-cases *n* (%)	ORs[a] (95% CI)	ORs[b] (95% CI)
Dental flossing				
Floss	13 (37.1)	55 (62.5)	1.00 (referent)	1.00 (referent)
Do not floss	22 (62.9)	33 (37.5)	2.81 (1.25–6.34)	2.89 (1.09–7.64)
P for chi-square	0.01			
Tooth brushing				
Brush	30 (83.3)	78 (88.6)	1.00 (referent)	1.00 (referent)
Do not brush	6 (16.7)	10 (11.4)	1.56 (0.52–4.71)	2.02 (0.55–7.49)
P for fisher exact test	0.55			
Self-reported tooth health				
Good	7 (19.4)	25 (28.1)	1.00 (referent)	1.00 (referent)
Fair/poor	29 (80.6)	64 (71.9)	1.64 (0.63– 4.25)	1.05 (0.34–3.21)
P for chi-square	0.32			
Self-reported gum health				
Good/excellent	14 (38.9)	43 (48.3)	1.00 (referent)	1.00 (referent)
Fair/poor	22 (61.1)	46 (51.7)	1.49 (0.67–3.30)	1.13 (0.44–2.92)
P for chi-square	0.34			

BMI, body mass index.
[a]ORs were adjusted for age and sex.
[b]ORs were adjusted for age, sex, race, BMI, smoking status, educational attainment and *Helicobacter pylori* status.

Table III. Adjusted means and ORs of oral health indices in relation to gastric precancerous lesions ($n = 91$)

Oral health indices	Adjusted means (SE)[a]			ORs[b] for gastric precancerous lesions (95% CI)		
	Cases $N = 28$	Non-cases $N = 63$	*P* value	SD	Model 1	Model 2
Caries indices						
Decayed/missing/filled teeth	10.4 (1.4)	13.4 (0.9)	0.07	7.4	0.63 (0.38–1.04)	0.56 (0.29–1.07)
Decayed teeth	1.7 (0.5)	1.2 (0.3)	0.39	2.6	1.21 (0.78–1.87)	1.09 (0.67–1.76)
Filled teeth	3.4 (0.9)	5.4 (0.6)	0.05	4.6	0.58 (0.34–1.00)	0.71 (0.39–1.29)
Missing teeth	5.0 (1.2)	5.8 (0.8)	0.56	6.5	0.87 (0.54–1.41)	0.74 (0.41–1.35)
Periodontal indices						
Mean attachment loss (CAL), mm	2.5 (0.2)	2.5 (0.1)	0.65	0.8	1.11 (0.71–1.73)	1.03 (0.63–1.71)
Percentage of sites with CAL ≥3 mm	36.9 (4.3)	35.5 (2.9)	0.78	22.1	1.07 (0.68–1.67)	0.97 (0.58–1.62)
Mean pocket depth (PD), mm	2.1 (0.1)	2.0 (0.1)	0.30	0.5	1.28 (0.81–2.00)	1.32 (0.76–2.30)
Percentage of sites with PD ≥3 mm	27.4 (3.7)	23.4 (2.5)	0.36	19.6	1.23 (0.78–1.95)	1.29 (0.72–2.29)
Percentage of bleeding sites	35.4 (3.5)	23.7 (2.4)	0.006	19.7	1.95 (1.19–3.19)	2.63 (1.37–5.05)

BMI, body mass index; SE, standard error.
[a]Means were adjusted for age and sex.
[b]ORs were estimated in relation to a standard deviation (SD) increase in oral health indices. Model 1 was adjusted for age and sex. Model 2 was further adjusted for race, BMI, smoking status, educational attainment and *Helicobacter pylori* status.

Our data are consistent with the literature that suggests oral health may play a role in gastric non-cardia cancer. Several epidemiologic studies have found positive associations of self-reported tooth loss or poor oral hygiene with the risk of gastric cancer. In Japan, a case–control study of 242 cases of gastric cancer and 484 controls found that having dentures and missing teeth were associated with an increased risk of gastric cancer (14). In Turkey, a case–control study of gastric cancer found that cases brushed their teeth less frequently and had fewer teeth (15). In a large prospective cohort study in China that followed 29,584 persons for 5 years, tooth loss was positively associated with the risk of dying from both non-cardia and cardia gastric cancer (13). In a prospective study of lung cancer among smokers in Finland, self-reported tooth loss was found to be positively associated with incidence of gastric non-cardia cancer, and the association was present among those with and without *H.pylori*.

We found that bleeding on probing was significantly associated with gastric precancerous lesions, independent of other risk factors for disease and confounding factors. Bleeding on probing is considered an objective indicator for detecting gingival inflammation (26) and is associated with active gingivitis and periodontitis. A growing body of epidemiologic and laboratory evidence has emerged showing that long-standing inflammation promotes tumor development, growth and progression (27). The paradigm suggests that chronic inflammation is a risk or prerequisite factor for the development of a number of human malignancies, including liver, colon, stomach, bladder, cervix, ovary and lung carcinomas. Several oral pathogens have been related to chronic systemic inflammation (28), which has been associated with increased risk of gastric cancer (29). The periodontal pathogen, *Aggregatibacter actinomycetemcomitans*, has been associated with increased secretion of interleukins 1α and 1β and tumor necrosis factor α, cytokines that are involved in the inflammatory response. High serum titer to *Porphyromonas gingivalis* and the presence of periodontitis have been independently related to high C-reactive protein levels (30). Recent large epidemiologic studies reported that bacterial species etiologically related to periodontitis were associated with bleeding on probing in sites with minimal PD and/or clinical attachment loss (31,32). Taken together, our findings suggest that periodontitis may play a role in the development of gastric precancerous lesions, and future large studies are needed to comprehensively examine specific oral pathogens and the composition of oral flora in relation to gastric precancerous lesions or gastric cancer.

We also observed a positive association between lack of dental flossing and precancerous gastric lesions, with evidence of a dose–response relationship when frequency of flossing was considered. In a previous analysis, we found that levels of bacterial species etiologically linked to periodontal disease were inversely associated with flossing (33). This concurs with findings from randomized trials in twins showing that flossing significantly reduces levels of periodontal bacteria and gingival bleeding (34,35). Moreover, the association between lack of flossing and precancerous gastric lesions is stronger among those positive for *H.pylori* infection in subgroup analyses. This suggests a potential effect modification by *H.pylori* that warrants further exploration in future studies.

There were several strengths of the present study. First, both caries and periodontal disease were measured objectively in a consistent fashion for all participants. Previous studies used self-report data and did not measure specific indices of either caries or periodontal disease. Second, the availability of data on important risk factors of gastric cancer and potential confounders including *H.pylori* status, *cagA* status of *H.pylori*, dietary factors, socioeconomic status, caries status and smoking status enhanced the ability to rigorously control for potential confounding and strengthened the validity of the study findings.

Several potential limitations, however, should also be noted. First, the study had a small sample size and therefore we have limited power to assess association between oral health indices and gastric precancerous lesions when oral health indices were treated as categorical variables. Future large studies are needed to confirm our findings and to further investigate the full dose–response relationships. Second, the study design was cross-sectional and precludes any causal inference. The time sequence of oral health conditions, behaviors and gastric precancerous lesions cannot be directly addressed in the present study. However, it is not likely that participants reported their oral health behaviors differently according to their disease status, as the disease status was determined based on biopsy findings subsequent to the interview. Importantly, the adjusted mean values for all periodontal indices were all significantly higher among those who did not floss compared with those who flossed (Supplementary Appendix III is available at *Carcinogenesis* Online), suggesting the validity of the information on self-reported oral health behaviors. Atrophic gastritis and gastric intestinal metaplasia are considered precancerous lesions; however, they are benign, and it is not likely that participants changed their oral health behaviors due to the conditions. Moreover, diagnoses of gastric precancerous lesions were made within 1 month of the scheduled oral examination, making it unlikely that any behavioral modification in the interim would have had a clinically meaningful impact. Third, although we cannot exclude the possibility of potential selection bias, it is not likely that cases with severe periodontal disease preferentially volunteered to be included in the study, since the hypotheses were not known by the participants and participants were unaware of their lesion status at the time of recruitment and oral health examination.

In this cross-sectional study of oral health and gastric precancerous lesions, we found positive associations of not flossing and level of bleeding on probing with gastric precancerous lesions. The findings suggest that oral health indices relevant to periodontitis may play a role in the etiology of gastric precancerous lesions and gastric cancer. Future large studies are needed to confirm the findings and further identify the pathogens for the underlying mechanisms.

Supplementary material

Supplementary Appendices I–IV can be found at http://carcin.oxfordjournals.org/

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