

Tooth loss, pancreatic cancer, and *Helicobacter pylori*¹⁻³

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ABSTRACT

Background: Poor dental health has been associated with increased risks of oral, esophageal, and gastric cancer and may also be associated with pancreatic cancer. In addition, *Helicobacter pylori* has been found in dental plaque and has been associated with periodontal disease and pancreatic cancer.

Objective: The objective was to investigate prospectively the relation between dentition history and pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort in Finland and the association between dentition history and *H. pylori* seropositivity in a cross-sectional sample of subjects without cancer ($n = 475$) from the same cohort.

Design: Of the 29 104 male smokers aged 50–69 y in the cohort for whom there were complete data, 174 developed pancreatic cancer from 1985 to 1997. Cox proportional hazard models were used to estimate age-, smoking-, education-, urban living-, and height-adjusted hazard ratios and 95% CIs for pancreatic cancer, and logistic regression models were used to estimate age- and education-adjusted odds ratios for *H. pylori* carriage.

Results: Tooth loss was positively associated with pancreatic cancer (edentulous compared with missing 0–10 teeth: hazard ratio = 1.63; 95% CI: 1.09, 2.46; P for trend = 0.02) but was not significantly associated with *H. pylori* seropositivity (edentulous compared with missing 0–10 teeth: odds ratio = 1.30; 95% CI: 0.73, 2.32; P for trend = 0.37).

Conclusion: Additional studies are needed to evaluate the association between tooth loss and pancreatic cancer, as well as cancers at other gastrointestinal sites, particularly with respect to possible biological mechanisms. *Am J Clin Nutr* 2003;78:176–81.

KEY WORDS Pancreatic cancer, *Helicobacter pylori*, tooth loss, male smokers, Finland

INTRODUCTION

Although pancreatic cancer (exocrine adenocarcinoma) is a relatively uncommon cancer, it is a major cause of cancer mortality, ranking eighth in the world, according to the International Agency for Research on Cancer, and fifth in the United States (1). It is most often diagnosed at advanced stages, which contributes to its survival rates being among the poorest. Only a few risk factors have been identified; of these, cigarette smoking is the most consistent.

The oral cavity provides a gateway between the external environment and the gastrointestinal tract, and it facilitates both food ingestion and digestion. Oral hygiene and tooth loss can potentially affect gastrointestinal flora and nutritional status, and thus

they have implications for the development of chronic diseases. Poor dental health, tooth loss, or both have been associated with increased risk for gastrointestinal malignancies, including oral (2–6), esophageal (7), and gastric (8–10) cancers. The consequences of poor oral hygiene are dental plaque, periodontal disease, and tooth loss (11). Tooth loss may be a surrogate measure of the bacterial load on teeth mediated through poor dental hygiene in the past (12, 13) and possibly a marker for the presence of endogenous bacteria in general, particularly gastrointestinal flora. Several studies suggested that dental plaque is a reservoir for *Helicobacter pylori* (14–20), and one large study ($n = 4500$) that used data from the United States National Health and Nutrition Examination Survey showed that periodontal disease, specifically periodontal pocket depth, was associated with seroprevalence of *H. pylori* (21). Furthermore, gastric carriage of *H. pylori* is a known risk factor for gastric cancer (22), with the cytotoxin-associated gene-A-positive (CagA+) strain having a greater propensity for inflammation, ulceration, and malignancy (22). Recently, we reported a positive association for *H. pylori* and CagA+ strain carriage and pancreatic cancer (23).

We hypothesize that tooth loss may be associated with pancreatic cancer, as well as *H. pylori* seropositivity. The purpose of this study is to examine the association between dentition history and pancreatic cancer in a prospective cohort of male smokers and that between dentition history and *H. pylori* seropositivity in a cross-sectional sample from the same cohort.

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SUBJECTS AND METHODS

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a placebo-controlled, double-blinded, 2×2 factorial design, primary prevention trial that tested the hypothesis of whether α -tocopherol or β -carotene reduced the incidence of lung cancer in male smokers (24). Between 1985 and 1988, 29 133 eligible men aged 50–69 y in southwestern Finland who smoked ≥ 5 cigarettes/d were randomly assigned to receive supplements (50 mg α -tocopherol/d, 20 mg β -carotene/d, or both) or placebo. Exclusion criteria from the study included a history of malignancy other than nonmelanoma cancer of the skin or carcinoma in situ, severe angina on exertion, chronic renal insufficiency, cirrhosis of the liver, chronic alcoholism, current anticoagulant therapy, other medical problems that might limit long-term participation, or current use of supplements containing vitamin E (> 20 mg/d), vitamin A ($> 20\,000$ IU/d), or β -carotene (> 6 mg/d). The trial ended 30 April 1993, and follow-up continued after randomization for the present study through November 1997 or until death, representing follow-up for ≤ 13 y (median: 10.2 y). The study was approved by the institutional review boards of both the US National Cancer Institute and the National Public Health Institute in Finland, and all study participants provided written informed consent before the initiation of the study. Details of the study rationale, design, and methods were described previously (24).

Baseline characteristics, smoking, and dietary factors

At their baseline visit, the study participants completed questionnaires on general background characteristics including self-reported medical, dentition, smoking, and dietary history. Dentition was assessed by asking subjects "How many permanent teeth are you missing: none, 1–5 teeth, 6–10 teeth, > 10 but not all teeth, or all teeth?" Diet was assessed with the use of a self-administered dietary history questionnaire, designed and validated specifically for the ATBC study, which determined the frequency of consumption and the usual portion size of > 200 food items during the past year, by using a booklet with color photographs as a guide for portion size (25). For 62 subjects with incomplete data on the number of years of smoking, we estimated that variable by subtracting the age at which each subject started smoking from his age at randomization. Height and weight was also measured at baseline.

Case ascertainment

Cases were identified from the Finnish Cancer Registry, which provides $\approx 100\%$ case ascertainment in Finland (26, 27). All relevant medical records for reported cases of pancreatic cancer were reviewed independently by 2 study physicians (24). Only cases confirmed by the study physicians as incident primary malignant neoplasm of the exocrine pancreas, coded ICD9–157 in the *International Classification of Diseases, 9th revision, Clinical Modification* (28), were used for this analysis. In 80% of these cases, the diagnosis was based on histopathologic and cytologic specimens. Because their etiology may differ from that of the exocrine tumors, islet cell carcinomas (ICD9–157.4; 28) were excluded. During the follow-up period, there were 174 confirmed cases of adenocarcinoma of the exocrine pancreas, all with complete dentition history.

Subjects with *H. pylori* serologic tests

Four hundred seventy-five controls from the ATBC study cohort with *H. pylori* serologic tests from 2 previous simultaneous

pancreas and colorectal cancer studies were used to assess the association between dentition and *H. pylori* carriage (23, 29). Fasting serum was collected at the prerandomization baseline visit and stored at -70°C . Frozen baseline serum samples from these subjects were assayed for antibodies to *H. pylori* whole cell (WC) and CagA antigen with previously described and validated methods (23, 30–32). Briefly, serologic tests for immunoglobulin G antibodies to *H. pylori* WC and CagA strain were performed with the use of an antigen-specific enzyme-linked immunosorbent assay. Serum samples were diluted 1:800 and 1:100, respectively, for the *H. pylori* WC and CagA antigen determinations, and optical density for each was calculated from the mean reading of duplicate assays of the same sera, run on separate days. Subjects were considered seropositive on the basis of established cutoffs: ie, the optical density of the immunoglobulin G antibodies for *H. pylori* WC was ≥ 1.0 or that for CagA was ≥ 0.35 . Overall disagreement on *H. pylori* classification between the first and second run was 8%. For those samples with discordant *H. pylori* classification between the duplicate assays, a third run was performed. After the third assay, the one with the greatest variation from the other 2 was discarded, and the results of the remaining 2 were averaged. The sensitivity and specificity for the *H. pylori* WC assay are $> 92\%$ (30) and those values for the CagA assay are 94% and 93% (31), respectively. Our samples had blinded, replicate, quality-control phantom samples (one *H. pylori*-seropositive subject and one -seronegative subject), placed toward the beginning and the end of each batch, constituting $< 10\%$ of each batch. The percentage agreement for classifying *H. pylori* seropositivity on the basis of cutoffs for the blinded repeated samples was 100% for the WC assay and 99% for the CagA assay.

Statistical analysis

Follow-up time for each participant was calculated from the date of randomization until the diagnosis of pancreas cancer, death, or November 1997; this totaled 278 044 person-years of observation. Only subjects with complete dentition and smoking history, anthropometry, education, and urban living data ($n = 29\,104$) were included in the analyses. Generalized linear models adjusted for age were used to estimate means and 95% CIs of the cohort characteristics by dentition history for continuous variables to help identify potential confounders. Because disease history variables were proportions, logistic regression was used to estimate age-adjusted proportions and 95% CIs by dentition history. A test for trend was performed for each characteristic across the 3 tooth-loss categories described below. The trend test used contrast coefficients based on the midpoint of each dentition category and centered these values on their mean (ie, the 3 tooth-loss categories used 19.3 teeth for the mean and yielded contrast coefficients of -14.3333 , 1.6667 , and 12.6667).

Cox proportional hazard models were used to determine hazards ratios (HR) and 95% CIs. Because the number of cases in which subjects lost no teeth or 6–10 teeth were low ($n = 3$ and 8 , respectively) and because we wanted to give more stable risk estimates and balance the teeth categories according to the distribution in the cohort, the dentition histories of the subjects who lost no teeth, 1–5 teeth, and 6–10 teeth were combined for the association models. This category was used as the reference and was compared with the category including the men who lost 11–31 teeth and those who were edentulous. Logistic regression was used to estimate odds ratios and 95% CIs for the cross-sectional analysis of tooth loss and *H. pylori* status. *H. pylori* serologic

TABLE 1Baseline age-adjusted characteristics by dentition history of selected subjects in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort¹

Characteristics	Dentition categories			P for trend
	0–10 teeth missing (n = 9393)	11–31 teeth missing (n = 10090)	Edentulous (n = 9621)	
Age (y)	55.4 (55.3, 55.5)	57.0 (56.9, 57.1)	59.2 (59.1, 59.3)	<0.0001
Height (cm)	174.3 (174.2, 174.4)	173.5 (173.4, 173.6)	173.0 (172.9, 173.1)	<0.0001
Weight (kg)	80.7 (80.5, 81.0)	79.1 (78.9, 79.4)	78.0 (77.8, 78.3)	<0.0001
BMI (kg/m ²)	26.54 (26.46, 26.62)	26.3 (26.2, 26.3)	26.0 (26.0, 26.1)	<0.0001
Living in a city (%)	49.1 (48.0, 50.0)	41.7 (40.7, 42.6)	36.6 (35.6, 37.6)	<0.0001
≤Primary school education (%)	66.3 (65.5, 67.2)	81.8 (81.1, 82.6)	88.3 (87.6, 88.9)	<0.0001
Disease history (%)				
Gallstones	6.0 (5.5, 6.4)	5.3 (4.9, 5.8)	5.1 (4.8, 5.7)	0.04
Pancreatitis	1.3 (1.0, 1.5)	1.5 (1.2, 1.7)	1.6 (1.4, 1.9)	0.08
Peptic or duodenal ulcers	15.8 (15.0, 16.6)	16.8 (16.0, 17.4)	20.0 (19.2, 20.8)	<0.0001
Diabetes mellitus	4.3 (3.9, 4.7)	4.1 (3.7, 4.5)	4.3 (3.9, 4.7)	0.85
Smoking history				
Cigarettes smoked/d (n)	19.3 (19.1, 19.5)	20.7 (20.6, 20.9)	21.2 (21.0, 21.4)	<0.0001
Years of smoking (n)	34.6 (34.5, 34.8)	36.3 (36.1, 36.4)	36.9 (36.8, 37.1)	<0.0001
Pack-years (n)	33.8 (33.5, 34.2)	37.8 (37.4, 38.1)	39.2 (38.8, 39.6)	<0.0001
Dietary intake ²				
Energy (kcal)	2755.8 (2739.1, 2772.4)	2833.0 (2817.2, 2848.8)	2852.4 (2835.8, 2869.0)	<0.0001
Carbohydrate (g)	294.7 (293.8, 295.6)	295.1 (294.3, 296.0)	297.6 (296.7, 298.5)	<0.0001
Fat (g)	118.0 (117.7, 118.4)	119.2 (118.8, 119.5)	119.6 (119.2, 120.0)	<0.0001
Saturated fat (g)	57.1 (56.8, 57.4)	59.2 (58.9, 59.5)	60.5 (60.3, 60.8)	<0.0001
Folate (μg)	339.6 (338.4, 340.8)	329.0 (327.8, 330.1)	320.1 (318.9, 321.3)	<0.0001
Alcohol (g)	19.5 (19.0, 19.9)	18.2 (17.8, 18.6)	16.3 (15.8, 16.7)	<0.0001

¹ \bar{x} ; 95% CI in parentheses.²Adjusted for energy, except alcohol intake, and cohort restricted to n = 27088.

results were defined as negative (having antibodies to neither WC nor CagA antigens), positive (having antibodies to WC or CagA+ antigens or both), positive with CagA– strain (having antibodies to WC antigen but not to CagA+ antigen), or positive with CagA+ strains (having antibodies to CagA+ antigen). Trends across dentition categories were tested with the use of a calculated score variable.

Potential confounders were added to individual models in a stepwise fashion and were included if they were associated with both the disease and the risk factor, changed the risk estimate $\geq 10\%$, had a P value ≤ 0.20 in the full model, or increased the precision of the risk estimates by narrowing the CI. Although none of the smoking history variables (number of years of smoking, cigarettes smoked/d, and cigarette pack-years) significantly altered the risk estimates, the number of years of smoking was included in the proportional hazards models because smoking is a consistent risk factor for pancreatic cancer. Other baseline variables examined as potential confounders included age; height; weight; body mass index (in kg/m²); urban living; education; medical history of gallstones, pancreatitis, peptic and duodenal ulcers, or diabetes mellitus; and dietary energy, energy-adjusted carbohydrate, fat, saturated fat, folate, and alcohol (1, 33–39). For the logistic regression models examining tooth loss and *H. pylori* seroprevalence, carotenoids, vitamins C and E, and serum β -carotene and cholesterol-adjusted α -tocopherol were also assessed for confounding (37, 38). The dietary variables used to examine confounding were energy-adjusted with the use of the residual method described by Willett and Stampfer (40); alcohol intake was an exception because it was not strongly correlated to energy. The analyses were initially restricted to subjects with complete dietary data, but, because the addition of these variables to

models did not alter risk estimates, this restriction was relaxed. Effect modification of tooth loss and pancreatic cancer by having complete dietary data was examined by stratification and by using the addition of interaction terms for the categorical diet and trend for tooth loss variable. All statistical analyses were performed with the use of SAS software, version 8.2 (SAS Institute Inc, Cary, NC), and statistical tests were two-tailed with statistical significance set at P = 0.05.

RESULTS

The age-adjusted baseline characteristics of the cohort by dentition history are shown in **Table 1**. Across the 3 tooth-loss categories, those with fewer teeth were older; were shorter; weighed less; had a lower BMI; lived in a more rural area; had less education; were more likely to have a history of gallstones and peptic and duodenal ulcers; smoked for more years and had greater daily and cumulative smoking doses (pack-years); and had greater energy and energy-adjusted carbohydrate, total fat, and saturated fat intake and less energy-adjusted folate and alcohol intake (for each characteristic: P < 0.05), but they did not differ significantly with respect to pancreatitis or diabetes mellitus.

Tooth loss was significantly associated with pancreatic cancer with a significant trend across categories (**Table 2**). Age confounded the risk estimates of the association between tooth loss and pancreatic cancer, whereas the other potential confounding variables did not significantly alter the risk estimates in the models; however, education, urban living, and height increased the precision of the risk estimates, and they were included in the multivariable models.

TABLE 2

Hazards ratios (HRs) for pancreatic cancer according to dentition history of selected subjects in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort

Dentition category	Person-years	Age-adjusted HR	95% CI	<i>P</i> for trend	Multivariate HR ¹	95% CI	<i>P</i> for trend
0–10 teeth missing (<i>n</i> = 42)	93 359	1.00 (reference)			1.00 (reference)		
11–31 teeth missing (<i>n</i> = 57)	96 852	1.20	0.80, 1.79		1.23	0.82, 1.85	
Edentulous (<i>n</i> = 75)	87 833	1.55	1.04, 2.30	0.03	1.63	1.09, 2.46	0.02

¹Adjusted for age, number of years of smoking, education, urban living, and height (by quintile trend variable).

Among the cohort subset with complete dietary data (cohort: *n* = 27 088; cases: *n* = 163), the risk estimates for tooth loss and pancreatic cancer were marginally nonsignificant in the age-, smoking-, education-, urban living-, and height-adjusted models (11–31 teeth missing: HR = 1.19; 95% CI: 0.78, 1.80; all teeth missing: HR = 1.50; 95% CI: 0.99, 2.28); however, there was a trend of borderline significance across tooth-loss categories (*P* for trend = 0.05). Further adjustment for the dietary factors in these models did not substantially change the risk estimates. Risk estimates for tooth loss and pancreatic cancer within the stratum for those with incomplete dietary data were not calculable with the use of the above dentition classification, because none of the 11 cases in the stratum were in the reference group of those having lost ≤ 10 teeth. Effect modification of the association by completion of the dietary questionnaire with dentition history categorized as edentulous or nonedentulous was not significant (unstratified adjusted risk ratio = 1.44; 95% CI: 1.04, 1.98; stratified adjusted risk ratio = 3.85; 95% CI: 0.98, 15.29; and risk ratio = 1.35; 95% CI: 0.97, 1.88, respectively, for incomplete and complete dietary data; *P* for interaction = 0.08). Subjects with incomplete dietary data were shorter (*P* < 0.001), weighed less (*P* = 0.02), were older (*P* < 0.001), had less education (*P* < 0.001), and had fewer teeth (*P* = 0.02) than did those with complete data, but the groups did not differ significantly by BMI or smoking habits (observations not shown, age-adjusted generalized linear models). Tooth loss was positively but not significantly associated with *H. pylori* or

CagA strain (Table 3), and age and education were the only factors that confounded the association.

DISCUSSION

We observed a significant positive association between tooth loss and pancreatic cancer and a weaker, nonsignificant positive association between tooth loss and prevalent *H. pylori* carriage. Also of interest is the fact that, compared with those with less tooth loss, the edentulous subjects were more likely to have peptic or duodenal ulcers, a condition for which *H. pylori* carriage is considered causal.

There are several mechanisms besides *H. pylori* carriage that may potentially explain the increased risk associated with tooth loss and pancreatic cancer. Tooth loss that occurs through poor dental hygiene may be a marker for more deleterious gastrointestinal flora and, consequently, greater endogenous nitrosation (41). Nitrosamines induce pancreatic cancer in animals and are considered potential human pancreatic carcinogens (1). Exogenous exposure to nitrate and nitrite comes from food and water and, in this study population, cigarette smoke. It has been estimated that 45%–75% of nitrosamine formation comes from endogenous formation by salivary and gastrointestinal bacteria converting nitrate to nitrite and nitrosamines (42–46), with the rest coming from immunostimulation and macrophage response via intermediate production of nitric oxide (47). In addition to *H. pylori*, a number of bacterial strains from various human

TABLE 3

Odds ratios (ORs) for *Helicobacter pylori* positivity according to dentition category in selected subjects in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort¹

Dentition category	<i>H. pylori</i> -positive	<i>H. pylori</i> -negative	Crude OR	95% CI	<i>P</i> for trend	Multivariate OR ²	95% CI	<i>P</i> for trend
0–10 teeth missing [<i>n</i> (%)] ³	115 (32)	39 (34)	1.00 (reference)			1.00 (reference)		
11–31 teeth missing [<i>n</i> (%)]	104 (29)	45 (39)	0.78	0.47, 1.29		0.72	0.43, 1.21	
Edentulous [<i>n</i> (%)]	141 (39)	31 (27)	1.54	0.91, 2.62	0.11	1.27	0.73, 2.20	0.45
CagA ⁴								
0–10 teeth missing [<i>n</i> (%)] ⁵	82 (31)	39 (34)	1.00			1.00		
11–31 teeth missing [<i>n</i> (%)]	74 (28)	45 (39)	0.78	0.46, 1.33		0.69	0.40, 1.20	
Edentulous [<i>n</i> (%)]	107 (41)	31 (27)	1.64	0.95, 2.85	0.07	1.30	0.73, 2.32	0.37

¹*n* = 475. CagA+, cytotoxin-associated gene-A-positive.

²Adjusted for age and education.

³From the following subcategories: 0, 1–5, and 6–10 teeth missing. *H. pylori*-negative: *n* = 0 (0%), 18 (15.7%), and 21 (18.3%) for the subjects with 0, 1–5, and 6–10 teeth missing, respectively. *H. pylori*-positive: *n* = 4 (1.1%), 53 (14.7%), and 58 (16.1%) for the subjects with 0, 1–5, and 6–10 teeth missing, respectively.

⁴Excluding *H. pylori*-positive, CagA-negative.

⁵From the following subcategories: 0, 1–5, and 6–10 teeth missing. CagA+: *n* = 3 (1.1%), 40 (15.2%), and 39 (14.8%) for the subjects with 0, 1–5, and 6–10 teeth missing, respectively.

sources, including *Escherichia coli*, *Campylobacter jejuni*, and *Neisseria cinerea*, catalyze the formation of nitrosamines (41, 42, 48). Endogenous formation of nitrosamines in the oral cavity in persons with poor oral hygiene is 8-fold that in persons with good hygiene (41). More studies are needed to examine oral hygiene and gastrointestinal bacteria to quantify nitrosamine formation in the small intestine in smokers and nonsmokers.

Tooth loss may also be an indicator of a less healthy lifestyle or of health status in general, and the association that we observed may be attributed to uncontrolled or residual confounding. Subjects who were edentulous tended to be older, to live in a more rural environment, to have less education, and to be shorter, although none of these factors except age confounded the association that was observed between tooth loss and pancreatic cancer. Living in a more rural environment and having less education are surrogates for socioeconomic status. Shorter stature may be a marker for poor nutrition and greater exposure to infections with exogenous pathogens and colonization of endogenous microbes during childhood (49). Tooth loss also reduces masticatory ability (50–52) and hence may lead to the consumption of a less healthy diet (37, 38, 50, 53), which could be associated with disease. Subjects who were edentulous had greater total and saturated fat intake and less folate intake; these dietary factors were associated with pancreatic cancer in our cohort (34, 54). However, the inclusion of these factors in models did not alter the association we found between tooth loss and pancreatic cancer. The risk estimates for the analysis limited to those with complete dietary information, although not as statistically significant as those for the analysis that included all subjects (Table 2), were similar in magnitude and in the same direction (compared with ≤ 10 missing teeth, 11–31 missing teeth: HR = 1.19; 95% CI: 0.78, 1.80; edentulous: HR = 1.50; 95% CI: 0.99, 2.28; P for trend = 0.05). Although confounding from unmeasured factors related to an inability to complete the dietary questionnaire (eg, intestinal bacteria or less healthy behavior) may explain this attenuated risk, it is more likely due to a smaller number of cases and marginal power to examine the association.

We did not find a significant association between tooth loss and *H. pylori* seropositivity (antibodies in the blood). In addition, in a separate analysis of all subjects (cases and controls) included in our previous study that showed an association between *H. pylori* and pancreatic cancer (23)—who may be considered to make up a sample that would provide a more direct measure of our hypothesis—dentition history was not associated with *H. pylori* seropositivity (observations not shown). The human gastric mucosa is presently thought to be the bacteria's only reservoir (55). One hypothesized mode for person-to-person *H. pylori* transmission is oral (gastric-oral) (55), and *H. pylori* has been cultured or its DNA detected from dental plaque (14–17, 19, 20, 56), tongue scrapings (18), saliva, and vomit (55). We did not measure *H. pylori* in the oral cavity, and therefore we cannot directly answer the question of whether oral hygiene or tooth loss provides an environment within which *H. pylori* can grow. In addition, those who are edentulous may have fewer surfaces with plaque for *H. pylori* to orally colonize. Tooth loss could, however, be a surrogate marker for past bacterial load on teeth and perhaps for the presence of endogenous bacteria in general. Because our subjects are part of an older population, it is also possible that the edentulous subjects in the cross-sectional analysis of *H. pylori* carriage may have had subclinical atrophic gastritis or intestinal metaplasia, conditions in which *H. pylori* disappears (22) and which could contribute to an attenuated association.

In conclusion, our study suggests a positive association between tooth loss and the development of pancreatic cancer. No association was observed between tooth loss and *H. pylori* carriage, however. The strength of this study is that it was large and prospective and included a substantial number of cases to provide adequate power to detect differences in risk. Because the subjects in this study were older male smokers (ie, a group at high risk of pancreatic cancer), our results may not be generalizable to non-smoking populations. Further studies are needed to evaluate the association of tooth loss and pancreatic cancer in other populations, as well as the possible role of gastrointestinal nitrosamine formation by intestinal bacteria in smokers and nonsmokers. ☞

RZS-S designed the study for tooth loss, pancreatic cancer, and *Helicobacter pylori*; performed the data analysis; and wrote the manuscript. KD advised and helped with the statistical analysis. MJB measured serum antibodies to *H. pylori* whole cell and cytotoxin-associated gene-A-positive antigen in his laboratory and provided comments on the manuscript. JV, co-principal investigator for the ATBC Study, contributed to the study design and data collection for the ATBC trial and the ongoing follow-up study and provided comments on the manuscript. PRT contributed to the study design and data collection for the ATBC trial and the ongoing follow-up study and provided comments on the manuscript. DA, co-principal investigator for the ATBC Study, contributed to the study design and data collection for the ATBC trial and the ongoing follow-up study and provided comments on the manuscript.

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