Periodontal Disease, Tooth Loss, and Risk of Serrated Polyps and Conventional Adenomas

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ABSTRACT

Growing data indicate an association between periodontal disease and the development of cancer. However, the evidence for colorectal cancer has been inconsistent and longitudinal study examining its precursor lesions is lacking. We prospectively collected information on periodontal disease and number of tooth loss in the Nurses' Health Study (1992–2002) and the Health Professionals Follow-up Study (1992–2010). Polyp diagnosis was acquired via self-reported questionnaires and confirmed through review of medical records. We used logistic regression to calculate the multivariate-adjusted ORs and 95% confidence intervals (CI) with adjustment for smoking and other known risk factors for periodontal disease and colorectal cancer. In this study, we included 17,904 women and 24,582 men. We documented 2,336 cases of serrated polyps and 4,102 cases of conventional adenomas among 84,714 person-endoscopies throughout follow-up. The ORs of serrated polyps and conventional adenomas comparing individuals with and without periodontal disease were 1.17 (95% CI, 1.06–1.29) and 1.11 (95% CI, 1.02–1.19), respectively. Compared with participants without tooth loss, those who lost ≥4 teeth had 20% (OR, 1.20; 95% CI, 1.03–1.39) greater risk of serrated polyps (P_{trend} 0.01). Among never smokers, similar associations with periodontal disease were observed for both serrated polyps (OR, 1.20; 95% CI, 1.02–1.41) and conventional adenomas (OR, 1.12; 95% CI, 1.00–1.26). History of periodontal disease and possibly higher number of tooth loss may modestly increase the risk of developing colorectal precursor lesions. Our findings advance our understanding of the interplay between oral health, microbiome, and early colorectal carcinogenesis.

Introduction

Periodontal disease refers to diseases that affect the gingiva, the supporting connective tissue, and alveolar bone (1). It is a prevalent health condition and may lead to eventual tooth loss. According to a recent report from the American Dental Association, periodontitis, the most severe form of periodontal disease, affects over 40% of the U.S. population aged 30 years and older (2). The past decade has seen a rapidly growing interest in the relationship between oral health and cancer risk. Much of the research focused on dysbiosis of the oral microbiome as a possible pathological mechanism that drives carcinogenesis (3–7). A dysbiotic oral microbiome may induce local and systemic inflammation (8) in the content of immune dysregulation (9, 10). Altered periodontal microbial community may also induce dysbiosis of the intestinal microbiota (11). The resulting "inflamed" microbiome could generate an environment conducive to colitis and gastrointestinal cancers (12, 13).

Although the link between inflammation and tumorigenesis is well-established in colorectal cancer (14, 15), epidemiologic evidence on the association of periodontal disease with colorectal neoplasia remains limited and inconsistent, with some studies reporting positive associations (4, 16–18) and some reporting null results (3, 5, 19, 20). Prior cross-sectional studies on colorectal cancer precursors (21, 22) suggested increased risk for conventional adenomas among individuals with periodontitis, especially proximal advanced adenomas, while no study has examined the association with serrated polyps. As such, robust evidence from prospective study examining colorectal cancer precursor lesions is lacking. Addressing this question is important to better understand the potential role of oral dysbiosis in the early stage of colorectal carcinogenesis.

In this prospective study, combining data from two nationwide cohorts with comprehensive assessment of oral health and

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polyp diagnosis, we examined the association of periodontal disease and tooth loss with risk of serrated polyps and conventional adenomas, two distinct groups of colorectal cancer precursors (23, 24).

Materials and Methods

Study population

The Nurses' Health Study (NHS) enrolled 121,700 registered U.S. female nurses ages 30–55 years in 1976 (25). The Health Professionals Follow-up Study (HPFS) enrolled 51,529 male health professionals between the ages of 40 and 75 in 1986 (26). Questionnaires were mailed to participants at enrollment and every 2 years thereafter, inquiring health and lifestyle information. Diet was assessed via validated food frequency questionnaires (FFQ) every 4 years. The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital (Boston, MA) and the Harvard T.H. Chan School of Public Health (Boston, MA), and those of participating registries as required. Informed consent from participants was indicated by questionnaire return.

Assessment of oral health and dentition

Information on periodontal disease, defined as a history of periodontal bone loss, was assessed in 1998 and 2000 in the NHS and biennially starting from 1986 in the HPFS. History of periodontal surgery was asked in the 1992 questionnaire in the NHS and was considered a good surrogate for periodontal bone loss (positive predictive value 78% and negative predictive value 71%; ref. 27). Self-reported history of periodontal disease was validated in the HPFS by obtaining radiographs from a subset of individuals with and without self-reported history of periodontal disease (27, 28).

We also collected information on the number of teeth lost in the prior 2 years in the 1992, 1996, and 2000 questionnaires in the NHS and biennially starting from 1988 in the HPFS. Self-reported number of teeth is highly correlated with actual number of teeth on clinical assessment in a general population ($r = 0.97$; ref. 29). For our analysis, we calculated the cumulative tooth loss by adding the number of tooth loss from previous and current questionnaires starting from baseline. Because the assessment of periodontal disease and tooth loss was not updated after 2000 in the NHS, we only considered cases that occurred by the first questionnaire after 2000 in the NHS.

Ascertainment of colorectal polyp cases and subtypes

In each follow-up questionnaire, we asked participants whether they had undergone a colonoscopy or sigmoidoscopy and whether they had been diagnosed with a colorectal polyp in the past 2 years. For those who reported yes to both questions, we asked for permission to acquire their endoscopic and pathologic records. Review of records and extraction of clinicopathologic data were conducted by investigators blinded to exposure information. Serrated polyps included hyperplastic polyps and mixed/serrated adenomas. Mixed/serrated adenomas included both mixed polyps (those with both adenomatous and hyperplastic changes in histology) and polyps with any serrated diagnosis (e.g., serrated adenoma, serrated polyp, and sessile serrated polyp/adenoma). Conventional adenomas included tubular, tubulovillous, and villous adenomas and adenomas with high-grade dysplasia. Advanced conventional adenomas were defined as having at least one conventional adenoma of 10 mm or greater in diameter or with advanced histology (tubulovillous/villous histologic features or high-grade or severe dysplasia). Polyp subsites were classified into proximal colon (cecum, ascending colon, hepatic flexure, transverse colon, or splenic flexure), distal colon (descending or sigmoid colon), and rectum (rectum or rectosigmoid junction). Because detailed histologic information of polyps was not collected until 1992, we used this as the baseline date for this study.

Assessment of covariates

Using biennial follow-up questionnaires, we obtained data on race, family history of colorectal cancer, smoking, body mass index (BMI), height, physical activity, aspirin use, and physical examination (30). For dietary factors, we used validated FFQs (31, 32) to assess intake of foods/nutrients related to colorectal cancer risk including folate, calcium, vitamin D, processed red meat, and alcohol (33). To address missing data of the covariates that occurred in the follow-up questionnaires, we carried forward the most recent available information from prior questionnaires.

Statistical analysis

Participants were followed from the return date of the baseline questionnaire to the date of first polyp diagnosis, date of colorectal cancer diagnosis, death, or the end of follow-up (June 1, 2002 for the NHS; and January 1, 2010 for the HPFS), whichever occurred first. Our analysis included participants who had at least one lower endoscopy since baseline (June 1, 1992) and excluded those who had been diagnosed with cancer (except nonmelanoma skin cancer), colorectal polyps, or inflammatory bowel disease at baseline. If a participant had more than one endoscopy during the study period, multiple records from the same participant were included in the analysis. To account for possible repeated data per participant and to handle time-varying exposure and covariates efficiently, we used an Andersen–Gill data structure with a new record for each 2-year follow-up period during which a participant underwent an endoscopy.

The primary exposures of the study included history of periodontal disease, which was modeled as a binary variable (no and yes), and number of tooth loss, which was categorized as 0, 1, 2–3, and ≥4 tooth loss. We calculated the ORs and 95% confidence intervals (CI) of colorectal polyps using multivariate logistic regression for clustered data (PROC GENMOD) with adjustment for age, sex, race, family history of colorectal cancer, history of diabetes mellitus, smoking status, smoking intensity, BMI, height, physical activity, dietary factors (folate, vitamin D, calcium, and processed red meat), alcohol intake, regular aspirin use, physical examination within the past

Table 1. Basic characteristics of study participants according to history of periodontal disease and number of tooth loss.[a]

	History of periodontal disease		Number of tooth loss	
	No	Yes	0	≥4
Age, year, mean (SD)	67 (8)	70 (9)	67 (8)	73 (9)
Male, %	65	75	65	77
White, %	92	91	92	90
Family history of CRC, %	22	21	21	22
Diabetes mellitus, %	8	10	8	14
Smoking, pack-year, mean (SD)	9.4 (15.8)	15.5 (19.9)	9.5 (15.6)	19.1 (22.5)
BMI, kg/m^2, mean (SD)	26.1 (4.2)	26.2 (4.2)	26.0 (4.1)	27.0 (4.7)
Height, cm, mean (SD)	173.5 (9.9)	173.2 (10.1)	173.5 (10.0)	173.3 (9.4)
Physical activity[b], MET-hour/week, mean (SD)	27.0 (21.8)	25.8 (21.3)	27.2 (22.0)	23.9 (21.2)
Total folate intake, mg/day, mean (SD)	566 (229)	559 (230)	567 (230)	556 (231)
Calcium intake, mg/day, mean (SD)	1,011 (356)	997 (352)	1,013 (356)	974 (347)
Vitamin D intake, IU/day, mean (SD)	440 (225)	436 (225)	440 (225)	436 (230)
Processed red meat intake, serving/week, mean (SD)	1.7 (1.7)	1.7 (1.8)	1.7 (1.7)	2.0 (2.2)
Alcohol intake, g/day, mean (SD)	9.1 (11.3)	9.7 (11.7)	9.4 (11.5)	8.7 (11.3)
Regular aspirin use[c], %	51	51	51	52
Physical examination within the past 2 years, %	74	73	73	74

Abbreviations: CRC, colorectal cancer; MET, metabolic equivalent of task.

[a]All variables are adjusted for age and sex except for age and sex. Cumulative average values across person-endoscopies are presented. Mean (SD) is presented for continuous variables and percentage for categorical variables.

[b]Physical activity was represented by the product sum of the MET of each specific recreational activity and hours spent on that activity per week.

[c]Regular aspirin users were defined as those who used at least two standard tablets (325 mg) per week.

2 years, as well as endoscopy-related factors, including time period of endoscopy, number of prior endoscopies, and time since the most recent endoscopy. All exposures and covariates were modeled as time-varying variables to account for changes over time. For number of tooth loss, we tested for linear trend by treating the median value of each category as a continuous variable. To examine whether the associations differ between serrated polyps and conventional adenomas, we conducted case-only analyses and calculated $P_{\text{heterogeneity}}$ (34). To assess the independent association for periodontal disease and tooth loss and the joint effect of both exposures, we also performed a joint analysis by using individuals who had no periodontal disease and tooth loss as the reference group. $P_{\text{interaction}}$ was calculated by including a cross-product interaction term between periodontal disease and tooth loss in the model and assessing the statistical significance using Wald test.

In secondary analyses, we examined the association with periodontal disease severity assessed in 1998 in the NHS, consistent with a prior study (16). We then examined the risk of polyps by size (<10 mm and ≥10 mm for serrated polyps), risk classification (nonadvanced and advanced for conventional adenomas), anatomic subsite (proximal colon, distal colon, and rectum), and number of polyps (single and multiple). $P_{\text{heterogeneity}}$ between case groups was calculated through case-only analysis. We also conducted stratified analysis according to selected risk factors for periodontal disease. $P_{\text{interaction}}$ was estimated by Wald test for the product term between the exposure and dichotomized stratifying factors.

We conducted all analyses using the SAS software (SAS Institute, Inc., Version 9.4). All statistical analyses were two-sided with a P value less than 0.05 indicating statistical significance.

Results

A total of 17,904 women in the NHS and 24,582 men in the HPFS were included in the study. The median length of follow-up for women and men was 10.0 and 17.6 years, respectively. Among 84,714 person-endoscopies, we documented 2,336 cases of serrated polyps and 4,102 cases of conventional adenomas. Individuals with a history of periodontal disease and more tooth loss were characterized by older age and higher percentage of male participants and patients with diabetes (**Table 1**). Other periodontal disease risk factors such as smoking, higher BMI, and lower calcium intake were also more prevalent in this population.

We found that history of periodontal disease was associated with increased risks of serrated polyps (OR, 1.17; 95% CI, 1.06–1.29) and conventional adenomas (OR, 1.11; 95% CI, 1.02–1.19; **Table 2**). These associations did not differ significantly between the two types of polyps ($P_{\text{heterogeneity}} = 0.93$). In the NHS, there was a trend of increasing risk for conventional adenomas across more severe periodontal disease ($P_{\text{trend}} = 0.02$; Supplementary Table S1). Number of tooth loss showed a positive association with the risk of serrated polyps but not conventional adenomas. Compared with participants who had no tooth loss, those who lost ≥4 teeth had 20% greater risk of serrated polyps ($OR_{\geq 4 \text{ vs. } 0 \text{ tooth loss}}$, 1.20; 95% CI, 1.03–1.39; $P_{\text{trend}} = 0.01$). In contrast, no association was found for conventional adenomas ($OR_{\geq 4 \text{ vs. } 0 \text{ tooth loss}}$, 1.05; 95% CI, 0.93–1.19; $P_{\text{heterogeneity}}$ by polyp type = 0.09). In the joint analysis, no history of periodontal disease with ≥4 tooth loss and a history of periodontal disease with 0, 1–3, and ≥ 4 tooth loss were associated with increased risk of serrated polyps compared with no periodontal disease and tooth loss, with the

Table 2. Multivariate associations of periodontal disease and number of tooth loss with serrated polyps and conventional adenomas.

	Nonpolyp	Serrated polyps		Conventional adenomas	
	Person-endoscopies (%)	*n*	OR (95% CI)[a]	*n*	OR (95% CI)[a]
History of periodontal disease					
No	62,301 (79)	1,710	1 (reference)	3,050	1 (reference)
Yes	16,804 (21)	626	1.17 (1.06–1.29)	1,052	1.11 (1.02–1.19)
P			0.001		0.01
$P_{heterogeneity}$[b]					0.93
Number of tooth loss					
0	55,238 (70)	1,513	1 (reference)	2,654	1 (reference)
1	10,618 (13)	319	1.02 (0.90–1.15)	597	1.06 (0.97–1.17)
2–3	7,893 (10)	272	1.07 (0.94–1.23)	482	1.05 (0.95–1.17)
≥4	5,356 (7)	232	1.20 (1.03–1.39)	369	1.05 (0.93–1.19)
P_{trend}[c]			0.01		0.32
$P_{heterogeneity}$[b]					0.09
History of periodontal disease + number of tooth loss					
No history + 0 tooth loss	46,801 (59)	1,236	1 (reference)	2,198	1 (reference)
No history + 1–3 tooth loss	13,033 (16)	369	0.98 (0.87–1.11)	703	1.02 (0.93–1.11)
No history + ≥4 tooth loss	2,467 (3)	105	1.29 (1.05–1.59)	149	0.98 (0.82–1.17)
Positive history + 0 tooth loss	8,437 (11)	277	1.14 (0.99–1.30)	456	1.05 (0.94–1.16)
Positive history + 1–3 tooth loss	5,478 (7)	222	1.26 (1.08–1.47)	376	1.18 (1.05–1.33)
Positive history + ≥4 tooth loss	28,89 (4)	127	1.19 (0.98–1.46)	220	1.14 (0.98–1.33)
$P_{interaction}$[d]			0.20		0.37
$P_{heterogeneity}$[b]					0.34

Abbreviation: MET, metabolic equivalent of task.

[a]Multivariate logistic regression model adjusted for time period of endoscopy (in 2-year intervals), number of prior endoscopies (continuous), time since the most recent endoscopy (continuous, year), age (continuous, year), sex (female and male), race (White and non-White), family history of colorectal cancer (no and yes), history of diabetes mellitus (no and yes), smoking status (never smoker, past smoker, and current smoker), smoking intensity (continuous, pack-year), BMI (<22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0 kg/m^2), height (continuous, cm), physical activity (<7.5, 7.5–14.9, 15.0–29.9, 30.0–59.9, and ≥60.0 MET-hour/week), dietary factors (folate, vitamin D, calcium, and processed red meat; in quartiles), alcohol intake (women: never, <3.5, 3.5–6.9, and ≥7.0 g/day; men: never, <7.0, 7.0–13.9, and ≥14.0 g/day), regular aspirin use (no and yes), and physical examination within the past 2 years (no and yes).

[b]$P_{heterogeneity}$ was calculated in case-only analysis.

[c]P_{trend} was calculated using the median of each stratum as a continuous variable.

[d]$P_{interaction}$ between periodontal disease and tooth loss was calculated by including a cross-product interaction term between periodontal disease and tooth loss in the model and estimating the statistical significance using Wald test.

ORs ranging from 1.14 to 1.29. No clear pattern was observed for conventional adenomas.

The associations with periodontal disease and number of tooth loss were generally stronger for small serrated polyps and advanced conventional adenomas (**Table 3**). The risk of advanced conventional adenomas associated with periodontal disease was significantly increased (OR, 1.23; 95% CI, 1.09–1.38). However, no statistically significant heterogeneity was detected within subgroups of serrated polyps and conventional adenomas ($P_{heterogeneity} = 0.57$ and 0.11). Compared with individuals with no periodontal disease and tooth loss, those with a history of periodontal disease experienced a gradual increase in the risk of advanced conventional adenomas over higher number of tooth loss, with ORs for those with 0, 1–3, and ≥4 tooth loss increasing from 1.13 (95% CI, 0.96–1.34) to 1.28 (95% CI, 1.06–1.53), and then to 1.36 (95% CI, 1.09–1.70).

In stratified analyses, among never smokers, periodontal disease remained significantly associated with increased risk of serrated polyps (OR, 1.20; 95% CI, 1.02–1.41) and conventional adenomas (OR, 1.12; 95% CI, 1.00–1.26; Supplementary Figs. S1 and S2). The association between number of tooth loss and risk of serrated polyps differed significantly by sex, with an inverse and positive association observed for women ($OR_{\geq 4 \text{ vs. } 0 \text{ tooth loss}}$, 0.74; 95% CI, 0.51–1.08) and men ($OR_{\geq 4 \text{ vs. } 0 \text{ tooth loss}}$, 1.31; 95% CI, 1.11–1.54), respectively ($P_{interaction} = 0.002$).

The association between history of periodontal disease and serrated polyps seemed to increase from proximal colon, distal colon, to rectum (Supplementary Table S2). In contrast, history of periodontal disease was associated with an increased risk of conventional adenomas in the proximal colon but not distal colon or rectum (Supplementary Table S3). Upon grouping by number of lesions, the associations did not differ for either type of polyps (Supplementary Table S4).

Discussion

While periodontal disease has gained increasing attention over the past decade for its role in cancer development, evidence from observational studies is conflicting for colorectal neoplasia. This study represents the first prospective investigation of the risk of serrated and conventional colorectal precursors associated with oral health. We found that a diagnosis of periodontal disease in the past was associated with a modest increase in the subsequent risk of serrated polyps and conventional adenomas and that more tooth loss

Table 3. Multivariate associations of periodontal disease and number of tooth loss with serrated polyps by size and conventional adenomas by risk classification.

		Serrated polyps				Conventional adenomas			
		Small serrated polyps		Large serrated polyps		Nonadvanced conventional adenomas		Advanced conventional adenomas	
	Nonpolyp Person-endoscopy (%)	*n*	OR (95% CI)[a]	*n*	OR (95% CI)[a]	*n*	OR (95% CI)[a]	*n*	OR (95% CI)[a]
History of periodontal disease									
No	62,301 (79)	1,446	1 (reference)	128	1 (reference)	1,935	1 (reference)	1,115	1 (reference)
Yes	16,804 (21)	523	1.18 (1.06–1.31)	45	1.05 (0.74–1.50)	616	1.04 (0.94–1.14)	436	1.23 (1.09–1.38)
P			0.003		0.77		0.45		0.0007
$P_{heterogeneity}$[b]					0.57				0.11
Number of tooth loss									
0	55,238 (70)	1,295	1 (reference)	102	1 (reference)	1,675	1 (reference)	979	1 (reference)
1	10,618 (13)	271	1.02 (0.89–1.17)	19	0.87 (0.52–1.43)	378	1.08 (0.96–1.22)	219	1.03 (0.89–1.20)
2–3	7,893 (10)	209	0.98 (0.84–1.14)	37	2.05 (1.37–3.05)	286	1.01 (0.89–1.16)	196	1.11 (0.95–1.30)
≥4	5,356 (7)	194	1.20 (1.02–1.41)	15	1.04 (0.58–1.86)	212	1.01 (0.86–1.17)	157	1.13 (0.95–1.36)
P_{trend}[c]			0.05		0.36		0.90		0.13
$P_{heterogeneity}$[b]					0.82				0.44
History of periodontal disease + number of tooth loss									
No history + 0 tooth loss	46,801 (59)	1,065	1 (reference)	82	1 (reference)	1,400	1 (reference)	798	1 (reference)
No history + 1–3 tooth loss	13,033 (16)	293	0.90 (0.79–1.03)	40	1.54 (1.04–2.27)	442	1.02 (0.91–1.14)	261	1.01 (0.87–1.17)
No history + ≥4 tooth loss	2,467 (3)	88	1.27 (1.01–1.60)	6	1.02 (0.45–2.32)	93	1.00 (0.80–1.25)	56	0.93 (0.70–1.24)
Positive history + 0 tooth loss	8,437 (11)	230	1.10 (0.95–1.28)	20	1.21 (0.74–1.97)	275	1.00 (0.88–1.15)	181	1.13 (0.96–1.34)
Positive history + 1–3 tooth loss	5,478 (7)	187	1.25 (1.06–1.48)	16	1.24 (0.71–2.18)	222	1.12 (0.97–1.30)	154	1.28 (1.06–1.53)
Positive history + ≥4 tooth loss	2,889 (4)	106	1.19 (0.96–1.47)	9	1.09 (0.51–2.32)	119	1.01 (0.83–1.24)	101	1.36 (1.09–1.70)
$P_{interaction}$[d]			0.41		0.58		0.97		0.19
$P_{heterogeneity}$[b]					0.90				0.22

Abbreviation: MET, metabolic equivalent of task.

[a]Multivariate logistic regression model adjusted for time period of endoscopy (in 2-year intervals), number of prior endoscopies (continuous), time since the most recent endoscopy (continuous, year), age (continuous, year), sex (female and male), race (White and non-White), family history of colorectal cancer (no and yes), history of diabetes mellitus (no and yes), smoking status (never smoker, past smoker, and current smoker), smoking intensity (continuous, pack-year), BMI (<22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0 kg/m^2), height (continuous, cm), physical activity (<7.5, 7.5–14.9, 15.0–29.9, 30.0–59.9, and ≥60.0 MET-hour/week), dietary factors (folate, vitamin D, calcium, and processed red meat; in quartiles), alcohol intake (women: never, <3.5, 3.5–6.9, and ≥7.0 g/day; men: never, <7.0, 7.0–13.9, and ≥14.0 g/day), regular aspirin use (no and yes), and physical examination within the past 2 years (no and yes).

[b]$P_{heterogeneity}$ was calculated in case-only analysis.

[c]P_{trend} was calculated using the median of each stratum as a continuous variable.

[d]$P_{interaction}$ between periodontal disease and tooth loss was calculated by including a cross-product interaction term between periodontal disease and tooth loss in the model and estimating the statistical significance using Wald test.

was associated with higher risk of serrated polyps, primarily in men. The association could also be observed among subgroups of participants stratified by risk factors. Our results provide further evidence for the link between periodontal inflammation resulting from oral dysbiosis and carcinogenesis in the gut.

Thus far, most studies on oral health and cancer risk point toward a strong association with head and neck cancer (6, 7). The evidence for colorectal cancer remains limited and conflicting. Previously, we reported a modest increase in risk of proximal colon cancer and rectal cancer in women with fewer teeth and a nonsignificant elevated colorectal cancer risk in women with moderate-severe periodontal disease (16). However, two studies using data from the HPFS reported no association between periodontal disease and colorectal cancer risk in men, among the overall cohort (3) and never smokers (5). Results in other studies have also been mixed, with three studies (4, 17, 18) demonstrating increased risk of colorectal cancer in relation to periodontal disease and two studies (19, 20) indicating null associations. Such discrepancy may be explained by the large variation in study design, exposure assessment, and confounding adjustment. For example, in our three prior studies, the authors used the number of teeth remaining in 1992 for the NHS (16) and 1986 for the HPFS (3, 5) to assess the relationship between tooth loss and colorectal cancer. Given that periodontal disease occurs more commonly in elderly population, this method may have mostly captured tooth loss caused by other conditions, such as injury and autoimmune diseases, and thus have limited specificity to reflect dysbiosis of the oral microbiome. As for colorectal precursor lesions, Kim and colleagues (21) and Lee and colleagues (22) observed an increased risk for colorectal adenomas among individuals with periodontitis, especially proximal and proximal advanced adenomas. While these two studies provided valuable insights into how periodontal pathology relates to early tumorigenesis in the colon, the cross-sectional design and lack of detailed covariates for confounding control limited their ability for causal inference.

Despite limited evidence from observational studies, a strong biological plausibility has been implicated in the literature. The oral cavity harbors a wide array of microbial communities. Commensal bacteria not only protect the host against pathogens but also promote the development of proper tissue structure and function (35). Various factors, including poor oral hygiene, genetic susceptibility, smoking, diabetes, and obesity, can induce a shift from a symbiotic microflora to a dysbiotic pathogenic community in the oral cavity (36). The resulting excess of oral pathogens may induce host inflammation and immune dysregulation, either directly through bacteremia/endotoxemia and systemic diffusion of inflammatory mediators (37, 38), or indirectly by alteration of gut microbial composition (11). Compared with healthy individuals, patients diagnosed with colorectal cancer had higher transmission rates of bacteria from the oral cavity to the gut, especially for strains associated with colorectal cancer, such as *Fusobacterium nucleatum, Parvimonas micra*, and *Peptostreptococcus stomatis* (39). These microbes may alter the composition of the gut microbiota through complex biofilms, resulting in intestinal dysbiosis (40). This orally driven disruption promotes aberrant immune and inflammatory responses, potentially through altering epithelial tight junctions and promoting infiltration and inflammation from mucosal immune cells (41), leading to colorectal cancer tumorigenesis. Indeed, several oral taxa, such as *Prevotella* and *Parvimonas*, have been shown to be differentially abundant in the oral samples of patients with colorectal cancer as compared with healthy individuals (42, 43). These bacterial taxa may colonize a subset of colorectal tumors and form bacterial coabundance networks similar to those found in the oral cavity. Collectively, these results suggest the potential role of the oral microbiome in colorectal carcinogenesis.

Colorectal polyps represent a spectrum of lesions with different levels of malignant potential. Compared with small serrated polyps and nonadvanced adenomas, large serrated polyps and advanced adenoma have been associated with increased risk of recurrent colorectal neoplasia and incident colorectal cancer (44–46). In this study, we found that the positive associations with periodontal disease tended to be stronger for small serrated polyps and advanced adenomas. Given the close link between inflammation, colorectal cancer–related gut microbiome features (e.g., *Fusobacterium nucleatum*), and molecular characteristics of the serrated pathway (e.g., microsatellite instability), it is possible that alterations in the oral microbiome may exert a particularly detrimental effect on early initiation of serrated polyps that begin as small lesions, whereas for conventional adenomas, the influence of oral health more strongly influences progression to advanced lesions. Furthermore, the conventional pathway accounts for two-thirds of sporadic colorectal cancers, of which advanced conventional adenomas are the major precursor lesions. Although further studies are needed to confirm the role of periodontal disease in serrated polyps, our data support the reported positive association of periodontal disease with colorectal cancer risk.

Notably, the risk of serrated polyps associated with number of tooth loss differs between women and men. This may, in part, be explained by the sex differences in tooth loss. Women are more likely to experience tooth loss due to reasons unrelated to dysbiosis of the oral microbiome. For example, estrogens may modulate immune function. Low estrogen production after menopause is associated with increased production of inflammatory mediators and may contribute to more intense gingival inflammation during periodontitis and subsequent oral bone loss, resulting in clinical attachment loss and tooth loss (47). Similarly, estrogens have inhibitory effects on osteoclastic functions. Osteoporosis commonly occurs in elderly women. The use of hormone replacement treatment has been associated with a reduced likelihood of edentulism (48). In addition, women are genetically more susceptible to a wide array of autoimmune diseases. Besides musculoskeletal symptoms, the dysregulated immune system may result in oral manifestations including periodontal disease and eventual tooth loss (49). Finally, given that serrated polyps are more prevalent in elderly population, the relatively short follow-up duration in women compared with men may also potentially explain why tooth loss was not positively associated with the risk of serrated polyps in women.

Our study has several strengths, including the prospective design that minimizes biases related to differential recall in case ascertainment and extensive information on covariates for confounding control. We were able to adjust for multiple shared risk factors between periodontal disease and colorectal neoplasia. In particular, given that smoking is strongly associated with both diseases, we controlled for both current smoking status and pack-years of smoking.

Several limitations should also be noted. First, self-reported periodontal disease status could have introduced measurement error, although these data have been reasonably validated against objective measures (3, 27, 28). The participants' background as healthcare professionals is expected to enhance the validity and accuracy of the exposure data acquired from the questionnaires. Second, due to the evolving nature and lack of consensus regarding the diagnostic criteria of specific subtypes of serrated polyps, we were unable to distinguish hyperplastic polyps from sessile serrated adenomas/polyps and traditional serrated adenomas. Although polyp size has been established as a strong predictor for the likelihood of progression into advanced neoplasia (44), a considerable fraction of sessile serrated adenomas/polyps can be under 10 mm (50). Compared with small serrated polyps ($n = 1{,}969$), the sample size for large serrated polyps is small ($n = 173$) and thus limits the statistical power to detect any association. Therefore, the observed null association between periodontal disease/tooth loss and large serrated polyps does not fully negate the role of oral health in serrated precursor lesions with higher malignant potential. Third, we were not able to examine participants who did not receive lower endoscopies. However, it is possible that these individuals were less likely to adhere to an overall healthy lifestyle and more likely to have periodontal disease, tooth loss,

and colorectal polyps. Not accounting for them may have attenuated our observed associations. Finally, our participants were mostly White. Caution should be used when generalizing the results to members of other races. Thus far, two cross-sectional studies have found positive associations among Asian population (21, 22). Studies on African-American and Hispanic populations are further warranted, as periodontal disease is more prevalent in these groups (2) and its association with risk of colorectal cancer may differ between ethnicities (18).

In conclusion, individuals with a history of periodontal disease and possibly higher number of tooth loss might be at a modestly increased risk of developing serrated polyps and conventional adenomas. The findings suggest a potential role of the oral microbiome in colorectal cancer and deserve confirmation in other, preferably racially diverse, populations.

Disclosure of Potential Conflicts of Interest

S. Ogino reports grants from NIH during the conduct of the study; and grants from NIH outside the submitted work. A.T. Chan reports grants and personal fees from Bayer Pharma AG, personal fees from Pfizer Inc., and personal fees from Boehringer Ingelheim outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The funders had no role in design and conduct of the study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

Authors' Contributions

C.-H. Lo: Conceptualization, formal analysis, writing-original draft, writing-review and editing. **L.H. Nguyen:** Formal analysis, methodology, writing-review and editing. **K. Wu:** Data curation, funding acquisition, methodology, writing-review and editing. **S. Ogino:** Resources, data curation, funding acquisition, writing-review and editing. **A.T. Chan:** Resources, data curation, supervision, funding acquisition, writing-review and editing. **E.L. Giovannucci:** Resources, data curation, supervision, funding acquisition, validation, writing-review and editing. **M. Song:** Conceptualization, resources, data curation, supervision, funding acquisition, writing-original draft, writing-review and editing.

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