HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Int J Cancer. 2017 February 01; 140(3): 646–652. doi:10.1002/ijc.30486.

Periodontal disease, tooth loss, and colorectal cancer risk: results from the Nurses' Health Study

Fatemeh Momen-Heravi[1,2,3], **Ana Babic**[2,4], **Shelley S. Tworoger**[1,2], **Libin Zhang**[5], **Kana Wu**[6], **Stephanie A. Smith-Warner**[1,6], **Shuji Ogino**[1,4,7], **Andrew T. Chan**[8,9], **Jeffrey Meyerhardt**[4], **Edward Giovannucci**[1,2,6], **Charles Fuchs**[4], **Eunyoung Cho**[1,10,11], **Dominique S. Michaud**[11,12], **Meir J. Stampfer**[1,2,6], **Yau-Hua Yu**[13], **David Kim**[13], and **Xuehong Zhang**[2]

[1]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA

[2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[3]Section of Oral and Diagnostic Sciences, Division of Periodontics, Columbia University College of Dental Medicine, New York, NY

[4]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

[5]Institute for Community Inclusion, University of Massachusetts Boston, MA

[6]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[7]Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[8]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA

[9]Division of Gastroenterology, Massachusetts General Hospital, Boston, MA

[10]Department of Dermatology, the Warren Alpert Medical School of Brown University, Providence, RI

[11]Department of Epidemiology, Brown University School of Public Health, Providence, RI

[12]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA

[13]Harvard School of Dental Medicine, Boston, MA

Abstract

Periodontal diseases including tooth loss might increase systemic inflammation, lead to immune dysregulation, and alter gut microbiota, thereby possibly influencing colorectal carcinogenesis.

Corresponding author: Dr. Xuehong Zhang, MD, ScD, Assistant Professor in Medicine | Harvard Medical School, Associate Epidemiologist | Brigham and Women's Hospital, 181 Longwood Avenue, Room 453, Boston, MA 02115, Tel: 617-525-0342, Fax: 617-525-2008, xuehong.zhang@channing.harvard.edu.

Conflict of interest: The authors declare that they have no conflicts of interest.

Few epidemiological studies have examined the association between periodontal diseases and colorectal cancer (CRC) risk. We collected information on the periodontal disease (defined as history of periodontal bone loss) and number of natural teeth in the Nurses' Health Study. A total of 77,443 women were followed since 1992. We used Cox proportional hazard models to calculate multivariable hazard ratios (HRs) and 95% confidence intervals (95% CIs) after adjustment for smoking and other known risk factors for CRC. We documented 1,165 incident CRC through 2010. Compared to women with 25–32 teeth, the multivariable HR (95% CI) for CRC for women with < 17 teeth was 1.20 (1.04–1.39). With regard to tumor site, the HRs (95% CIs) for the same comparison were 1.23 (1.01–1.51) for proximal colon cancer, 1.03 (0.76–1.38) for distal colon cancer, and 1.48 (1.07–2.05) for rectal cancer. Additionally, compared to those without periodontal disease, HRs for CRC were 0.91 (95% CI 0.74–1.12) for periodontal disease, and 1.22 (95% CI 0.91–1.63) when limited to moderate to severe periodontal disease. The results were not modified by smoking status, body mass index, or alcohol consumption. Women with fewer teeth, possibly moderate or severe periodontal disease, might be at a modest increased risk of developing CRC, suggesting a potential role of oral health in colorectal carcinogenesis.

Keywords

Colorectal cancer; periodontal disease; tooth loss; oral health; microbiota

INTRODUCTION

Colorectal cancer is the third most common cancer in the US and often arises within the context of increased inflammation and altered immunity as well as changes in the gut microbiota[1–3]. Previous studies have shown that aspirin, a nonsteroidal anti-inflammatory drug (NSAID), is associated with a lower risk of colorectal cancer[4]. In addition, plasma levels of certain inflammatory biomarkers or proinflammatory cytokines, such as soluble tumor necrosis factor receptor 2 (TNFRSF1B, or sTNFR-2), interleukin-8 (IL8), and interleukin-6 (IL6) were associated with an increased risk of colorectal cancer in some but not all studies[5–8].

Poor oral health might increase systemic inflammation, lead to local overly aggressive immune response, and potentially alter gut microbiota by pathogens that cause periodontal disease, and thus could have important implications for colorectal cancer development[9, 10]. Two commonly used measures of oral health are periodontal disease and tooth loss[11, 12]. Periodontal disease is a chronic inflammatory disease of the supporting tissues of the teeth[13], and in older populations, tooth loss is the main manifestation of persistent periodontal disease. This process develops over many years through the spread of bacterial infections and inflammation of the gums to the ligaments and bone that support the teeth[14–16].

Previous studies have reported positive associations between periodontal diseases and risk of cancers at various sites including oral cancer, lung cancer, pancreas cancer, breast cancer, and upper gastrointestinal cancer[17–24]. In addition, some studies have reported that tooth loss was independently associated with an increased risk of head and neck cancer, esophageal cancer, and lung cancer[25–27]. However, the association between periodontal disease, tooth loss, and colorectal cancer remains much less studied. Among the four studies identified, null associations were reported for history of periodontal disease with colorectal cancer risk[20, 26, 28, 29]. In contrast, another study observed that periodontal disease was associated with excess colorectal cancer mortality[30]. Hence, although oral health might play an important role in colorectal carcinogenesis, related epidemiological studies are limited and have not resulted in definitive conclusions.

Herein, we conducted this study and hypothesized that individuals with a history of periodontal disease and tooth loss might be at a greater risk for development of colorectal cancer, independent of smoking, an important contributor to tooth loss. We tested this hypothesis in the Nurses' Health Study (NHS).

METHODS

Study population

The NHS has been described in detail elsewhere[31, 32]. Briefly, the NHS is an ongoing prospective cohort study of 121,700 female nurses aged 30–55 years in 1976 living in 11 states in the United States. Since 1976 participants have completed questionnaires regarding information on medical history and lifestyle factors and newly diagnosed diseases every two years. The follow-up rate has been greater than 90%. The study was approved by the Brigham and Women's Hospital institutional review board, and return of the questionnaires was considered to imply informed consent.

Assessment of periodontal disease and tooth loss

Information on periodontal disease, defined as a history of periodontal bone loss, was first assessed in 1998 and then again in 2000. If periodontal bone loss was reported, participants indicated the severity of the bone loss (none, mild, moderate/severe). Although self-reported history of periodontal disease was not validated in the NHS cohort, it has been validated by medical/dental records or radiograph review in the Health Professionals Follow-up Study (HPFS), a comparable cohort of male health professionals[26, 33, 34]. The validation of this question in the male health professionals was done by obtaining radiographs from subset of individuals with and without self-reported history of periodontal disease. Interproximal bone loss was evaluated for each participant in all posterior teeth (premolars and molars) except third molars by a clinician who was masked to the self-report. Interproximal bone loss is an indicator of cumulative periodontal disease. Among non-dentists male health professionals in that study, the positive predictive value of the question on periodontal bone loss was 0.80 and the negative predictive value was 0.68[34].

On the 1992 questionnaire we also collected information on the number of natural teeth (none,1–10, 11–16, 17–24, 25–32). The question does not consider the replaced teeth (implant or bridge) as natural teeth. Again, this question was not validated in NHS, however, the correlation between self-reported number of teeth and the number of teeth from a clinical assessment in a general population sample was 0.97[35]. In addition, women were also asked the number of tooth lost in the prior 2 years (on the 1992, 1996, and 2000 questionnaire).

Assessment of other colorectal cancer risk factors

Information on height was obtained in 1976. Alcohol consumption and other dietary factors, such as intakes of folate, calcium, and vitamin D, were first assessed in 1980 using a validated semi quantitative food frequency questionnaire, and every nearly 4 years thereafter[36]. The baseline and biennial questionnaires collected information on other colorectal cancer risk factors such as adult body weight, physical activity (METs-hrs/wk), cigarette smoking, history of sigmoidoscopy/colonoscopy screening, family history of colorectal cancer, aspirin use, and postmenopausal hormone use (PMH).

Ascertainment of cases of colorectal cancer

The ascertainment of colorectal cancer cases has been described in detail elsewhere[37]. Briefly, participants were asked on biennial questionnaires to report a diagnosis of colorectal cancer and other diseases. When a diagnosis was reported, medical and pathology records were obtained and the incidence of colorectal cancer was confirmed. The physicians assessing medical records were blinded to exposure information. Colorectal cancer was defined according to the International Classification of Diseases, Ninth Revision (ICD-9). Deaths were identified through the registry of National Death Index[38] or by family report.

Statistical analysis

We used 1992 as baseline for number of teeth analysis and 1998 as baseline for periodontal disease (i.e., self-reported periodontal bone loss) because the information was first assessed in those years. We excluded participants with a history of cancer at or before baseline (except non-melanoma skin cancer), death before baseline, with ulcerative colitis or Crohn diseases, and with missing information on the exposure of interest. The analytic cohort included 77,449 women with 1,291,462 person-years through 2010 for the analysis of number of teeth, and 69,656 women with 779,439 person-years through 2010 for the periodontal bone loss analysis. Person-years were calculated from baseline questionnaire return date to the date of colorectal cancer diagnosis, death or the end of follow-up (May 31, 2010), whichever occurred first. Women with other cancers were censored at their date of diagnosis.

We used Cox proportional hazards models[39] to estimate the age- and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for tooth loss or periodontal bone loss. Consistent with the categories used in a previous study[26], we analyzed the data on number of teeth using 25–32 as the reference group (other two groups were: 17–25 and 0–16). For the analysis on periodontal disease, we first categorized periodontal bone as a binary variable (no vs. mild/moderate/severe), and further evaluated the association with severity (no vs. mild vs. moderate/severe). As a sensitivity analysis, we examined the association with combined categories of number of teeth and periodontal bone loss. We also evaluated these associations by anatomic subsites (i.e., colon, proximal colon, distal colon and rectal cancers). Lastly, we evaluated whether the associations varied by smoking status (never, ever), body mass index (BMI; < 25, ≥ 25 kg/m^2), and alcohol consumption (< 5, ≥ 5 g/day). We used a Wald test to examine whether the coefficients of the cross-product terms between these variables and each of periodontal disease measures were statistically significant.

All models were stratified by age (continuous in months) and calendar time. We observed no violation of the proportional hazard assumption based on the likelihood ratio test. We adjusted for known colorectal cancer risk factors and accounted for covariates that can change over time, such as weight and physical activity (see table footnote for these variables and their categorizations). All analyses were conducted using Statistical Analysis Software version 9.3 (SAS) (Cary, North Carolina).

RESULTS

We documented 1,165 incident colorectal cancer cases over 18 years of follow-up for number of teeth analysis, and 739 cases for the periodontal bone loss analysis. Women with fewer teeth (0–16) at baseline were older and more likely to be past or current smokers and have type 2 diabetes, but less likely to use PMH, and had lower intakes of alcohol, calcium and vitamin D (Table 1). A greater proportion of women with history of periodontal bone loss had ever smoked compared to those with no history of periodontal disease. Alcohol consumption was slightly higher in women with history of periodontal bone loss.

Among women with information on both number of teeth and periodontal disease in 1998, 3,079 of 12,245 (17%) of the participants with <17 remaining teeth, 2,652 of 15,150 (18%) of those with 17–24 remaining teeth, and 5,638 of 46,457 (12%) of those with over 24 remaining teeth had periodontal disease. Thus, tooth loss and periodontal disease were partially correlated and provide different information on oral health.

Compared with women with 25–32 teeth, women with <17 teeth were at a higher risk of incident colorectal cancer (HR: 1.20, 95% CI: 1.04–1.39) (Table 2). Positive associations were observed for proximal colon cancer (HR: 1.23, 95% CI: 1.01–1.51) and rectal cancer (HR: 1.48, 95% CI: 1.07–2.05), but not with distal colon cancer (HR: 1.03, 95% CI: 0.76–1.38), although none of the heterogeneity test by subsite was statistically significant (all *p*-values > 0.05). In addition, any incident tooth loss (measured 1992–2000) during follow-up was not associated with colorectal cancer risk (HR: 0.89; 95% CI: 0.76–1.03).

Compared to women with no reported history of bone loss, self-reported history of periodontal bone loss was not associated with colorectal cancer risk overall (HR: 0.89, 95% CI: 0.72–1.10) or by subsite (Table 3). Interestingly, when considering severity, women with moderate or severe periodontal disease were at a suggestively higher risk of colorectal cancer (HR: 1.22, 95% CI: 0.91–1.63) compared to women without history of bone loss.

When we jointly considered the number of teeth and history of periodontal disease, none of results reached statistical significance except that individuals who had both history of periodontal bone loss and <17 teeth had a significantly higher risk of rectal cancer (HR: 2.20, 95% CI: 1.05–4.63, based on eight cases) compared to those with neither (Supplementary Tables 1, 2). Lastly, the observed results for number of teeth or periodontal diseases were not modified by smoking status, BMI, or alcohol consumption (all *p*-value for interaction > 0.10, data not shown).

DISCUSSION

In this prospective cohort study, women with <17 teeth were at a modest 20% higher risk for developing colorectal cancer compared to women with over 24 teeth, independent of smoking and other known colorectal cancer risk factors. Significant positive association was seen for proximal colon cancer but not distal colon cancer, and consistently appeared to be stronger for rectal cancer, although the difference by tumor subsite was not statistically significant. History of self-reported periodontal disease with bone loss was not associated with colorectal cancer risk, although a suggestive positive association was seen for moderate to severe periodontal disease bone loss.

The majority of published studies on tooth loss and cancer have been on upper gastrointestinal cancers, including oral and gastric cancers[15]. We identified two studies that have examined the association between tooth loss and colorectal cancer and both did not observe statistically significant associations for colorectal cancer although tooth loss was positively associated with total cancer in one study[26] and with orodigestive cancer in the other[29]. In contrast, we observed, for the first time, that women with fewer teeth were at a modestly increased risk of developing colorectal cancer. Although chance or residual confounding cannot be ruled out, this finding may be biologically plausible. *Fusobacteria*, a well-known periodontal pathogen, is found at increased abundance in stool samples of colorectal cancer patients, and are enriched in colorectal cancer tumors relative to normal colon tissue[40, 41]. In addition, immune cells are key components of tumors. *Fusobacteria* has been shown to accelerate colorectal carcinogenesis by modulating the tumor immune microenvironment[41]. In the *Apc*$^{Min/+}$ mouse model of colonic tumors, an increase in intratumoral immune cells (i.e., the myeloid) was observed in the tumors with *Fusobacterium*-treated but not in control group[41]. Moreover, introduction of *Fusobacteria* to *Apc*$^{Min/+}$ mice resulted in activation of NF-κB proinflammatory pathway, a central link between inflammation and cancer[42]. Furthermore, early oral dysbiosis that contributes to tooth loss may also promote colorectal specific dysbiosis that also promote colorectal cancer[43, 44]. Other oral related bacteria such as P.gingivalis was reported to be associated with risk of orodigestive and pancreatic cancers[30, 45]. Genus level studies showed that the microbial composition was significantly different in cancerous areas compared to the noncancerous lesions. Periodontal associated genera such as *Fusobacterium, Prevotella,* and *Bacteroides* were more enriched in the cancerous tissue than adjacent noncancerous lesions[40]. Although test of difference by subsite was not statistically significant, we observed a significant positive association for proximal colon cancer, the site most strongly associated with distinct feature of microbial organization[46]. Presence of structured invasive polymicrobial bacterial biofilms was reported at 89% on proximal tumors in contrast to 12% of distal colon tumors[46]. Lastly, the consistently observed stronger association of tooth loss with rectal cancer might be due to chance (limited number of cases) or partly because *Prevotella* was reported to be among the most abundant bacterial species in the rectum[40, 47]. Take together, epidemiological data on oral health and colorectal cancer is limited, and clearly, more study is needed to confirm our findings.

The overall null results of periodontal disease with bone loss and colorectal cancer risk were consistent with four other studies[20, 26, 28, 29] but not with another study that examined colorectal cancer mortality[30]. The lack of association with periodontal disease in this study might be due to more under-report of periodontal disease than for number of teeth[18]. Interestingly, some studies reported positive associations of other cancers with periodontal disease but not with tooth loss, suggesting that oral bacteria profiles might be different with inflammation (caused by periodontal disease) and with tooth loss[15, 48]. Nonetheless, although extent of tooth loss may not be the ideal surrogate for periodontal disease and capture other measures of oral health, it may provide new insights into the overall role of oral health in relation to development of cancer.

Although the present study has several strengths, including a large sample size, prospective nature of the study design, and extensive information on covariates, it has some limitations. First, the main exposures of number of teeth and history of periodontal bone loss were self-reported which was subjected to error. However, these self-reported measures were reasonably validated against objective measures in the comparable HPFS cohort, and these measures were previously associated with overall cancer risk[34, 49]. Second, although we have adjusted for known colorectal cancer risk factors, unmeasured or residual confounding may still exist, because tooth loss may be related to childhood social economic status or early life exposures. Lastly, generalizability of our findings to other racial/ethnic groups is limited because women in our study population are mainly of European ancestry and relatively homogeneous with similar social economic status. Studies on African-Americans and Hispanic US population are clearly warranted because periodontal disease is more prevalent in these populations[50].

In summary, women with fewer teeth (0–16) and possibly those who have moderate or severe periodontal bone loss might be at a modest increased risk of developing colorectal cancer. Given limited research on this topic, more prospective studies with objective measures of periodontal disease such as clinical attachment loss, radiographic bone loss, histological and serological markers of periodontal disease, and different dimensions of oral health are warranted to confirm this finding and consider underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a grant from the National Institutes of Health (NIH) grants UM1 CA186107 (to M.J. Stampfer), P50CA127003 (to C.S. Fuchs), P01CA87969 (to M.J. Stampfer), R01CA151993, R35 CA197735 (to S Ogino), R01 CA137178, K24 DK098311 (A.T. Chan). R03CA176717, K07 CA188126 (to X Zhang). A. Babic was supported by a training grant (5T32CA009001-38). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

We would like to thank the participants and staff of the Nurses' Health Study, for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY.

References

1. Sears CL, Garrett WS. Microbes, microbiota, and colon cancer. Cell host & microbe. 2014; 15:317–328. [PubMed: 24629338]

2. Tahara T, Yamamoto E, Suzuki H, Maruyama R, Chung W, Garriga J, Jelinek J, Yamano HO, Sugai T, An B, Shureiqi I, Toyota M, et al. Fusobacterium in colonic flora and molecular features of colorectal carcinoma. Cancer research. 2014; 74:1311–1318. [PubMed: 24385213]

3. Mima K, Sukawa Y, Nishihara R, Qian ZR, Yamauchi M, Inamura K, Kim SA, Masuda A, Nowak JA, Nosho K, Kostic AD, Giannakis M, et al. Fusobacterium nucleatum and T Cells in Colorectal Carcinoma. JAMA Oncol. 2015; 1:653–661. [PubMed: 26181352]

4. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, Meade TW. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010; 376:1741–1750. [PubMed: 20970847]

5. Chan AT, Ogino S, Giovannucci EL, Fuchs CS. Inflammatory markers are associated with risk of colorectal cancer and chemopreventive response to anti-inflammatory drugs. Gastroenterology. 2011; 140:799–808. quiz e11. [PubMed: 21115010]

6. Knupfer H, Preiss R. Serum interleukin-6 levels in colorectal cancer patients--a summary of published results. Int J Colorectal Dis. 2010; 25:135–140. [PubMed: 19898853]

7. Candela M, Turroni S, Biagi E, Carbonero F, Rampelli S, Fiorentini C, Brigidi P. Inflammation and colorectal cancer, when microbiota-host mutualism breaks. World J Gastroenterol. 2014; 20:908–922. [PubMed: 24574765]

8. Kantola T, Klintrup K, Vayrynen JP, Vornanen J, Bloigu R, Karhu T, Herzig KH, Napankangas J, Makela J, Karttunen TJ, Tuomisto A, Makinen MJ. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. Br J Cancer. 2012; 107:1729–1736. [PubMed: 23059742]

9. Ajwani S, Mattila KJ, Narhi TO, Tilvis RS, Ainamo A. Oral health status, C-reactive protein and mortality--a 10 year follow-up study. Gerodontology. 2003; 20:32–40. [PubMed: 12926749]

10. Blasco-Baque V, Garidou L, Pomie C, Escoula Q, Loubieres P, Le Gall-David S, Lemaitre M, Nicolas S, Klopp P, Waget A, Azalbert V, Colom A, et al. Periodontitis induced by Porphyromonas gingivalis drives periodontal microbiota dysbiosis and insulin resistance via an impaired adaptive immune response. Gut. 2016

11. Slots J. Casual or causal relationship between periodontal infection and non-oral disease? J Dent Res. 1998; 77:1764–1765. [PubMed: 9786630]

12. Oluwagbemigun K, Dietrich T, Pischon N, Bergmann M, Boeing H. Association between Number of Teeth and Chronic Systemic Diseases: A Cohort Study Followed for 13 Years. PLoS One. 2015; 10:e0123879. [PubMed: 25945503]

13. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Cdc Periodontal Disease Surveillance workgroup: James Beck GDRP. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res. 2012; 91:914–920. [PubMed: 22935673]

14. Liljestrand JM, Havulinna AS, Paju S, Mannisto S, Salomaa V, Pussinen PJ. Missing Teeth Predict Incident Cardiovascular Events, Diabetes, and Death. J Dent Res. 2015; 94:1055–1062. [PubMed: 25991651]

15. Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. Cancer Causes Control. 2008; 19:895–907. [PubMed: 18478344]

16. van Kempen LC, de Visser KE, Coussens LM. Inflammation, proteases and cancer. Eur J Cancer. 2006; 42:728–734. [PubMed: 16524717]

17. Freudenheim JL, Genco RJ, LaMonte MJ, Millen AE, Hovey KM, Mai X, Nwizu N, Andrews CA, Wactawski-Wende J. Periodontal Disease and Breast Cancer: Prospective Cohort Study of Postmenopausal Women. Cancer Epidemiol Biomarkers Prev. 2015

18. 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; 99:171–175. [PubMed: 17228001]

19. Stolzenberg-Solomon RZ, Dodd KW, Blaser MJ, Virtamo J, Taylor PR, Albanes D. Tooth loss, pancreatic cancer, and Helicobacter pylori. Am J Clin Nutr. 2003; 78:176–181. [PubMed: 12816788]

20. Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. Ann Epidemiol. 2003; 13:312–316. [PubMed: 12821269]

21. Abnet CC, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes Control. 2001; 12:847–854. [PubMed: 11714113]
22. Velly AM, Franco EL, Schlecht N, Pintos J, Kowalski LP, Oliveira BV, Curado MP. Relationship between dental factors and risk of upper aerodigestive tract cancer. Oral Oncol. 1998; 34:284–291. [PubMed: 9813724]
23. Rosenquist K, Wennerberg J, Schildt EB, Bladstrom A, Goran Hansson B, Andersson G. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. Acta Otolaryngol. 2005; 125:1327–1336. [PubMed: 16303683]
24. Chang JS, Tsai CR, Chen LT, Shan YS. Investigating the Association Between Periodontal Disease and Risk of Pancreatic Cancer. Pancreas. 2016; 45:134–141. [PubMed: 26474422]
25. 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; 17:1222–1227. [PubMed: 18483345]
26. 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; 9:550–558. [PubMed: 18462995]
27. Shakeri R, Malekzadeh R, Etemadi A, Nasrollahzadeh D, Abedi-Ardekani B, Khoshnia M, Islami F, Pourshams A, Pawlita M, Boffetta P, Dawsey SM, Kamangar F, et al. Association of tooth loss and oral hygiene with risk of gastric adenocarcinoma. Cancer Prev Res (Phila). 2013; 6:477–482. [PubMed: 23503651]
28. Wen BW, Tsai CS, Lin CL, Chang YJ, Lee CF, Hsu CH, Kao CH. Cancer risk among gingivitis and periodontitis patients: a nationwide cohort study. QJM. 2014; 107:283–290. [PubMed: 24336850]
29. Ansai T, Takata Y, Yoshida A, Soh I, Awano S, Hamasaki T, Sogame A, Shimada N. Association between tooth loss and orodigestive cancer mortality in an 80-year-old community-dwelling Japanese population: a 12-year prospective study. BMC Public Health. 2013; 13:814. [PubMed: 24011063]
30. Ahn J, Segers S, Hayes RB. Periodontal disease, Porphyromonas gingivalis serum antibody levels and orodigestive cancer mortality. Carcinogenesis. 2012; 33:1055–1058. [PubMed: 22367402]
31. Belanger CF, Hennekens CH, Rosner B, Speizer FE. The nurses' health study. Am J Nurs. 1978; 78:1039–1040. [PubMed: 248266]
32. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. Nat Rev Cancer. 2005; 5:388–396. [PubMed: 15864280]
33. Joshipura KJ, Douglass CW, Garcia RI, Valachovic R, Willett WC. Validity of a self-reported periodontal disease measure. J Public Health Dent. 1996; 56:205–212. [PubMed: 8906704]
34. Joshipura KJ, Pitiphat W, Douglass CW. Validation of self-reported periodontal measures among health professionals. J Public Health Dent. 2002; 62:115–121. [PubMed: 11989206]
35. Douglass CW, Berlin J, Tennstedt S. The validity of self-reported oral health status in the elderly. J Public Health Dent. 1991; 51:220–222. [PubMed: 1941773]
36. Chiuve SE, Fung TT, Rexrode KM, Spiegelman D, Manson JE, Stampfer MJ, Albert CM. Adherence to a low-risk, healthy lifestyle and risk of sudden cardiac death among women. JAMA. 2011; 306:62–69. [PubMed: 21730242]
37. Zhang X, Wu K, Giovannucci EL, Ma J, Colditz GA, Fuchs CS, Willett WC, Stampfer MJ, Nimptsch K, Ogino S, Wei EK. Early life body fatness and risk of colorectal cancer in u.s. Women and men-results from two large cohort studies. Cancer Epidemiol Biomarkers Prev. 2015; 24:690–697. [PubMed: 25777804]
38. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. American journal of epidemiology. 1994; 140:1016–1019. [PubMed: 7985649]
39. Cox DR. Regression models and life-tables. J R Stat Soc. 1972; 34:187–220.
40. Gao Z, Guo B, Gao R, Zhu Q, Qin H. Microbiota disbiosis is associated with colorectal cancer. Front Microbiol. 2015; 6:20. [PubMed: 25699023]

41. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, El-Omar EM, Brenner D, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe. 2013; 14:207–215. [PubMed: 23954159]

42. Shimizu T, Marusawa H, Endo Y, Chiba T. Inflammation-mediated genomic instability: roles of activation-induced cytidine deaminase in carcinogenesis. Cancer Sci. 2012; 103:1201–1206. [PubMed: 22469133]

43. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nat Rev Microbiol. 2012; 10:717–725. [PubMed: 22941505]

44. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, Barnes R, Watson P, Allen-Vercoe E, Moore RA, Holt RA. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012; 22:299–306. [PubMed: 22009989]

45. Michaud DS. Role of bacterial infections in pancreatic cancer. Carcinogenesis. 2013; 34:2193–2197. [PubMed: 23843038]

46. Dejea CM, Wick EC, Hechenbleikner EM, White JR, Mark Welch JL, Rossetti BJ, Peterson SN, Snesrud EC, Borisy GG, Lazarev M, Stein E, Vadivelu J, et al. Microbiota organization is a distinct feature of proximal colorectal cancers. Proc Natl Acad Sci U S A. 2014; 111:18321–18326. [PubMed: 25489084]

47. Consensus report. Periodontal diseases: pathogenesis and microbial factors. Ann Periodontol. 1996; 1:926–932. [PubMed: 9118284]

48. Michaud DS, Kelsey KT, Papathanasiou E, Genco CA, Giovannucci E. Periodontal disease and risk of all cancers among male never smokers: an updated analysis of the Health Professionals Follow-up Study. Ann Oncol. 2016

49. Babic A, Poole EM, Terry KL, Cramer DW, Teles RP, Tworoger SS. Periodontal bone loss and risk of epithelial ovarian cancer. Cancer Causes Control. 2015; 26:941–947. [PubMed: 25837263]

50. Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, Taylor GW, Page RC, Beck JD, Genco RJ. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. J Periodontol. 2015; 86:611–622. [PubMed: 25688694]

Author Manuscript

Author Manuscript

Author Manuscript

Impact and Novelty

Data on oral health including periodontal diseases and colorectal cancer risk are scarce. We conducted a prospective study among 77,443 women during 18 years of follow-up in the Nurses' Health Study. We found that independent of smoking and other risk factors, women with fewer teeth were at a modest increased risk of developing colorectal cancer, suggesting a potential role of oral health in colorectal carcinogenesis.

Table 1

Baseline age-adjusted characteristics of participants by number of teeth (1992) and periodontal disease with bone loss (1998) in the Nurses' Health Study

	Number of natural teeth			History of periodontal disease with bone loss	
	25–32 (n=45,252)	**17–24 (n=14,932)**	**0–16 (n=12,564)**	**No (n=59,931)**	**Yes (n=9,725)**
Age, years *	57.0(7.0)	59.8(6.9)	61.9(6.2)	64.3(7.2)	64.5(6.9)
White, %	97.9	96.9	96.7	97.5	97.4
Body mass index [a], kg/m^2	24.5(4.1)	25.3(4.5)	25.8(4.8)	25.3(4.4)	24.8(4.1)
Activity, METs [b] -hrs/week	17.3(18.1)	16.0(18.1)	14.9(17.2)	17.5(16.8)	17.4(16.3)
Family history of colorectal cancer, %	13.5	13.6	13.4	14.5	14.5
Regular aspirin use (2 or more tablets/wk), %	37.1	38.9	39.7	42.6	42.0
Past smoking, %	42.0	45.6	46.0	43.4	52.7
Current smoking, %	7.5	12.3	19.4	9.6	17.5
Type 2 diabetes, %	2.9	4.3	5.7	5.8	5.5
History of sigmoidoscopy/colonoscopy, %	18.8	16.0	13.9	31.6	32.7
Postmenopausal status, %	96.6	97.4	98.1	96.6	97.3
PMH use among menopausal women, %	68.7	64.0	57.7	67.6	70.5
Multivitamin use, %	43.5	41.6	40.3	59.0	60.1
Dietary intakes [c]					
Alcohol, g/day	6.3(9.2)	6.0(9.3)	5.6(9.3)	5.6(8.4)	6.8(9.3)
Total calcium intake, mg/d	933(339)	888(327)	856(333)	1015(364)	1036(372)
Total folate intake, ug/d	404(185)	386(178)	373(182)	458(178)	456(177)
Total vitamin D, IU/d	338(203)	324(196)	315(200)	363(190)	368(193)
Red meat, servings/wk	2.1(1.3)	2.1(1.3)	2.1(1.3)	1.9(1.1)	1.9(1.1)
Processed meat, servings/wk	0.9(1.1)	1.0(1.2)	1.1(1.2)	0.9(1.0)	0.9(1.0)

Values are means(SD) or percentages and are standardized to the age distribution of the study population.

[a] Body mass index was calculated as weight in kilograms divided by the square of height in meters.

[b] Hours of metabolic equivalent tasks.

[c] Dietary intakes were estimated with food-frequency questionnaire (1992 used for number of natural teeth; 1998 used for periodontal disease with bone loss).

* Value is not age adjusted

Table 2

Age and multivariable[a] adjusted hazard ratios for colorectal cancer according to number of natural teeth in the Nurses' Health Study

	Number of natural teeth		
	25–32	**17–24**	**0–16**
Colorectal cancer			
No. cases (n=1,165)	618	245	302
Age-adjusted	1 (reference)	1.03 (0.89–1.20)	1.44 (1.25–1.66)
Multivariable[a]	1 (reference)	0.94 (0.80–1.09)	1.20 (1.04–1.39)[b]
Colon cancer			
No. cases (n=926)	499	189	238
Multivariable[a]	1 (reference)	0.88 (0.74–1.04)	1.14 (0.97–1.35)
Proximal colon cancer			
No. cases (n=600)	317	121	162
Multivariable[a]	1 (reference)	0.89(0.72–1.10)	1.23 (1.01–1.51)[c]
Distal colon cancer			
No. cases (n=305)	169	64	72
Multivariable[a]	1 (reference)	0.86(0.64–1.16)	1.03 (0.76–1.38)[c]
Rectal cancer			
No. cases (n=239)	119	56	64
Multivariable[a]	1 (reference)	1.20(0.88–1.67)	1.48 (1.07–2.05)[c]

[a]: Multivariable hazard ratios were adjusted for age (in month), race (Caucasian or not), smoking before age 30 (0, 1–4, 5–< 10, or ≥10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of sigmoidoscopy / colonoscopy (yes or no), current physical activity (< 3, 3 –< 27, ≥ 27 METs-hrs/wk), regular aspirin use (yes or no), multivitamin use (yes or no), type 2 diabetes (yes or no), alcohol consumption (< 5, 5 –<15, or ≥ 15 g/d), adult BMI (< 25, 25 –< 27.5, 27.5– < 30, ≥ 30 kg/m^2), energy-adjusted intake of total calcium, vitamin D, folate, red meat and processed meat (all in tertiles) and postmenopausal hormone use (premenopausal, never, past, or current user).

[b]: HR was 1.24 (95% CI: 0.92–1.66) among never smokers.

[c]: *p*-values for heterogeneity were 0.33 comparing proximal colon cancer and distal colon cancer, 0.35 comparing proximal colon cancer and rectal cancer, and 0.11 comparing distal colon cancer and rectal cancer.

Table 3

Age and multivariable adjusted hazard ratios for colorectal cancer according to self-reported periodontal disease with bone loss in the Nurses' Health Study.

	Periodontal disease with bone loss		Periodontal disease with bone loss severity		
	No	Yes	No	Mild	Moderate-severe
Colorectal cancer					
No. cases (n=739)	641	98	641	48	50
Age-adjusted	1 (reference)	0.91 (0.74–1.12)	1 (ref)	0.72 (0.54–0.97)	1.30 (0.97–1.74)
Multivariable[a]	1 (reference)	0.89 (0.72–1.10)	1 (ref)	0.73 (0.55–0.98)	1.22 (0.91–1.63)
Colon cancer					
No. cases (n=596)	518	78	518	40	38
Multivariable[a]	1 (reference)	0.88 (0.70–1.12)	1 (ref)	0.76 (0.55–1.04)	1.13 (0.81–1.58)
Proximal colon cancer					
No. cases (n=395)	341	54	341	29	25
Multivariable[a]	1 (reference)	0.89(0.67–1.18)	1 (ref)	0.81 (0.55–1.19)	1.12 (0.74–1.70)
Distal colon cancer					
No. cases (n=185)	162	23	162	10	13
Multivariable[a]	1 (reference)	0.89(0.58–1.36)	1 (ref)	0.64 (0.34–1.21)	1.27 (0.71–2.27)
Rectal cancer					
No. cases (n=143)	123	20	123	8	12
Multivariable[a]	1 (reference)	0.92(0.57–1.49)	1 (ref)	0.65 (0.31–1.33)	1.60 (0.87–2.95)

[a]: Multivariable hazard ratios were adjusted for age (in month), race (Caucasian or not), smoking before age 30 (0, 1–4, 5–< 10, or ≥10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of sigmoidoscopy / colonoscopy (yes or no), current physical activity (< 3, 3 –< 27, ≥ 27 METs-hrs/wk), regular aspirin use (yes or no), multivitamin use (yes or no), type 2 diabetes (yes or no), alcohol consumption (< 5, 5 –<15, or ≥ 15 g/d), adult BMI (< 25, 25 –< 27.5, 27.5– < 30, ≥ 30 kg/m^2), energy-adjusted intake of total calcium, vitamin D, folate, red meat and processed meat (all in tertiles) and postmenopausal hormone use (premenopausal, never, past, or current user).