Published in final edited form as:
Lancet Oncol. 2008 June ; 9(6): 550–558. doi:10.1016/S1470-2045(08)70106-2.

Periodontal Disease, Tooth Loss and Cancer Risk in a Prospective Study of Male Health Professionals

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SUMMARY

Background—A number of studies suggest that tooth loss and periodontal disease may increase the risk of various cancers; however, it has been difficult to tease apart the role of oral health from that of smoking. We conducted an analysis to examine whether periodontal disease or tooth loss is associated with cancer risk.

Methods—The analysis was conducted in a prospective study of U.S. male health professionals aged 40 to 75 years. For this analysis, 48,375 men and 18 years of follow-up were available (1986 to January 31, 2004; median follow-up is 17.7 yrs), during which time 5720 incident cancer cases were documented (excluding nonmelanoma skin cancer and nonaggressive prostate cancer); the five most common cancers were colorectal (n=1043), melanoma of the skin (n=698), lung (n=678), bladder (n=543), and advanced prostate (n=541). Endpoints for this study were total cancer and individual cancers with more than 100 cases. Multivariate hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazard models.

Findings—After adjusting for known risk factors, including detailed smoking history and dietary factors, periodontal disease history was associated with an increased risk of total cancer (HR = 1.14, 95% CI = 1.07–1.22, compared with no history of periodontal disease); by cancer site, statistically significant associations were observed for lung (HR = 1.36, 95% CI = 1.15–1.60), kidney (HR = 1.49, 95% CI = 1.12–1.97), pancreatic (HR = 1.54, 95% CI = 1.16–2.04; results previously published), and hematopoietic cancers (HR = 1.30, 95% CI = 1.11–1.53). Fewer teeth at baseline (0–16) was associated with a non-significant increase in risk of total cancer (HR = 1.09, 95% CI = 0.99–1.20, compared to 25–32 teeth); a statistically significant association was observed for lung cancer (HR = 1.70, 95% CI = 1.37–2.11, for 0–16 vs. 25–32 teeth). Among never smokers, periodontal

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disease was associated with statistically significant increases in total and hematopoietic cancers (HR = 1.21, 95% CI = 1.06–1.39, HR = 1.35, 95% CI = 1.01–1.81, respectively); in contrast, no association was observed for lung cancer (HR = 0.96, 95% CI = 0.46–1.98).

Interpretation—Periodontal disease was associated with a small, but statistically significant, increase in overall cancer risk which persisted among never smokers. The associations observed for lung cancer are likely to be due to residual confounding by smoking. The increased risks observed for hematopoietic, kidney and pancreatic cancers require confirmation but suggest that periodontal disease may either be a marker of a susceptible immune system or may directly effect cancer risk.

Keywords

cancer risk; periodontal disease; tooth loss; prospective cohort study

INTRODUCTION

The role of oral infection, especially periodontal infection, in chronic diseases has gained strength over recent years as supportive evidence from basic to population research has accumulated [1–3]. Basic laboratory studies have demonstrated that infections with one of the periodontal infection pathogens, *P. gingivalis*, can accelerate atheroma deposition in animal models [1]. Periodontal infection in the mouth has systemic implications; individuals with periodontal infections have elevated concentrations of circulating inflammatory markers [4,5], severity of disease directly correlates with serum concentrations of inflammatory markers [6], and treatment of periodontal infection can lower markers of systemic inflammatory and endothelial dysfunction within 2–6 months [7–10]. Taken together, data from multidisciplinary studies support the possibility of causal associations for diabetes, stroke and cardiovascular disease [11]. However, differing opinions remain on the relative role of confounding and bias and the causal component of these associations [12].

At this time it is unknown whether systemic inflammation, pathogenic invasion into the blood stream, or the immune response to periodontal infection might have an effect on cancer risk overall, or at various tumor sites. Interest in the effect of oral health on risk of head and neck cancers has led to numerous studies examining the relation between oral health, especially tooth loss, for those cancers; these studies, all case-control designs, have reported strong associations for tooth loss and oral cancer even after controlling for tobacco smoke and alcohol [13–17]. Elevated risks have also been observed for tooth loss and esophageal [18], upper gastrointestinal [19], gastric [18,20,21], and pancreatic cancers [22]. Tooth loss is most commonly caused by dental caries and periodontal disease, but the percent contribution from each condition depends on age, as well as other factors; tooth loss at an older age is more likely caused by chronic periodontal disease while teeth lost at younger ages is usually caused by dental caries [23]. Therefore, while tooth loss may be a marker of periodontal disease, the association between tooth loss and periodontal disease is not always strong. To date, only two studies have examined the relation between periodontal disease *per se* and any cancer risk[24, 25] (one of these was from the present cohort) and four studies have reported on the association between tooth loss [19,26,27] or periodontal disease [24] and risk of total cancer death.

To address the role of oral health on cancer, we examined the relationship between periodontal disease, teeth number and tooth loss during follow-up, and cancer incidence in a large prospective study of male health professionals. Our aim was to examine whether periodontal disease with bone loss is associated with an increase in risk of overall cancer and cancer at specific sites. Periodontal disease develops over many years, can progress in some individuals despite treatment, and causes loss of supporting connective tissue and bone; the question on periodontal disease in this cohort study specifically asked about bone loss, and therefore

focuses on the cumulative disease burden. The Health Professionals Follow-up Study (HPFS) population is well-suited to examine this issue as it is homogeneous with respect to socio-economic status and education level, and includes a large group of never smokers. To our knowledge, this the first comprehensive study on periodontal disease and cancer incidence.

METHODS

Populations

The Health Professionals Follow-Up Study (HPFS) was initiated in 1986 when 51,529 predominantly white U.S. men (50,121; 97.3%) aged 40–75 years responded to a questionnaire mailed by the Department of Nutrition, Harvard University School of Public Health. Participants in this cohort were those who returned a completed questionnaire and consist of dentists (29,683; 57.6%), veterinarians (10,096; 19.6%), pharmacists (4,185; 8.1%), optometrists (3,745; 7.3%), osteopathic physicians (2,220; 4.3%), and podiatrists (1,600; 3.1%). Individual data on behavioral and lifestyle characteristics, including smoking history, physical activity and diet, as well as medical conditions and medications were obtained on the baseline questionnaire. Participants are contacted biennially; they often inform us of a change of address or we obtain it from the postal service. Data on newly diagnosed medical conditions and lifestyle factors are obtained biennially, and diet is updated every four years, using questionnaire mailings. Deaths of most members of this cohort are reported by family members or by the postal service in response to questionnaire mailings. In addition, the National Death Index is searched biennially for non-respondents; this method has been shown to have a sensitivity of 98% [28]. Through 2002, follow-up rate for the HPFS cohort was greater than 96% of the total potential person-years (includes active and death follow-up). This study was approved by the Human Subjects Committee of the Harvard School of Public Health and conforms to the STROBE guidelines for observational studies.

In the main analyses, 48,375 men were eligible after excluding participants diagnosed with cancer before 1986 (other than non-melanoma skin cancer, n=2076), and those with missing data on periodontal disease (n=1078).

Assessment of dental measures

Periodontal disease—At baseline, HPFS participants were asked whether they had a history of periodontal disease with bone loss. This question was validated among dentists [29] and non-dentists [30] in the HPFS cohort by obtaining radiographs from subsets of individuals with and without a self-reported history of periodontal disease. Radiographs for each participant were examined to assess bone loss in all posterior teeth present except for the third molars. Both interproximal sites, mesial and distal, were measured for the two premolars and for the first and second molars of each quadrant for a total of 32 possible sites. Bone loss from radiographs was measured by blinded examiners and used as the standard measure of cumulative periodontal disease. Among dentists, the positive and negative predictive values were 0.76 and 0.74, respectively [29]. Among non-dentists, the positive and negative predictive values were 0.80 and 0.68, respectively [30].

Tooth loss—Participants reported number of natural teeth at baseline and any tooth loss during the past two years was reported biennially on follow-up questionnaires. Self-reported number of teeth is highly correlated with the actual number of teeth on clinical examination in a general population (r=0.97)[31]. Accordingly, we expect self-reported number of teeth and tooth loss during follow-up to be well reported in this cohort of educated health professionals.

Smoking history and other risk factors

Smoking status and history of smoking were obtained at baseline and in all subsequent questionnaires. Current smokers also reported amount of smoking (mean number of cigarettes smoked per day) on each questionnaire. Past smokers reported when they last smoked, and the time since quitting was also calculated for those who quit during follow-up.

Height and current weight were reported by participants at baseline and current weight was obtained in the biennial questionnaires. We estimated body mass index (BMI) from weight and height (i.e., kg/[height in meters]^2) as a measure of total adiposity.

Physical activity was estimated using eight different activities and a weekly physical-activity score was derived by multiplying the time spent in each activity per week by its typical energy-expenditure requirements expressed in metabolic equivalents (METs)[32].

Participants were also asked about history of diabetes and non-steroidal anti-inflammatory drug (NSAID) use at baseline and in all subsequent questionnaires.

Dietary Assessment

A 131-item semi-quantitative food frequency questionnaire (FFQ) was mailed to all participants in 1986. Participants were asked to report their mean frequency of intake over the previous year for a specified serving size of each food. Nutrient intakes, such as calcium, were calculated by multiplying the reported frequency of each food item by the nutrient content for the specified portion size. In addition, on each questionnaire, participants reported the brand of breakfast cereal, duration, frequency of use and brand of vitamin supplements, including specific supplements. We have nutrient content from approximately 1,400 multivitamins, which are updated every four years. These specific data on supplements are utilized in computing nutrient intakes. Food composition data are primarily based on values obtained from the U.S. Department of Agriculture supplemented with other data.

Vitamin D exposure was based on a score variable derived from factors that independently predicted circulation plasma 25-hydroxy-vitamn D concentrations in a subset of the HPFS cohort [33]; these factors include geographic region, vitamin D intake, physical activity, BMI, and race.

Identification of cancer cases

Participants reported any new cancer diagnosis on the mailed biennial questionnaires and written permission to obtain the related medical records or pathology reports was then obtained from those men (or their next-of-kin). If previously unreported cancer was noted on a death certificate, we contacted a family member to obtain permission to retrieve medical records or to confirm the diagnosis of cancer. Approximately 90% of cases were confirmed by medical records review and the remaining cases were confirmed with information from the participant or a family member or by death certificate.

After exclusions (previous cancer and missing data on periodontal disease at baseline), we confirmed 5720 cases of total incident cancers (excluding nonmelanoma skin cancers and nonaggressive, organ-confined prostate cancer) which were diagnosed between the return of the baseline questionnaire and January 31, 2004. We excluded organ-confined prostate cancers because of their favorable prognosis, high incidence, and because their detection usually results from a prostate-specific antigen (PSA) screening test. In addition, we examined individual cancer sites for which at least 100 cases were available.

Statistical analysis

We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of cancer diagnosis, death from any cause, or the end of follow-up (January 31, 2004), whichever came first. Incidence rates of cancer were calculated by dividing the number of incident cases by the number of person-years in each category of exposure. We computed the hazard ratios for each of the exposed categories (e.g., history of periodontal disease) by dividing the rates in these categories by the rate in the non-exposure category.

We estimated hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazard models adjusting for potential confounders. A new data record was created for every questionnaire cycle at which a participant was at risk, using covariates values at the time that the questionnaire was returned (i.e., time-varying covariates were used for variables that can change over time, such as smoking, BMI, diabetes). For the periodontal disease analyses, baseline data on periodontal disease was used without updating because periodontal disease is chronic and generally progresses slowly. Total number of teeth determined at baseline was used in the main analyses. In a secondary analysis, we updated periodontal disease status using the biennial follow-up questionnaires. We also calculated cumulative incident tooth loss (i.e., any tooth loss occurring during follow-up) in a secondary analysis and examined recent tooth loss (within the past four years only). The Cox proportional hazards models all satisfied the proportionality of hazards assumption.

All models were stratified by age (continuous in months) and calendar time. Other factors included in the models were: race (White, Asian, Black), BMI (<22, 22–24,9, 25–29.9, 30+), physical activity (quintiles), smoking history (never, past quit ≤10 yrs, past quit >10 yrs, current 1–14 cig/d, 15–24 cig/d, 25+ cig/d), pack-years (continuous), history of diabetes (yes/no), region (West, Midwest, South, Northeast), height (quintiles), alcohol (quartiles), vitamin D score (deciles), calcium intake (quintiles), fruits and vegetables intake (quintiles), red meat intake (quintiles), and total caloric intake (quintiles). Most of these factors have been linked to both periodontal disease and cancer, and consequently, could be confounding factors in this analysis. Individuals with missing data were excluded from the analyses. All statistical procedures were performed using SAS release 9.1 (SAS Institute, Cary, NC).

Role of the funding source

The U.S. National Cancer Institute funded this study. The funding source had no role in the study design, collection, analysis, or interpretation of the data, or in the writing of the report. All authors had full access to the raw data. The corresponding author had final responsibility to submit for publication.

RESULTS

Periodontal disease in this study is defined by the self-report of periodontal disease "with bone loss" which was predictive of periodontal disease assessed using radiographs (reflecting cumulative damage from periodontal disease) in our validation studies [29,30]. Table 1 summarizes baseline characteristics for this population across categories of tooth loss and periodontal disease; this table provides some indication of which factors might be confounding variables in the main analysis. Participants with a history of periodontal disease were older, more likely to have a history of diabetes or be current smokers than those who had no reported history of periodontal disease at baseline (Table 1). Similarly, men with fewer teeth at baseline (0–16 remaining) were older, more likely to be current smokers and have a history of diabetes than men with most of their natural teeth (25–32 remaining). In addition, men with fewer teeth were more likely to be taking NSAIDs, were less physically active, had lower intakes of

calcium, vitamins C and D, and were consuming more calories than men with more teeth (Table 1).

Teeth number at baseline reflects tooth loss due to dental caries, periodontal disease, injury and orthodontic treatment. At baseline (among participants with no missing data), 42% (1215/2910) of the participants with 0–16 teeth remaining had periodontal disease, 29% (1722/5899) of those with 17–24 teeth remaining had periodontal disease, and 13% (5357/41,288) of those with 25–32 teeth remaining had periodontal disease. Therefore, although there is overlap between teeth number and periodontal disease, the two exposures can be mutually exclusive.

Men who reported a history of periodontal disease had a slightly higher total cancer incidence compared with men who had no periodontal disease at baseline (HR = 1.14, 95% CI = 1.07–1.22; Table 2) controlling for known risk factors (unadjusted HR = 1.28, 95% CI = 1.20–1.36). No statistically significant association was observed for men with only 0–16 teeth at baseline compared to men with 25–32 teeth in the multivariable model (HR = 1.09, 95% CI = 0.99–1.20; unadjusted HR = 1.30, 95% CI = 1.19–1.43). The HR was identical for periodontal disease in a model simultaneously adjusting for periodontal disease and teeth number, but the association was slightly attenuated for teeth number (HR = 1.06, 95% CI = 0.96–1.16).

After controlling for smoking and other risk factors, periodontal disease was statistically significantly associated with an increased risk of lung, kidney, pancreatic and hematopoietic cancers (Table 2). The association for esophageal cancer was also increased, but the association was not statistically significant (HR = 1.44, 95% CI = 0.98–2.11). Few teeth (0–16 vs. 25–32), which is similarly correlated with smoking, was only associated with an increased risk of lung cancer (Table 2). Statistically significant inverse associations were observed for tooth loss and melanoma of the skin and prostate cancer; no associations with periodontal disease were noted for these two cancer sites.

Associations were stronger for periodontal disease and teeth number when smoking was not included in the models of smoke-related cancers (Table 2), confirming that smoking is a strong confounder of these associations. However, for pancreatic and kidney cancers, the associations remained strong after controlling for smoking.

In addition to the baseline questions, information on periodontal disease was collected biennially during follow-up. In a secondary analysis we examined the relation between updated periodontal disease status and risk of cancer. Overall, associations were similar or slightly weaker after updating periodontal status during follow-up (data not shown), with the exception of the association with lung cancer where the relationship was stronger in an updated model (HR = 1.48, 95% CI = 1.26–1.74) compared with the baseline model (HR = 1.36, 95% CI = 1.15–1.60).

The associations for lung cancer varied by histology (after controlling for smoking and other covariates); the strongest associations for periodontal disease were observed for small cell carcinoma (n=75 cases, HR = 2.03, 95% CI = 1.24–3.32) and squamous cell carcinoma (n=104, HR = 1.68, 95% CI = 1.11–2.55). The association was weaker for adenocarcinoma (n=224, HR = 1.29, 95% CI = 0.96–1.74). Teeth number were associated with squamous cell carcinoma (HR = 1.72, 95% CI = 1.03–2.85, for 0–16 teeth vs. 25–32) but not with the other subtypes of lung cancers.

We further explored the potential for residual confounding by smoking by restricting the analyses to never smokers (excludes ever cigarette, pipe and cigar smokers). We collapsed certain cancer sites together due to small numbers of cases among never smokers (Table 3). For total cancers, a small but statistically significant increase in risk was observed with

periodontal disease in this subset of the population (HR = 1.21, 95% CI = 1.06–1.39; Table 3). We observed a statistically non-significant increase in risk for smoking-related cancers (Table 3), but no increase for lung cancer risk (HR = 0.96, 95% CI = 0.46–1.98). Among never smokers, the increase in risk for hematopoietic cancers was similar to the overall finding for this group of cancers (Table 3).

All 3 major cancers contributing to hematopoietic cancers, i.e., non-Hodgkin lymphoma, leukemia and multiple myeloma, were associated with similar increased risks with periodontal disease, although the association was only statistically significant for non-Hodgkin lymphoma (Table 4).

We conducted stratified analyses to explore potential interactions of other factors with periodontal disease. For total cancer, the associations did not vary substantially by age, BMI, multivitamin use, or by number of teeth at baseline. For lung cancer, however, the associations were stronger among lean men (BMI<25 kg/m^2; HR= 1.69, 95% CI = 1.31–2.17, 284 cases) and non-users of multivitamins (HR = 1.56, 95% CI = 1.27–1.92, 406 cases). For hematopoietic cancers, associations were stronger among younger men (<70 y; HR = 1.48, 95% CI = 1.19–1.83, 538 cases), nonusers of multivitamins (HR = 1.41, 95% CI =1.15–1.73, 521 cases), and those with elevated BMI (>25 kg/m^2; HR = 1.44, 95% CI = 1.17–1.77, 509 cases). The stronger findings for lung cancer among those who are lean and not taking multivitamins suggest that residual confounding by smoking may be at play given that those two groups are more likely to be smokers. Some of these differences, however, could be due to the smaller number of cases in the stratified groups.

As dentists may be less prone to under-report history of periodontal disease with bone loss than other health professionals, we examined the relation of periodontal disease on risk separately by healthcare profession. We observed similar associations for total and lung cancers among dentists and other health professionals (data not shown), but associations were slightly stronger among dentists for periodontal disease and hematopoietic cancers (HR = 1.37, 95% CI = 1.12–1.67 among dentists, 561 cases; HR = 1.22, 95% CI = 0.91–1.63 among non-dentist health professionals, 372 cases).

Any incident tooth loss during follow-up (1988–2004) compared to no tooth loss was not associated with the risk of total cancer (OR = 1.02, 95% CI = 0.95–1.09), and only with a small increase in lung cancer (OR = 1.18, 95% CI = 0.99–1.41). Similarly, recent tooth loss (i.e., during the previous 4 years) was not associated with total cancer (HR = 0.99, 95% CI = 0.92–1.07, compared with no tooth loss during the past 4 years) or with lung cancer risk (HR = 1.05, 95% CI = 0.86–1.28).

DISCUSSION

In this cohort study of health professionals, a small increase in the risk of total cancer was observed among men who reported having periodontal disease compared with those who did not. The increase in risk persisted among never smokers for total cancer, but not for lung cancer, suggesting that the increase in risk of malignancy overall is not due to residual confounding by smoking. A similar increase in risk was observed for teeth number and total cancer risk but this association was attenuated and non-significant after adjusting for smoking, and further attenuated after adjusting for periodontal disease.

For individual cancer sites, periodontal disease was associated with increased risks of a number of solid tumors, including lung, pancreas, and kidney. For pancreatic and kidney cancers (but not lung cancer), the hazard ratios from the multivariable model without smoking were not substantially different from the model with tight smoking adjustment (Table 2), suggesting that smoking is not likely to account for the excess risks at those cancer sites. Furthermore, for

kidney and pancreatic cancers, teeth number was not associated with risk, as one would expect if smoking or another confounder associated with smoking and oral health was driving the association. We considered that the associations for kidney and pancreatic cancers may be explained by other risk factors shared by both diseases, such as diabetes and obesity. However, our results were similar in multivariable models with and without BMI or diabetes (data not shown), or after removing diabetics from the analysis (data not shown), suggesting that these two known risk factors are not likely to be responsible for the associations observed with periodontal disease.

A statistically significant increase in risk of hematopoietic cancers was observed for men reporting periodontal disease compared to those with no periodontal disease. The increase in risk was similar for non-Hodgkins lymphoma (NHL), leukemia and for multiple myeloma, although individually, only NHL was statistically significant. This is the first report of such an association and must be interpreted with caution. However, the consistency across the different types of hematopoietic cancers suggests that the associations may not be due to chance alone. These findings may reflect a commonality in the immune function and response to inflammation which results in susceptibility to both periodontal disease and hematologic malignancies. Alternatively, the systemic effect of periodontal disease on the immune system may be directly related to the risk. Because the risk of NHL has been associated with immune modulation [34] and inflammatory conditions [35,36], our observation with lymphoma needs to be investigated further.

The bulk of the literature on tooth loss or periodontal disease and cancer has been on upper gastrointestinal cancers, including oral and stomach cancers. For these cancer sites we did not observe statistically significant associations for tooth loss or periodontal disease; however, our numbers were limited for these analyses. For lung cancer, a strong association was observed for men with few teeth number and the association remained elevated among never smokers, although it was weaker and not statistically significant. Teeth number is a marker of lifetime oral health and is highly correlated with socioeconomic status and access to dental care and thus residual confounding by SES may be responsible for these findings. Alternatively, a causal mechanism may be hypothesized; associations have been reported between oral hygiene and chronic respiratory diseases and it has been suggested that aspiration of oropharyngeal bacteria may be responsible for these observations [37,38].

The inverse associations observed for teeth number and melanoma of the skin and prostate cancer should be interpreted with caution. As with the findings for hematopoietic cancers, these findings may be due to chance as we examined a large number of cancer sites. Alternatively, a risk factor not adjusted for, such as sun exposure for melanoma of the skin, which may be related to number of teeth and thus be a confounding variable, may have resulted in the observed inverse associations.

To minimize confounding by education or SES, we conducted our study in a cohort of health professionals which is fairly homogeneous with respect to education and SES. Although individuals with periodontal disease may change their diet as their gums become more sensitive or as they start losing teeth, controlling for a variety of dietary factors, including intake of fruits and vegetables, and vitamins C and D, had no effect on the hazard ratios in this study. The detailed information on smoking (including dose at each decade of life prior to study and every other year during follow-up; duration calculated at baseline and time-varying over follow-up period; and time since cessation for those who quit), allowed us to control finely for this factor; in addition, we were able to examine the periodontal associations among the large number of never smokers in this group.

We did not collect information on treatment of periodontal disease in this study. We were interested in the association between periodontal disease with bone loss and cancer risk. Individuals with irreversible damage from chronic periodontal disease (i.e, bone loss) will have experienced chronic inflammation related to periodontitis at some point in their life. While periodontal disease can be treated/managed to reduce further damage and grafting may be occasionally used to fill the bone loss, individuals who have periodontal disease cannot be cured in the sense that the effects of past periodontal disease will generally manifest as attachment loss and bone loss. Our approach is similar to other studies relating periodontitis and systemic diseases that focus on attachment loss or pocket depth that also measure overall burden rather than specific treatments and progressions. Hence we do not think that the lack of treatment data is an important concern. At this point, we feel that any recommendations for prevention of cancer based on these findings are premature; patients with periodontal diseases should seek care from their dentists regardless of the effect on cancer.

Limitations of this study include assessment of periodontal disease through self-report and inadequate power to examine less common cancers. Self-report of periodontal disease status could have introduced measurement error which would most likely have been non-differential and resulted in attenuation towards the null (given the binary exposure) of any underlying association. However, misclassification is unlikely to be substantial given that, (1) the self-reported question on periodontal disease has good positive and negative predictive values when compared to radiographs in a sub-sample of this cohort[29,30], and (2) this measure was previously associated with stroke in this cohort[39]. Furthermore, the prevalence of periodontal disease in this study (16%) is similar to the prevalence in US adults aged 30 to 90 years (13% for moderate or severe form of periodontitis based on National Health and Nutrition Examination Survey III data)[40] suggesting that under-reporting of periodontal disease was not likely to be high. However, some misclassification of periodontal disease is likely to have occurred and, consequently, actual associations may in fact be stronger than those observed. Another limitation of this study was that our findings for some of the less common cancers are based on few case numbers and thus, other studies, or additional follow-up, are necessary to better examine the associations between periodontal disease and oropharyngeal, esophageal and subsites of gastric cancers. Given that this study was conducted in men, the findings may not be generalisable to women.

Given the systemic effects of periodontal disease and the potential involvement of the immune system, as a marker of susceptibility or through changes in immune surveillance, we believe that further investigation on the role of periodontal disease and cancer, especially hematopoietic cancers, is warranted.

Acknowledgement

We thank Dr. Walter Willett for his valuable advice, support, and dedication to the success of the Health Professionals Follow-up Study.

Contributors

DSM contributed to the statistical analysis, interpretation of findings and writing of the report. MM, YL contributed to statistical support. EG contributed to data collection, funding, and editing of manuscript. KJ contributed to data collection, interpretation and editing of manuscript.

Funding. This study was supported by grant number P01CA055075, National Cancer Institute, National Institutes of Health, US.

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Table 1

Age-standardized baseline characteristics (mean or %) of the Health Professionals Follow-up Study (48,375) by periodontal disease and number of teeth*

	Teeth Number			History of Periodontal Disease	
	25–32	17–24	0–16	No	Yes
No. of participants	40,113	5576	2686	40,512	7863
Age (yrs)	53.2 (9.4)†	59.0 (9.5)	63.2 (8.2)	53.7 (9.7)	58.3 (9.2)
Height (inches)	70.1 (3.4)	70.1 (3.4)	70.1 (4.0)	70.1 (3.3)	70.0 (3.7)
BMI (kg/m^2)	25.5 (5.0)	25.7 (5.5)	25.9 (5.8)	25.5 (5.0)	25.7 (5.5)
Physical activity (MET hr/wk)	21.5 (30.6)	19.4 (25.4)	15.9 (22.0)	21.2 (30.1)	19.8 (26.9)
Race (%)±,					
White	91	89	88	91	89
Asian	2	2	3	2	2
African-American	1	2	3	1	2
Other§	2	3	3	2	3
Smoking history (%)±					
Never	47	37	29	48	29
<10 pack-years	10	8	7	10	8
10–24 pack-years	18	20	17	18	20
25–44 pack-years	13	19	23	13	22
45+ pack-years	6	12	19	6	15
Current smoker	8	14	21	8	16
Disease history (%)					
Diabetes	3	4	5	3	5
Cholecystectomy	3	4	5	3	3
Medication use (current, %)					
Aspirin use	29	32	32	29	29
NSAID use	6	6	6	6	5
Multivitamin use	42	42	41	42	40
Dietary intake (per day)					
Calories (kcal)	1978 (616)	2012 (618)	2049 (658)	1988 (620)	1968 (613)
Calcium (mg)	905 (425)	879 (433)	860 (421)	904 (428)	871 (417)
Vitamin D (IU)	412 (313)	395 (318)	386 (306)	409 (311)	405 (323)
Vitamin C (mg)	436 (479)	401 (443)	372 (418)	430 (473)	421 (468)
Alcohol (grams)	11.2 (15.1)	11.7 (16.6)	12.0 (17.6)	11.0 (15.1)	12.7 (17.0)

*All variables (except age) are age-standardized.

†Mean (SD) for all such values.

±Percent don't add to 100% due to missings.

§Answered "other ancestral origin" on questionnaire.

Table 2

Teeth number, periodontal disease and risk of cancer incidence in the HPFS cohort (1986–2004) with hazard ratios provided before and after adjusting for smoking variables (714,294 person-years).

Cancer site	Teeth number			Periodontal disease	
	25–32	17–24	0–16	No	Yes
Total cancer*	4375	813	532	4404	1316
MV HR (95% CI)†	1.0 (referent)	1.02 (0.94–1.10)	1.26 (1.15–1.38)	1.0 (referent)	1.27 (1.19–1.35)
MV HR (95% CI)±	1.0 (referent)	0.95 (0.88–1.02)	1.09 (0.99–1.20)	1.0 (referent)	1.14 (1.07–1.22)
Lung	405	146	127	442	236
MV HR (95% CI)†	1.0 (referent)	1.85 (1.52–2.24)	2.94 (2.38–3.63)	1.0 (referent)	2.08 (1.77–2.45)
MV HR (95% CI)±	1.0 (referent)	1.34 (1.10–1.63)	1.70 (1.37–2.11)	1.0 (referent)	1.36 (1.15–1.60)
Oropharyngeal	88	17	13	92	26
MV HR (95% CI)†	1.0 (referent)	1.27 (0.75–2.16)	1.86 (0.99–3.50)	1.0 (referent)	1.30 (0.83–2.03)
MV HR (95% CI)±	1.0 (referent)	1.18 (0.69–2.01)	1.60 (0.84–3.04)	1.0 (referent)	1.15 (0.73–1.81)
Esophageal	94	18	19	90	41
MV HR (95% CI)†	1.0 (referent)	0.94 (0.58–1.63)	1.77 (1.05–2.98)	1.0 (referent)	1.75 (1.20–2.55)
MV HR (95% CI)±	1.0 (referent)	0.86 (0.51–1.43)	1.34 (0.78–2.30)	1.0 (referent)	1.44 (0.98–2.11)
Stomach	77	18	11	79	27
MV HR (95% CI)†	1.0 (referent)	1.21 (0.72–2.05)	1.33 (0.69–2.58)	1.0 (referent)	1.31 (0.83–2.04)
MV HR (95% CI)±	1.0 (referent)	1.11 (0.65–1.88)	1.10 (0.56–2.16)	1.0 (referent)	1.13 (0.72–1.79)
Pancreas	189	44	20	176	77
MV HR (95% CI)†	1.0 (referent)	1.20 (0.86–1.68)	1.08 (0.67–1.73)	1.0 (referent)	1.70 (1.29–2.23)
MV HR (95% CI)±	1.0 (referent)	1.08 (0.77–1.52)	0.91 (0.56–1.47)	1.0 (referent)	1.54 (1.16–2.04)
Colorectal	805	145	93	828	215
MV HR (95% CI)†	1.0 (referent)	0.94 (0.78–1.12)	1.11 (0.89–1.38)	1.0 (referent)	1.06 (0.91–1.24)
MV HR (95% CI)±	1.0 (referent)	0.93 (0.78–1.12)	1.10 (0.87–1.37)	1.0 (referent)	1.05 (0.90–1.23)
Kidney	224	26	21	197	74
MV HR (95% CI)†	1.0 (referent)	0.67 (0.44–1.01)	1.04 (0.65–1.66)	1.0 (referent)	1.64 (1.25–2.15)
MV HR (95% CI)±	1.0 (referent)	0.61 (0.40–0.93)	0.88 (0.54–1.41)	1.0 (referent)	1.49 (1.12–1.97)
Bladder	402	87	54	398	145
MV HR (95% CI)†	1.0 (referent)	1.12 (0.89–1.42)	1.32 (0.98–1.77)	1.0 (referent)	1.43 (1.17–1.73)
MV HR (95% CI)±	1.0 (referent)	0.98 (0.77–1.24)	1.00 (0.74–1.35)	1.0 (referent)	1.17 (0.96–1.43)
Advanced prostate	405	95	41	434	107
MV HR (95% CI)†	1.0 (referent)	1.03 (0.82–1.29)	0.72 (0.52–1.00)	1.0 (referent)	0.90 (0.73–1.12)
MV HR (95% CI)±	1.0 (referent)	1.02 (0.81–1.28)	0.70 (0.50–0.97)	1.0 (referent)	0.89 (0.71–1.10)
Hematopoietic	739	126	69	720	214
MV HR (95% CI)†	1.0 (referent)	0.93 (0.76–1.13)	0.96 (0.75–1.24)	1.0 (referent)	1.29 (1.11–1.51)
MV HR (95% CI)±	1.0 (referent)	0.93 (0.76–1.12)	0.96 (0.74–1.24)	1.0 (referent)	1.30 (1.11–1.53)
Brain	106	16	10	110	22
MV HR (95% CI)†	1.0 (referent)	0.98 (0.57–1.68)	1.28 (0.65–2.51)	1.0 (referent)	0.99 (0.62–1.58)
MV HR (95% CI)±	1.0 (referent)	0.99 (0.58–1.70)	1.31 (0.66–2.59)	1.0 (referent)	0.99 (0.61–1.59)
Melanoma	605	67	26	580	118
MV HR (95% CI)†	1.0 (referent)	0.73 (0.57–0.95)	0.60 (0.40–0.89)	1.0 (referent)	1.01 (0.82–1.23)
MV HR (95% CI)±	1.0 (referent)	0.75 (0.58–0.96)	0.62 (0.41–0.93)	1.0 (referent)	1.06 (0.86–1.30)

*Total cancers excludes nonmelonoma skin cancers and nonaggressive, organ-confined prostate cancers. Cancer sites with fewer than 100 cases were not examined separately; thus, total cancer cases are greater than the sum of each cancer presented in this table.

[†]Hazard ratios (HR) and 95% confidence intervals (CI) controlling for age (continuous), race (White, Asian, Black), physical activity (quintiles), history of diabetes (yes/no), alcohol (quartiles), body mass index (<22, 22–24,9, 25–29.9, 30+), geographic location (South, West, Northeast, Midwest), height (quintiles), calcium intake (quintiles), total caloric intake (quintiles), red meat intake (quintiles), fruit and vegetable intake (quintiles), and vitamin D score (deciles).

[±]Adjusted for all covariates in model above *plus* smoking history (never, past quit ≤10 yrs, past quit >10 yrs, current 1–14 cig/d, 15–24 cig/d, 25+ cig/d) and pack-years (continuous).

Table 3

Teeth number, periodontal disease and risk of cancer among never cigarette, pipe or cigar smokers in the HPFS cohort (1986–2004, 308,928 person years)

NEVER SMOKERS	Teeth number			Periodontal disease	
Cancer site	**25–32**	**17–24**	**0–16**	**No**	**Yes**
Total	1600	181	99	1626	254
HR (95% CI)*	1.0 (referent)	0.89 (0.76–1.04)	1.24 (1.00–1.53)	1.0 (referent)	1.21 (1.06–1.39)
Smoking-related†	442	61	33	458	78
HR (95% CI)*	1.0 (referent)	1.05 (0.80–1.38)	1.45 (1.01–2.10)	1.0 (referent)	1.26 (0.99–1.61)
Lung	49	12	5	57	9
HR (95% CI)*	1.0 (referent)	1.52 (0.78–2.94)	1.59 (0.60–4.16)	1.0 (referent)	0.96 (0.46–1.98)
Upper GI‡	78	8	7	81	12
HR (95% CI)*	1.0 (referent)	0.77 (0.37–1.62)	1.74 (0.77–3.94)	1.0 (referent)	1.15 (0.62–2.15)
Hematopoietic	307	31	20	304	54
HR (95% CI)*	1.0 (referent)	0.76 (0.52–1.11)	1.21 (0.76–1.94)	1.0 (referent)	1.35 (1.01–1.81)

*Hazard ratios (HR) and 95% confidence intervals (CI) controlling for age (continuous), race (White, Asian, Black), physical activity (quintiles), history of diabetes (yes/no), alcohol (quartiles), body mass index (<22, 22–24,9, 25–29.9, 30+), geographic location (south, west, northeast, midwest), height (quintiles), calcium intake (quintiles), total caloric intake (quintiles), red meat intake (quintiles), fruit and vegetable intake (quintiles), and vitamin D score (deciles).

†Includes lung, bladder, kidney, oropharyngeal, esophagus, stomach, pancreas, leukemia.

‡Includes oropharyngeal, esophagus and stomach.

Table 4

Teeth number, periodontal disease and risk of leukemia, non-Hodgkin lymphoma and multiple myeloma in the HPFS cohort (1986–2004, 714,294 person-years)

Cancer site	Teeth number			Periodontal disease	
	25–32	17–24	0–16	No	Yes
Non-Hodgkin lymphoma	430	60	34	403	121
HR (95% CI)*	1.0 (referent)	0.76 (0.58–1.00)	0.80 (0.56–1.16)	1.0 (referent)	1.31 (1.06–1.62)
Leukemia	195	37	18	194	56
HR (95% CI)*	1.0 (referent)	1.05 (0.73–1.50)	1.02 (0.62–1.70)	1.0 (referent)	1.34 (0.98–1.82)
Multiple myeloma	101	25	15	106	35
HR (95% CI)*	1.0 (referent)	1.28 (0.81–2.01)	1.42 (0.80–2.53)	1.0 (referent)	1.30 (0.88–1.94)

*Hazard ratios (HR) and 95% confidence intervals (CI) controlling for age (continuous), race (White, Asian, Black), physical activity (quintiles), history of diabetes (yes/no), alcohol (quartiles), body mass index (<22, 22–24,9, 25–29.9, 30+), geographic location (south, west, northeast, midwest), height (quintiles), calcium intake (quintiles), total caloric intake (quintiles), red meat intake (quintiles), fruit and vegetable intake (quintiles), vitamin D score (deciles), smoking history (never, past quit ≤10 yrs, past quit >10 yrs, current 1–14 cig/d, 15–24 cig/d, 25+ cig/d) and pack-years (continuous).