A Prospective Study of Periodontal Disease and Pancreatic Cancer in US Male Health Professionals

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Two previous cohort studies reported positive associations between tooth loss or periodontitis and pancreatic cancer risk. Data on periodontal disease were obtained at baseline and every other year thereafter in a cohort of 51529 male health professionals aged 40–75 years. A total of 216 patients were diagnosed with incident pancreatic cancer during 16 years of follow-up. Multivariable relative risks (RRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models controlling for potential confounders, including detailed smoking history. All statistical tests were two-sided. Compared with no periodontal disease, history of periodontal disease was associated with increased pancreatic cancer risk (overall, multivariable RR = 1.64, 95% CI = 1.19 to 2.26; *P* = .002; crude incidence rates: 61 versus 25 per 100 000 person-years; among never smokers, multivariable RR = 2.09, 95% CI = 1.18 to 3.71; *P* = .01; crude incidence rates: 61 versus 19 per 100000 person-years). In contrast, baseline number of natural teeth and cumulative tooth loss during follow-up were not strongly associated with pancreatic cancer. The association between periodontal disease and increased risk of pancreatic cancer may occur through plausible biologic mechanisms, but confirmation of this association is necessary.

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Cancer of the pancreas, the fourth leading cause of cancer death in the United States, is a rapidly fatal malignancy (1). The only established modifiable risk factor for pancreatic cancer is cigarette smoking, although data suggest that diabetes, obesity, and insulin resistance are also associated with risk (2–5). In addition, chronic pancreatitis has been associated with extremely high risks of pancreatic cancer (6), suggesting that inflammation may be involved in the initiation and/or promotion of pancreatic cancer. Inflammation may enhance cellular proliferation and mutagenesis, reduce adaptation to oxidative stress, promote angiogenesis, inhibit apoptosis, and increase secretion of inflammatory mediators (7).

Serum levels of C-reactive protein and of other biomarkers of systemic inflammation are consistently higher in individuals with periodontal disease than in those who have no periodontal disease (8,9). Periodontitis is the primary cause of tooth loss in adults and develops over many years as a result of bacterial infection and inflammation of the gum that spread to the ligaments and bone that support the teeth. Positive associations between tooth loss and pancreatic cancer were reported in two recent studies (10,11). Data from these studies were obtained prospectively, thereby ruling out potential recall bias, but residual confounding by amount of smoking remains a possible explanation, given that all participants were smokers in one study (10), and no adjustments for smoking were presented in the analyses of pancreatic cancer in the other (11).

We therefore examined the relationship between periodontitis and tooth loss and the subsequent risk of pancreatic cancer in a large prospective cohort of health professionals. This cohort provides a homogeneous population with respect to socioeconomic status, and detailed data on smoking history allow for tight adjustments for smoking.

The Health Professionals Follow-Up Study (HPFS) was initiated in 1986 and included 51529 predominantly white US men aged 40–75 years. Participants in this cohort are dentists (57.6%), veterinarians (19.6%), pharmacists (8.1%), optometrists (7.3%), osteopathic physicians (4.3%), and podiatrists (3.1%). Individual data on lifestyle and medical conditions, including cancer, were obtained on the baseline questionnaire and on subsequent biennial questionnaires. Deaths of most members of this cohort were reported by family members or by the postal service in response to questionnaire mailings. In addition, the National Death Index was searched biennially for nonrespondents; this method has been shown to have a sensitivity of 98% (12). Most diagnoses of pancreatic cancer (reported or detected through the death follow-up) were confirmed with medical records (95%). Remaining self-reported cancers were confirmed by a secondary source (e.g., death certificate, physician, or telephone interview of a family member). This study was approved by the Human Subjects Committee of the Harvard School of Public Health. Written informed consent was assumed on completion of the questionnaires.

On the baseline questionnaire, participants responded to the following question: "Have you had periodontal disease with bone loss?" This question was validated among dentists (13) and nondentists (14) in the HPFS cohort by obtaining radiographs from subsets of individuals with and without a self-reported history of periodontal disease. Among dentists, the positive and negative predictive values were 0.76 and 0.74, respectively (13). Among nondentists, the positive and negative predictive values were 0.80 and 0.68, respectively (14).

Participants reported number of natural teeth at baseline, and any tooth loss during the past 2 years was reported biennially on

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CONTEXT AND CAVEATS

Prior knowledge

Tooth loss or periodontal disease, inflammation of the gums caused by bacterial infection that leads to tooth loss, was shown to be associated with increased risk of pancreatic cancer in two studies. In one study, all subjects were smokers, and in the other, no adjustment was made for smoking, a known risk factor for pancreatic cancer.

Study design

Questionnaire-based prospective study of pancreatic cancer incidence and history of periodontal disease among male health professionals that includes adjustment for smoking status.

Contribution

History of periodontal disease was independently associated with an increased risk of pancreatic cancer overall and in never smokers; recent tooth loss was associated with additional increased risk.

Implications

The association may be due to systemic inflammation and/or increased levels of carcinogenic compounds generated by bacteria in the oral cavity of individuals with periodontal disease.

Limitations

History of periodontal disease was self-reported and may be subject to measurement error.

follow-up questionnaires. Self-reported number of teeth is highly correlated with the actual number of teeth on clinical examination (r = .97) (15). Accordingly, we expect self-reported number of teeth and tooth loss during follow-up to be accurate in this cohort of educated health professionals.

In the main analyses, 48 375 men were eligible after excluding participants who were diagnosed with cancer (other than nonmelanoma skin cancer) before 1986 and those with missing data on periodontal disease (N = 1118). After exclusions, a total of 216 confirmed incident pancreatic cancer case patients were available for analyses. For the incident tooth loss analyses, with follow-up starting in 1988, 190 case patients were available.

We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up (January 31, 2002), whichever came first. Relative risks (RRs) adjusted for potential confounders and their 95% confidence intervals (CIs) were approximated by Cox proportional hazards regression. For the periodontal disease analyses, baseline data on periodontal disease were used without updating because periodontal disease is chronic and generally progresses slowly. However, in a secondary analysis, we updated periodontal disease over each 2-year cycle. For the analyses of tooth loss, we examined the effect of tooth loss during the study period because remote tooth loss is more likely to reflect caries than periodontal disease. For the incident tooth loss analyses, follow-up started in 1988 because the baseline questionnaire did not assess recent tooth loss. We calculated cumulative incident tooth loss for our analysis. Details on analyses and power calculations are available online as Supplementary Data.

Models were stratified by age and calendar time (i.e., time metameter in Cox proportional hazards models) and adjusted for cigarette smoking (time-varying) (16), diabetes (cumulative updating), baseline body mass index (BMI) (17), race (African American/other), height, physical activity, nonsteroidal anti-inflammatory drug use (18), multivitamin use, geographic regions (to serve as vitamin D proxy), profession (dentist versus other), and history of cholecystectomy (cumulative updating) (19). In addition, we controlled for a number of dietary factors, including baseline intakes of vitamin D, calcium, sucrose, fruits and vegetables, and total calories. Alcohol was not included because it is not related to pancreatic cancer in this cohort (20), and including it in the multivariable model did not change the estimates. The Cox proportional hazards models all satisfied the proportionality of hazards assumption. In the tables, models with the dietary covariates are shown separately because 1546 individuals, including eight patients, with inadequate dietary data were removed from the analysis. All P values (two-sided) were calculated using a chi-square test. All statistical procedures were performed using SAS release 9.1 (SAS Institute, Cary, NC).

Participants with periodontal disease were older, more likely to have a history of diabetes, and more likely to be current smokers than those who had no reported history of periodontal disease at baseline (Supplementary Table 1, available online). Other potential pancreatic cancer risk factors, including BMI, were similar across periodontal disease status.

History of periodontal disease was associated with increased risk for pancreatic cancer, after adjusting for age (Table 1). The association was attenuated in a multivariable model adjusting for potential confounders (smoking accounted for most of the attenuation in risk) but remained statistically significant (Table 1). Further adjustment for a number of dietary variables did not affect this association (RR = 1.64, 95% CI = 1.19 to 2.26; P = .002; crude incidence rates: 61 versus 25 per 100 000 person-years; Table 1). In a secondary analysis, we updated periodontal disease status throughout the follow-up period and observed a similar, albeit slightly weaker, association for pancreatic cancer (multivariable RR = 1.52, 95% CI = 1.13 to 2.05).

Number of natural teeth at baseline was not associated with pancreatic cancer (Table 1). However, cumulative incident tooth loss during follow-up (1988–2002), which was modeled as a time-varying exposure in a Cox proportional hazards model, was associated with a statistically nonsignificant increase in pancreatic cancer (Table 1). When periodontal disease was added to the model, the association between incident tooth loss and pancreatic cancer was further attenuated, suggesting that tooth loss may not be an independent risk factor (Table 1). Tooth loss during the past 4 years was more strongly associated with pancreatic cancer than cumulative tooth loss (Table 1). This association was also attenuated after controlling for periodontal disease at baseline but remained statistically significant (Table 1). In this model, the association between periodontal disease and pancreatic cancer was similar (RR = 1.58, 95% CI = 1.13 to 2.22; P = .007).

In a joint analysis, periodontal disease with recent tooth loss was associated with a 2.7-fold increase in pancreatic cancer, compared with no periodontal disease and no recent tooth loss (Table 2). This joint effect suggests that timing and severity of periodontal disease, as reflected by those who experience recent tooth loss, are important factors in this association, and periodontal disease may increase risk

Table 1. Periodontal disease, tooth loss, and baseline teeth number and risk of pancreatic cancer in the Health Professionals Follow-up Study cohort*

Characteristic	N	Person-years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI)†	Multivariable RR (95% CI)‡	Multivariable RR (95% CI)§
Periodontal disease at baseline (follow-up: 1986–2002)						
No	149	590 844	1.0 (referent)	1.0 (referent)	1.0 (referent)	
Yes	67	109 184	1.83 (1.36 to 2.45)	1.63 (1.19 to 2.22)	1.64 (1.19 to 2.26)	
No. of natural teeth at baseline (follow-up: 1986–2002)						
25–32	160	588 527	1.0 (referent)	1.0 (referent)	1.0 (referent)	
17–24	37	77 308	1.20 (0.83 to 1.73)	1.09 (0.75 to 1.58)	1.00 (0.67 to 1.48)	
0–16	19	34 055	1.22 (0.75 to 1.99)	1.02 (0.61 to 1.69)	1.02 (0.61 to 1.71)	
Updated tooth loss (follow-up: 1988–2002)‖						
Incident during follow-up						
None	130	465 498	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Any	60	107 646	1.40 (1.02 to 1.93)	1.31 (0.94 to 1.84)	1.31 (0.92 to 1.85)	1.21 (0.86 to 1.71)
Incident in the past 4 y						
None	139	499 779	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Any	51	73 365	1.73 (1.24 to 2.41)	1.63 (1.16 to 2.31)	1.61 (1.13 to 2.31)	1.53 (1.08 to 2.17)

* RR = relative risk; CI = confidence interval.

† Adjusted for age, smoking history (never; quit ≥15 years; quit <15 years, ≤25 pack-years; quit <15 years, >25 pack-years; current ≤25 pack-years; current >25 pack-years), profession (dentist/others), race (African American/other), geographic location (northeast, south, midwest, west), physical activity (quintiles), history of diabetes (yes/no), body mass index (quintiles), height (quintiles), history of cholecystectomy (yes/no), nonsteroidal anti-inflammatory drug use (yes/no), multivitamin use (yes/no), and in addition, for periodontal and tooth loss models, baseline teeth number (0–16, 17–24, 25–32).

‡ Additionally controlling for dietary intakes (quintiles) of fruits and vegetables, vitamin D, calcium, sucrose, and total calories. $P = .002$ for periodontal disease at baseline, $P = .009$ for tooth loss in past 4 years, calculated using two-sided chi-square tests.

§ Adjusting for periodontal disease in addition to other covariates in model (†) above. $P = .02$ for tooth loss in the past 4 years, calculated using a two-sided chi-square test.

‖ Excludes edentulous participants (as reported in 1986). Follow-up for this analysis starts in 1988 and includes 190 cases.

through promotion of initiated cells. Alternatively, the joint classification of recent tooth loss and periodontal disease may improve the classification of periodontal disease, thereby reducing measurement error and refining the association.

We conducted stratified analyses to assess the possibility of any residual confounding by known pancreatic cancer risk factors (Table 3). The association between periodontal disease and pancreatic cancer appeared similar among younger and older participants, suggesting that age is unlikely to be confounding the overall association. Moreover, the influence of periodontal disease appeared to be stronger among men who were never smokers (RR = 2.09, 95% CI = 1.18 to 3.71; $P = .01$; crude incidence rates: 61 versus 19 per 100 000 person-years) or among men with BMI less than 25 kg/m^2 (RR = 2.20, 95% CI = 1.34 to 3.61; $P = .002$), suggesting that smoking or obesity is unlikely to explain the association. In addition, when men with a history of diabetes were excluded from the analysis, a statistically significant association for periodontal disease was still observed

Table 2. History of periodontal disease, incident tooth loss, and risk of pancreatic cancer in the Health Professionals Follow-up Study (1988–2002)*

Periodontal disease†	N	Person-years	Multivariable RR (95% CI)‡	*P*§
No				
No tooth loss in past 4 y	106	435 031	1.0 (referent)	
Tooth loss in past 4 y	24	50 818	1.29 (0.81 to 2.06)	.28
Yes				
No tooth loss in past 4 y	33	64 748	1.38 (0.92 to 2.09)	.12
Tooth loss in past 4 y	27	22 547	2.71 (1.70 to 4.32)	<.001

* Excludes edentulous participants (as reported in 1986). Follow-up for this analysis starts in 1988 and includes 190 patients. RR = relative risk; CI = confidence interval.

† As reported at baseline (1986).

‡ Adjusted for age, smoking history (never; quit ≥15 years; quit <15 years, ≤25 pack-years; quit <15 years, >25 pack-years; current ≤25 pack-years; current >25 pack-years), profession (dentist/others), race (African American/other), geographic location (northeast, south, midwest, west), physical activity (quintiles), history of diabetes (yes/no), body mass index (quintiles), height (quintiles), history of cholecystectomy (yes/no), nonsteroidal anti-inflammatory drug use (yes/no), multivitamin use (yes/no), and baseline teeth number (0–16, 17–24, 25–32).

§ *P* values were calculated using a two-sided chi-square test.

Table 3. Periodontal disease and risk of pancreatic cancer in the Health Professionals Follow-up Study cohort 1986–2002, by smoking status, body mass index (BMI), age, and profession*

Characteristic	Periodontal disease	N	Person-years	Multivariable RR (95% CI)‡	*P*‡
Smoking					
Never					
	No	55	288269	1.0 (referent)	
	Yes	19	31159	2.09 (1.18 to 3.71)	.01
Ever					
	No	87	279452	1.0 (referent)	
	Yes	47	73632	1.63 (1.12 to 2.37)	.01
BMI, kg/m^2					
<25					
	No	53	270320	1.0 (referent)	
	Yes	29	46768	2.20 (1.34 to 3.61)	.002
≧25					
	No	92	306661	1.0 (referent)	
	Yes	35	58998	1.32 (0.87 to 2.00)	.19
Age, y					
<65					
	No	49	405727	1.0 (referent)	
	Yes	19	57094	1.85 (1.06 to 3.24)	.03
≧65					
	No	100	185117	1.0 (referent)	
	Yes	48	52092	1.59 (1.11 to 2.29)	.01
Profession					
Dentist					
	No	83	333443	1.0 (referent)	
	Yes	51	73842	1.91 (1.31 to 2.78)	<.001
Other health profession					
	No	66	257401	1.0 (referent)	
	Yes	16	35343	1.17 (0.65 to 2.11)	.59

* Seven patients missing BMI; eight missing smoking status.

† RR = relative risk; CI = confidence interval. Adjusted for age, race (African American/other), geographic location (northeast, south, midwest, west), physical activity (quintiles), history of diabetes (yes/no), BMI (quintiles), height (quintiles), history of cholecystectomy (yes/no), nonsteroidal anti-inflammatory drug use (yes/no), multivitamin use (yes/no), profession (dentist/others, except in models stratified by profession), and smoking history (never; quit ≥15 years; quit <15 years, ≤25 pack-years; quit <15 years, >25 pack-years; current ≤25 pack-years; current > 25 pack-years, except in model of never smokers).

‡ *P* values were calculated using a two-sided chi-square test.

(RR = 1.70, 95% CI = 1.23 to 2.35; *P* = .001, n = 191 cases).

Because dentists may be less likely to underreport periodontal disease with bone loss (as asked on the questionnaire) than other health professionals, we assessed associations separately by healthcare profession. We observed a stronger association among dentists than among other health professionals in this cohort (Table 3). The accuracy of self-reported periodontal disease was slightly higher among dentists than for other health professionals in validation studies of self-reported history of periodontal disease in this cohort (13,14). Therefore, undifferential measurement error from potential underreporting of periodontitis in the nondentist group may explain the weaker association in that group. A similar difference between dentists and nondentists was observed for periodontal disease and ischemic stroke in this cohort (among dentists, RR = 1.46, 95% CI = 1.07 to 2.00, versus among nondentists, RR = 1.13, 95% CI = 0.73 to 1.72) (21). The prevalence of periodontal disease in this study (16%) is similar to the prevalence in US adults aged 30–90 years (13% for moderate or severe form of periodontitis based on National Health and Nutrition Examination Survey III data) (22).

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 had no effect on the relative risks. Finally, because periodontal disease and tooth loss were assessed before any diagnosis of pancreatic cancer, recall and selection biases were minimized, and thus the need for proxy interviews was eliminated.

Several mechanisms could potentially explain the observations from this study. Inflammation appears to play an important role in pancreatic cancer pathogenesis (23), although the inflammatory mediators that lead to the development of pancreatic cancer remain poorly defined. An association between periodontal disease and systemic inflammation has been observed using biomarkers (8). In the HPFS, plasma C-reactive protein levels were 30% higher in individuals with a history of periodontal disease than in those with no history (9). We hypothesize that periodontal disease may promote pancreatic carcinogenesis through inflammation.

Alternatively, periodontal disease could influence pancreatic carcinogenesis through increased generation of carcinogens, namely nitrosamines (10,24). Individuals with periodontal disease and poor oral hygiene have elevated levels of oral bacteria and have much higher nitrosamine levels in their oral cavity (25) due to nitrate-reducing bacteria (26). Nitrosamines and gastric acidity have been hypothesized to have an important role in pancreatic cancer; numerous studies support this hypothesis (27).

In this study, history of periodontal disease was self-reported, and measurement error due to inaccurate reporting could have occurred; this error would be nondifferential, however, and would produce attenuation toward the null given the binary exposure, thereby weakening the underlying association. Although our population is fairly homogeneous, we did not have income level or other socioeconomic status data on participants in this cohort and cannot additionally adjust for these factors; if an unknown risk factor of pancreatic cancer was associated with socioeconomic status, it may have confounded our association.

In summary, we observed an association between history of periodontal disease and risk of pancreatic cancer that was independent of other known or suspected risk factors for this malignancy. Moreover, increased severity of periodontal disease, as manifested by periodontitis with recent tooth loss, was associated with the greatest risk. Given our limited understanding of pancreatic cancer etiology, we believe that

further investigation into this relation and the role of systemic inflammation in pancreatic carcinogenesis is warranted.

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Notes

Dr D. S. Michaud had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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