Research Article

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Oral Health in Relation to Pancreatic Cancer Risk in African American Women

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Abstract

Background: Incidence of pancreatic cancer is higher in African Americans than in U.S. whites. We hypothesized that poor oral health, disproportionately common in African Americans and associated with increased risk of pancreatic cancer in several studies of predominantly white populations, may play a role in this disparity.

Methods: We examined the relation of self-reported measures of oral health (periodontal disease and adult tooth loss) in relation to pancreatic cancer incidence in the prospective Black Women's Health Study (BWHS). Cox proportional hazard analyses were used to calculate HRs of pancreatic cancer for women with periodontal disease, tooth loss, or both, relative to women who reported neither. Multivariable models adjusted for age, cigarette smoking, body mass index (BMI), type 2 diabetes, and alcohol consumption.

Results: Participants aged 33 to 81 were followed for an average of 9.85 years from 2007 through 2016, with occurrence of 78 incidence cases of pancreatic cancer. Multivariable HRs for pancreatic cancer incidence were 1.77 [95% confidence interval (CI) 0.57–5.49] for periodontal disease with no tooth loss, 2.05 (95% CI, 1.08–3.88) for tooth loss without report of periodontal disease, and 1.58 (95% CI, 0.70–3.57) for both tooth loss and periodontal disease. The HR for loss of at least five teeth, regardless of whether periodontal disease was reported, was 2.20 (95% CI, 1.11–4.33).

Conclusions: The poor oral health experienced by many African Americans may contribute to their higher incidence of pancreatic cancer.

Impact: Future research will assess associations between the oral microbiome and pancreatic cancer risk in this population.

Introduction

A history of periodontal disease and/or adult tooth loss has been associated with increased risk of pancreatic cancer in a number of studies from the United States and Europe (1–7). The presence of circulating antibodies to selected oral periodontal pathogens was also associated with increased risk of pancreatic cancer in one study (8). In addition, two periodontal pathogens, *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans,* characterized by sequencing of microbial DNA from saliva obtained from study participants years before diagnosis, were positively associated with risk of pancreatic cancer (9).

Pancreatic cancer incidence is higher in African Americans than in U.S. whites, and the reasons for the disparity are largely unknown (10). The prevalence of poor oral health, including periodontal disease, is also higher in African Americans (11–13). It is possible that the higher pancreatic cancer incidence may be explained, in part, by poor oral health, but this has not been examined directly. To date, only one cohort study has examined associations between oral health and cancer risk separately in African Americans, but risk of pancreatic cancer was not assessed because of the small number of cases (14). We utilized data from the prospective Black Women's Health Study (BWHS) for the first analysis of periodontal disease and pancreatic cancer in African Americans.

Materials and Methods

Study population

The BWHS was established in 1995 when 59,000 African American women aged 21 to 69 years from across the United States completed mailed health questionnaires (15). Biennial follow-up questionnaires (mail or online) are used to update information on exposures and outcomes and the National Death Index (NDI) is searched every year to ascertain deaths and cause of death. Follow-up is complete through 2016 for 85% of total person-time since 1995. The Institutional Review Board of Boston University (Boston, MA) approved the protocol and reviews the study annually.

At baseline, participants were asked about weight, height, reproductive history, physical activity, alcohol consumption, cigarette smoking, years of education, and history of major health conditions, including cancers and type 2 diabetes. Follow-up questionnaires ascertained the occurrences of incident cancers and updated information on smoking, alcohol consumption, weight, diabetes, and other variables.

Oral health

Questions designed to ascertain periodontal disease were asked in 1997 and 1999 (gingivitis, bleeding gums), 2011 (gum disease with bone loss), and 2015 (periodontitis or gum disease). Questions on adult tooth loss (number of teeth lost) were asked in 2007, 2011, and 2015. We carried forward responses to the questions, such that women who reported gingivitis in 1997 were considered to be positive for periodontal disease in all subsequent

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cycles of follow-up. Women who did not report gingivitis in 1997 were considered not to have periodontal disease unless they answered yes to gingivitis, gum disease, or periodontitis in one of the later questionnaires, at which point they were classified as positive. To have a reference category of women who were least likely to have periodontal disease, those who reported no tooth loss and had never reported gum disease, we restricted all analyses to follow-up from 2007 through the end of 2016. We combined data from the gum disease and tooth loss questions to create a combined oral health variable with the following categories: (i) no to both gum disease and tooth loss; (ii) no to gum disease, with loss of at least one tooth; (iii) yes to gum disease with no tooth loss; and (iv) both gum disease and tooth loss.

We previously carried out a validation study of self-reported periodontal disease in the BWHS by inviting participants in the Boston area to appear at the Boston University School of Dental Medicine for a dental examination (16). Exam results were compared with self-reports. The positive predictive value of the question that asked participants whether they had ever been told they had gum disease was 0.90 [95% confidence interval (CI) 0.74–0.98], indicating that 90% of women who reported gum disease actually had gum disease upon dental exam. Sensitivity was much lower, 0.46 (95% CI, 0.33–0.59), indicating that many women were not aware of their gum disease. Underdiagnosis of gum disease in the entire cohort is expected to be nondifferential with regard to pancreatic cancer status and therefore would, if anything, bias results toward the null. Questions on tooth loss were not tested in the validation study, but are likely to be less prone to under-reporting.

Covariates

Cigarette smoking was ascertained every 2 years. A variable representing pack-years of smoking was computed on the basis of duration of smoking reported at baseline, current smoking status at each follow-up period, and number of cigarettes per day reported on each questionnaire.

On baseline and follow-up questionnaires, participants were asked whether they had ever been diagnosed with diabetes and the age at first diagnosis. In a validation study, 217 of 229 (94%) self-reports of diabetes were confirmed by the participants' physicians (17). Given the high accuracy of self-report, we accepted self-report to classify participants as having type 2 diabetes. In data from NHANES (1999–2002), the prevalence of undiagnosed diabetes among non-Hispanic black women was estimated to be 4.1% (18); therefore, most participants classified as not having diabetes will be correctly classified. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Weight was updated by questionnaire every 2 years, allowing calculation of BMI for each 2-year period.

Pancreatic cancer cases

Each BWHS questionnaire asks about new diagnoses of specific cancers and year of diagnosis. In addition, each year we link with state cancer registries to identify cancers in study participants who have died or have become lost to follow-up. Cancer registry data include the cancer diagnosis, along with tumor characteristics, and month and year of diagnosis. Deaths are ascertained each year through the NDI, with data available through 2016 at the time of this analysis. Most pancreatic cancer cases are identified through cancer registries or the NDI rather than by self-report, presumably because patients diagnosed with the disease are too ill or have already died before having a chance to complete a new questionnaire. Case definition was incident pancreatic adenocarcinoma (ICD-10 codes C25.0–25.9, histology code 8140).

Statistical analysis

Women who had been diagnosed with any cancer before the start of follow-up in 2007 ($N = 3{,}088$) were excluded from the analysis. Each participant contributed person-years from 2007 until diagnosis of pancreatic cancer, death from other causes, or end of follow-up in 2016, whichever came first. Exposure data for each participant were taken from the questionnaire cycle before the end of her follow-up or carried forward from previous questionnaires if not asked on the most recent one. We used Cox proportional hazards regression, stratified by age and questionnaire cycle, to calculate HR and 95% CI, with adjustment for cigarette smoking (never, past, current), and pack-years of smoking (<10, 10–29, ≥30); BMI (<25, 25–29, ≥30 kg/m^2); type 2 diabetes diagnosed more than 2 years before the cancer diagnosis (yes/no); and alcohol intake (current/nondrinker). Covariates were updated throughout follow-up. We repeated the analyses stratified on current smoking status (smoker/nonsmoker) because smoking is strongly associated with risk of pancreatic cancer and a few previous studies observed stronger associations among nonsmokers. We used interaction terms and Wald statistics to test for multiplicative interaction (19).

Results

Among women in the analytic cohort, 7% reported adult tooth loss and periodontal disease, 41% reported tooth loss without periodontal disease, 5% reported periodontal disease without tooth loss, and 47% reported neither measure of poor oral health. Characteristics of participants according to periodontal disease and tooth loss are shown in Table 1. Relative to women without either tooth loss or periodontal disease, women who reported both or either were older, more likely to have type 2 diabetes, more likely to be current smokers, and had a greater number of pack-years of smoking.

A total of 78 incident pancreatic cancers occurred during follow-up from 2007 through 2016, with participants contributing an average of 9.85 years of follow-up. Relative to the reference category of women who never reported either tooth loss or periodontal disease, multivariable HRs were 1.77 (95% CI

Table 1. Age-adjusted characteristics according to oral health status at baseline in 2007

	No periodontal disease/no tooth loss ($N = 18{,}258$)	Self-reported periodontal disease and/or tooth loss ($N = 20{,}728$)
Age in years (mean, SD)	46.6 (9.0)	53.0 (10.2)
BMI in kg/m^2 (mean, SD)	29.5 (6.7)	30.9 (7.3)
Smoking status, %		
Never smoked	69.8	61.1
Current smoker	15.2	22.4
Past smoker	15.0	16.5
≥20 Pack-years of smoking, %	17.8	24.1
Current alcohol use (drinks/week), %		
1–6	34.8	32.0
≥7	3.8	3.5
Type 2 diabetes, %	9.6	12.5

NOTE: Values are standardized to the age distribution of the study population.

Table 2. Measures of oral health in relation to incidence of pancreatic cancer

Self-reported oral health					
Periodontal disease	**Tooth loss**	**Pancreatic cancer cases**	**Person-years of follow-up**	**Age-adjusted HR (95% CI)**	**Multivariable HR (95% CI)**
No	No	13	158,999	Reference	Reference
No	Yes	49	152,071	2.25 (1.19–4.23)	2.05 (1.08–3.88)
Yes	No	4	25,963	1.76 (0.57–5.43)	1.77 (0.57–5.49)
Yes	Yes	12	46,953	1.72 (0.76–3.87)	1.58 (0.70–3.57)
Any tooth loss		61	199,024	2.13 (1.14–3.96)	1.94 (1.04–3.64)
1–4 Teeth lost		23	115,397	1.78 (0.89–3.56)	1.72 (0.86–3.43)
≥5 Teeth lost		38	83,627	2.51 (1.29–4.90)	2.20 (1.11–4.33)

NOTE: Multivariable HRs adjusted for age, smoking status (never, past, current), pack-years of smoking, alcohol consumption, BMI, and type 2 diabetes.

0.57–5.47) for periodontal disease with no tooth loss, 1.58 (95% CI 0.70–3.57), for periodontal disease with tooth loss, and 2.05 (95% CI 1.08–3.88) for tooth loss without periodontal disease (Table 2). The multivariable HR for any tooth loss, regardless of whether or not there was a report of periodontal disease, was 1.94 (95% CI, 1.04–3.64; Table 2). HRs for 1 to 4 and 5 or more teeth lost were 1.72 (0.86–3.43) and 2.20 (1.11–4.33), respectively.

Results of analyses stratified on smoking status during the at-risk periods are shown in Table 3. Tooth loss and periodontal disease were associated with increased risk of pancreatic cancer among nonsmokers (never and past smokers), with little evidence of an association among current smokers. Among the nonsmokers, the HR for tooth loss regardless of whether or not periodontal disease was reported was 2.42 (1.09–5.37).

Discussion

The current analysis, based on data from a large sample of African American women, indicates that relative to women who showed no signs of poor oral health, those who reported adult tooth loss had a substantially increased risk of pancreatic cancer. The association was stronger for loss of at least five teeth and was observed primarily among nonsmokers who have a lower baseline risk of pancreatic cancer. No statistically significant associations with self-reported periodontal disease were observed, although HRs were above 1.5.

In observational studies that examined the relation of periodontal disease to pancreatic cancer risk or mortality, periodontal disease status was determined by a number of different measurements: self-reported history of periodontal disease, claims data for treatment of periodontal disease, "tooth mobility," and dental examination data. Despite the different measurements used across these studies, almost all prospective cohorts or registry linkages identified positive associations with pancreatic cancer, with relative risks of at least 1.5 (1–7). In contrast, the Women's Health Initiative cohort found no association of periodontal disease with pancreatic cancer risk (20). Findings on tooth loss (which can be a marker of severe periodontitis) in relation to risk of pancreatic cancer have been less consistent (21). In a recent report from the Atherosclerosis Risk in Communities (ARIC) study, in which dental exams were the source of exposure data, both tooth loss and periodontal disease were associated with an increased risk of cancer, specifically lung and colorectal cancer (14); as noted previously, this study did not provide results on pancreatic cancer due to limited data.

A few studies have examined the relation between oral bacteria and pancreatic cancer risk. In a large prospective cohort study with blood samples collected prior to cancer diagnosis, a greater than 2-fold increase in pancreatic cancer was reported among subjects with high levels of antibodies to a pathogenic strain of *P. gingivalis* (OR 2.38; 95% CI, 1.16–4.90, comparing >200 ng/mL vs. <200 ng/mL) after adjusting for known risk factors, including smoking (8). No associations were detected for other oral bacteria tested in that study. In a separate study, which combined data from two large prospective cohort studies of Caucasian women, a 1.6-fold increased risk of pancreatic cancer was reported for presence of *P. gingivalis* taxa in the oral microbiome from saliva, and a 2-fold increased risk was observed for higher mean of *Aggregatibacter actinomycetemcomitans* taxa, another periodontal pathogen (9).

One of the keystone bacteria for periodontal disease, *P. gingivalis*, has been extensively studied because of its unique ability to evade the immune response (22) and its potential role in cardiovascular disease. Although the biological mechanisms through which this bacteria may cause cancer are complex and multifaceted, *P. gingivalis* has been shown to alter dendritic cell maturation, and promote expansion of myeloid-derived suppressor cells (23), thereby influencing the key immune pathways known to play a role in carcinogenesis. In an oral-specific chemical carcinogenesis murine model (24), chronic infection with *P. gingivalis* was shown to promote tumor growth. Other oral pathobionts may also be involved in cancer growth and promotion through modulation of the immune response, and may play a role in pancreatic cancer; for example, *Fusobacterium nucleatum*, an oral bacterium associated with colorectal cancer, was recently identified in pancreatic tumors (25). Research in this field is quickly evolving, and substantial effort will be needed to elucidate pathways and causality.

Table 3. Measures of oral health in relation to incidence of pancreatic cancer, stratified by cigarette smoking

Self-reported oral health		Nonsmokers		Current smokers	
Periodontal disease	**Tooth loss**	**Cases, *N***	**Multivariable HR (95% CI)**	**Cases, *N***	**Multivariable HR (95% CI)**
No	No	8	Reference	5	Reference
No	Yes	31	2.53 (1.12–5.68)	18	1.41 (0.51–3.91)
Yes	No	4	2.92 (0.87–9.81)	0	––
Yes	Yes	8	2.05 (0.74–5.70)	4	0.96 (0.25–3.76)
Any tooth loss		39	2.42 (1.09–5.37)	22	1.31 (0.48–3.58)

NOTE: Multivariable HRs adjusted for age, pack-years of smoking, alcohol consumption, BMI, and type 2 diabetes.

Pancreatic cancer is a rare disease; thus, even in this cohort of over 38,000 women followed for 10 years after providing data on oral health, there were only 78 incident cases available for analysis. The small sample size did not permit further stratification beyond current/nonsmoker. The exposure measures, number of teeth lost during adulthood, and gingivitis or periodontal disease, were self-reported. A validation study carried out in BWHS data indicated that women who reported periodontal disease did actually have that condition, but that many women were unaware of the disease. It is likely that an appreciable number of women with periodontal disease were classified as not having the condition in this analysis. This may explain why a statistically significant positive association was observed for any tooth loss in relation to pancreatic cancer risk, regardless of whether the participant also reported periodontal disease. Because the data on tooth loss and periodontal disease were obtained prior to the diagnosis of pancreatic cancer, misclassification of the exposures would have been nondifferential with regard to disease outcome. Such misclassification may have reduced the power to observe a true association, but would not have biased results toward an association.

Racial disparities in oral health are widely documented in the United States; African Americans have higher rates of tooth decay, root caries, tooth loss, edentulism, and periodontal disease than whites (11–13, 26). For example, in National Health and Nutrition Examination Survey (NHANES) data from 2011 to 2012, 60% of African Americans aged 30 and older had periodontitis compared with 39% of whites (12). Incidence of pancreatic cancer is also disproportionately high in African Americans, and the difference does not appear to be accounted for by known risk factors such as cigarette smoking (10, 27, 28). In fact, the prevalence of ever smoking and of heavy smoking is lower in African American women than in U.S. white women (29).

Results from this study suggest that poor oral health may play a role in racial disparities in pancreatic cancer incidence. The next step will be to determine whether specific micro-organisms found in the oral cavity are associated with incidence of pancreatic cancer in this population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The results reported do not necessarily represent the views of the NIH.

Authors' Contributions

Conception and design: J.R. Palmer
Development of methodology: J.R. Palmer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y.C. Cozier, J.R. Palmer
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Gerlovin, D.S. Michaud, Y.C. Cozier, J.R. Palmer
Writing, review, and/or revision of the manuscript: H. Gerlovin, D.S. Michaud, Y.C. Cozier, J.R. Palmer
Study supervision: J.R. Palmer

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