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Tooth loss and liver cancer incidence in a Finnish cohort

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Abstract

Purpose—Periodontal disease, a major cause of tooth loss in adults, may have systemic effects and has been associated with higher risk of several cancer types. However, the associations of periodontal disease or tooth loss with liver cancer have only been examined prospectively in two studies, neither of which were sufficiently powered. In addition, no studies assessed the potential confounding by viral hepatitis or *Helicobacter pylori* infection status.

Methods—In this study, we examined the association between tooth loss and primary liver cancer incidence in a prospective cohort of Finnish male smokers (n = 29,096). We used Cox proportional hazards models to calculate multivariable-adjusted hazard ratios (HRs) and 95% CIs. As a sensitivity analysis, we conducted a nested case-control study within the original cohort to assess confounding by hepatitis B or C virus infection and seropositivity of *H. pylori*.

Results—A total of 213 incident primary liver cancers occurred during a mean follow-up of 17 years. Having 11–31 permanent teeth lost (HR 1.42, 95% CI 1.01–1.98) or all 32 teeth lost (HR 1.45, 95% CI 1.00–2.10) was each associated with higher risk of liver cancer, compared to having 0–10 teeth lost. Adjusting for *H. pylori* seropositivity yielded a small attenuation of the effect estimate.

Conclusions—Greater number of teeth lost was associated with higher risk of primary liver cancer in our study. The role of periodontal infection in the development of liver cancer warrants further investigation.

Keywords

oral health; tooth loss; liver cancer; cohort study

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Introduction

Liver cancer is the sixth most commonly occurring cancer in the world and the second leading cause of cancer mortality [1]. Risk factors for liver cancer include hepatitis B virus (HBV), hepatitis C virus (HCV), consumption of aflatoxin-contaminated foods, excessive alcohol consumption, cigarette smoking, obesity and diabetes [2]. These risk factors cause chronic hepatic inflammation which can progress to fatty liver disease, fibrosis, cirrhosis, and eventually, liver cancer [2]. As the effectiveness of liver cancer screening is low [3] and prognosis is poor [4], it is critical to identify modifiable risk factors and develop preventive strategies to reduce the burden of liver cancer.

Periodontal disease, a highly prevalent condition worldwide, is defined as any inherited or acquired disorder of the tissue surrounding and supporting the teeth [5]. Severe periodontal infection (periodontitis) can result in loss of connective tissue and bone support [5], which is an important cause of tooth loss in older populations [6]. A major cause of periodontal disease is infection by oral microorganisms, such as *Porphyromonas gingivalis* [5]. It has been reported that oral administration of *P. gingivalis* in mice leads to increased dissemination of enterobacteria to the liver [7], which could be potentially hepatocarcinogenic [8]. However, only two studies prospectively examined the association of periodontal disease or tooth loss with liver cancer mortality (which can provide insights into liver cancer incidence due to the high fatality of this disease), and both studies had small number of outcomes. In the NHANES III, the crude mortality rate for liver cancer was five-fold higher for those with periodontitis, but the number of liver cancer death was too small (n=14) to permit the calculation of adjusted relative risks [9]. A Japanese cohort study reported no association between tooth loss and liver cancer mortality, but the analysis was based on a total of 13 liver cancer deaths [10]. In addition, another Japanese study used a case-control design with 167 liver cancer cases, and observed higher risk of liver cancer for those with 9–20 teeth remaining, but not for those with <9 teeth remaining [11]. Notably, none of the studies above evaluated potential confounding by HBV or HCV infection, major risk factors for liver cancer [2]. There is also evidence that *Helicobacter pylori* infection may be associated with poor periodontal health [12] as well as increased risk of liver cancer [13], thus making it a potential confounder; however, confounding by *H. pylori* infection has not been assessed in previous studies.

Given the dearth of literature and gaps in knowledge, we examined the association between tooth loss and primary liver cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study.

MATERIALS AND METHODS

Study population and data collection

The ATBC study was a randomized controlled trial to test the effects of α -tocopherol and β -carotene on cancer incidence among Finnish male smokers [14]. To be eligible, the participants had to be male, aged 50–69 years at baseline, and smokers of at least five cigarettes per day at study entry. Potential participants were excluded if they had malignant cancer (other than non-melanoma skin cancer), severe cirrhosis, chronic alcoholism, or other

conditions that would limit their participation in the trial [14]. The study was approved by the Institutional Review Boards of both the National Institutes of Health of the United States and the National Public Health Institute of Finland.

At trial baseline (1985–1988), 29,133 Finnish men were randomized to three intervention groups (50 mg α -tocopherol/day, 20 mg β -carotene/day, or both) or to a placebo group and completed a questionnaire that collected information on demographics, medical history, diet, and lifestyle factors. Dentition was assessed at baseline 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?” Participants also provided blood samples at baseline. After excluding participants with missing dentition information (n=9) and any history of cirrhosis (n = 28), 29,096 participants remained in our analysis.

The trial ended in 1993, but participants continue to be followed for cancer incidence and mortality; the current analysis uses data censored at December 31, 2012. We identified all cases of primary liver cancer (defined based on International Classification of Diseases [ICD]-9 codes 155.0 and 155.1) via the Finnish Cancer Registry.

Laboratory analysis

Seropositivity for *H. pylori*, defined using 15 specific *H. pylori* antigens, was previously measured using a multiplex serology assay in a subset of the ATBC study participants. Seropositivity for 4 antigens was defined as being *H. pylori* seropositive. Details of the assay, including the assay validation and sensitivity, have been previously described [13, 15].

Assays to determine hepatitis B virus surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and antibody to hepatitis C virus (anti-HCV) were previously conducted at the SAIC NCI-Frederick National Laboratory [16]. HBsAg was determined using an enzyme immunoassay from Bio-Rad Laboratories (Redmond, WA). Anti-HBc and anti-HCV were determined using ELISAs from Ortho-Clinical Diagnostics (Raritan, NJ).

Statistical analysis

We used Cox proportional hazards modeling to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Person-time for each participant was calculated from the date of randomization until the date of liver cancer diagnosis, death, or the end of follow-up, whichever came first. Tooth loss was categorized as missing 0–10 teeth (reference group), 11–31 teeth, and all 32 teeth (edentulous). We combined the first three categories of tooth loss on the questionnaire (0, 1–5, and 6–10 teeth missing) because of relatively small numbers in each category. The Wald test was used to assess linear trends for the association of tooth loss with liver cancer incidence and liver disease mortality; we assigned the middle value between the upper and lower limits for each category (i.e., for the category of 11–31 teeth lost we assigned the value of 21) and modeled it as a continuous variable. We stratified the baseline hazard function by age at baseline (5-year group). Additionally, we adjusted for education (elementary school or less with no vocational training, elementary school or less with some vocational training, and high school or above), body mass index (BMI, kg/m², <25, 25–<30, and ≥ 30), smoking pack-years (quartiles), alcohol consumption (quartiles) and coffee consumption (quartiles) because these variables changed the HR estimate for tooth

loss by >10%. Because age is a strong risk factor for tooth loss, we performed analyses with additional adjustment of age and age squared in the model, but our estimates for tooth loss did not change materially. Other variables that were examined but not included in the final model because they did not alter the estimate were trial randomization arm, history of diabetes, number of cigarettes per day, and consumption of fruits/vegetables, vitamin C, vitamin D, vitamin E, and red/processed meat. Furthermore, we evaluated effect measure modification by the following factors selected *a priori*: age, education, body mass index, smoking pack-years, cigarettes per day, and alcohol consumption, using likelihood ratio tests.

In a sensitivity analysis, we assessed confounding by *H. pylori* seropositivity, HBV infection, and HCV infection in a subset of cases and matched controls who had available data on these variables. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for the same set of covariates as in the Cox models, with or without additional adjustment of *H. pylori* seropositivity, HBV infection, and HCV infection. Other sensitivity analyses performed included 1) using age as the underlying time metric; and 2) excluding the first two years of follow-up to reduce the possibility that preclinical, undiagnosed liver cancer may have caused tooth loss (reverse causation).

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). All statistical tests were two sided, and p values of less than 0.05 were considered statistically significant.

RESULTS

Table 1 presents the characteristics of study participants according to the number of permanent teeth that were missing at baseline. Individuals with greater tooth loss were older, less well-educated, had greater overall smoking exposure, consumed less alcohol and consumed more coffee.

During a mean follow-up of 17.0 years, 213 incident primary liver cancers occurred. As shown in Table 2, after multivariable adjustment, having 11–31 permanent teeth lost was associated with a 42% higher risk of liver cancer (HR 1.42, 95% CI 1.01–1.98), and having all 32 teeth lost was associated with a 45% higher risk of liver cancer (HR 1.45, 95% CI 1.00–2.10), compared to having 0–10 teeth lost. Adjusting for coffee consumption and education had the most influence on the multivariable HR. However, there was no linear association between the number of teeth lost and liver cancer risk ($p_{\text{trend}} = 0.68$). Using age as the underlying time metric or excluding the first 2 years of follow-up did not materially change the estimates, and no effect modification was observed by age, education, body mass index, cigarette smoking dose, alcohol consumption, and coffee consumption (stratified results shown in Supplementary Table 1).

Data on *H. pylori* seropositivity, HBV and HCV were available on 112 cases and 269 controls. Among the 112 cases, 2 were positive for HBV, 7 were positive for HCV, and 106 were seropositive for *H. pylori*. Among the 269 controls, 2 were positive for HBV, 3 were

positive for HCV, and 245 were seropositive for *H. pylori*. As shown in Table 3, compared to the model with the same set of covariates as the Cox model, the model with additional adjustment for *H. pylori* seropositivity yielded an approximately 8% decrease in OR, whereas the models with additional adjustment for HBV or HCV infection did not materially change the OR.

DISCUSSION

In this cohort of Finnish male smokers, we observed that a greater number of permanent teeth lost was associated with moderately increased risk of primary liver cancer, after adjusting for age and other important covariates. This is the first prospective study with sufficient power to examine the association between tooth loss and liver cancer incidence.

Previous studies have reported positive associations of periodontal infection (including studies using tooth loss as a proxy) with several cancer outcomes, including oral cancer [17], gastric cancer [18], esophageal cancer [19], and pancreatic cancer [20]. Although liver cancer has been included in studies that examined all-cancer incidence or mortality, it has been rarely examined as an individual outcome. A prospective study based on NHANES III reported higher mortality rate for liver cancer for those with periodontitis, but it is unclear how much this association was due to confounding as this comparison was made without adjusting for covariates [9]. In addition, in a Japanese case-control study there was some suggestion of increased risk of liver cancer with tooth loss, however this association was not consistently observed among various categories of tooth loss [11].

In our large prospective cohort, we observed higher risk of liver cancer with increased number of permanent teeth lost. Several mechanisms underlying this association are hypothesized. Tooth loss could be the result of periodontal disease, especially among the older population [6]. It is established that oral bacterial infection is a major cause of periodontal disease [5]. Oral bacteria may locally accelerate the activation of smoking- and alcohol-related carcinogens, however this mechanism may be more relevant to oral cancer than cancers at distant sites such as the liver [21]. For cancers at distant sites, systemic effects following periodontal infection may be involved in carcinogenesis, including impaired glycemic control and endothelial function and an increased level of inflammation [21, 22]. Specifically, there is evidence in murine studies that oral administration of *P. gingivalis* [5] leads to impaired gut barrier function, increased serum endotoxin levels, and dissemination of enterobacteria to the liver [7], which could be hepatocarcinogenic [8]. Finally, periodontal disease could be a proxy measure of an individual's immune dysfunction, as failure in clearing infection may indicate deficiency in tumor surveillance and may have implications in cancer development [22].

Alternatively, our results could be partially explained by confounding. As suggested by our subset analyses (Table 3), additional adjustment of *H. pylori* seropositivity yielded a small attenuation of the effect estimates. Age is a strong predictor of both tooth loss and liver cancer risk, and although we extensively adjusted for age using multiple approaches, residual confounding remains possible. Previous studies have constructed median tooth loss at each age by a loess smooth of age-specific medians, and categorized the main exposure

based on this loess-predicted median [23], however our study was not able to use this fine approach to adjust for age as we lack the exact number of teeth lost for each individual. Other major potential confounders, as summarized in a recent review article, include smoking, socioeconomic factors, history of diabetes, and change of diet [22]. We included pack-years of smoking and education in the model; diabetes and dietary factors were evaluated as potential confounders but did not confound risk estimates for tooth loss.

The major strengths of this study include its prospective design and large sample size. We were able to assess potential confounding by a large number of demographic, diet and lifestyle factors. Of note, we demonstrated for the first time that the tooth loss-liver cancer association might be modestly confounded by *H. pylori* seropositivity (which may in fact reflect seropositivity to *Helicobacter* species other than *Pylori*), and this could be an important consideration for future studies. This study also had a number of limitations. Tooth loss is largely caused by periodontal disease in older populations [6] and has often been used as a proxy measure of periodontal disease in epidemiologic studies [22]; however, self-reported or clinically recorded periodontal disease would be more ideal for the exposure assessment [22]. We lack data on the exact number of teeth lost for each individual, which prohibits more precise control of age as a potential confounder, using loess smooth of age-specific medians as discussed above [23]. It has been suggested that studies on periodontal infection and disease outcomes be restricted to never-smokers to eliminate confounding by smoking [24]. Our study, by design, included only smokers. Nevertheless, we adjusted for pack-years of smoking, and given the moderate strength of association between cigarette smoking and liver cancer [25], it is unlikely that any residual confounding is substantial. Because our analysis only included smokers, the generalizability of our findings may be limited.

In conclusion, in this large prospective study of male Finnish smokers, a greater number of teeth lost was associated with increased risk of primary liver cancer. Further investigations are needed to clarify the role of periodontal infection in the development of liver cancer, or explore other mechanisms by which tooth loss may be involved in liver cancer etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HBV	hepatitis B virus
HCV	hepatitis C virus
ATBC	Alpha-Tocopherol, Beta-Carotene

ICD	International Classification of Diseases
HBsAg	hepatitis B virus surface antigen
anti-HBc	antibody to hepatitis B core antigen
anti-HCV	antibody to hepatitis C virus
HR	hazard ratio
CI	confidence interval
BMI	body mass index
OR	odds ratio

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Table 1

Baseline characteristics of participants by the number of permanent teeth lost, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

	Number of permanent teeth lost		
	0–10 (n=9,391)	11–31 (n=10,085)	32 (edentulous) (n=9,620)
Age at randomization, years, mean (SD)	55.4 (4.3)	56.9 (4.9)	59.1 (5.1)
Body mass index, kg/m ² , mean (SD)	26.6 (3.7)	26.3 (3.9)	26.0 (3.8)
Total number of cigarettes/day, mean (SD)	20.0 (9.1)	20.8 (8.8)	20.5 (8.6)
Smoking pack-years, mean (SD)	33.5 (17.8)	37.8 (18.1)	39.7 (18.5)
Alcohol consumption, grams/day, mean (SD)	20.4 (22.7)	18.3 (21.4)	15.3 (20.1)
Coffee consumption, grams/day, mean (SD)	564 (335)	615 (352)	643 (360)
Education, n (%)			
Elementary school or less, no vocational training	1,973 (21.0)	3,423 (33.9)	4,136 (43.0)
Elementary school or less, some vocational training	4,257 (45.3)	4,825 (47.8)	4,338 (45.1)
High school or above	3,158 (33.6)	1,830 (18.2)	1,131 (11.8)
Original randomization arm, n (%)			
Placebo	2,409 (25.7)	2,484 (24.6)	2,387 (24.8)
Beta-Carotene only	2,330 (24.8)	2,554 (25.3)	2,389 (24.8)
Alpha-Tocopherol only	2,348 (25.0)	2,509 (24.9)	2,420 (25.2)
Alpha-Tocopherol + Beta-Carotene	2,304 (24.5)	2,538 (25.2)	2,424 (25.2)

Abbreviations: SD, standard deviation.

Table 2

Association of tooth loss with primary liver cancer incidence, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

Number of permanent teeth lost	Events, n	Person-years	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI) ^a
0–10 teeth	66	178,787	Ref	Ref
11–31 teeth	81	171,693	1.26 (0.90, 1.74)	1.42 (1.01, 1.98)
32 teeth	66	144,419	1.15 (0.80, 1.63)	1.45 (1.00, 2.10)
P _{trend}			0.42	0.68

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Adjusted for age at baseline, education, body mass index, smoking pack-years, alcohol consumption and coffee consumption.

Table 3

Association between tooth loss and liver cancer incidence with and without adjustment for *Helicobacter pylori* seropositivity, HBV infection, and HCV infection in a subset of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

Number of permanent teeth lost	Cases (n=112) No.	Controls (n=269) No.	Multivariable-adjusted OR (95% CI)
Model with original set of covariates ^a			
0–10 teeth	28	100	Ref
11–32 teeth	84	169	1.90 (0.90–4.04)
Model with additional adjustment of <i>H. pylori</i> only			
0–10 teeth	28	100	Ref
11–32 teeth	84	169	1.75 (0.81–2.78)
Model with additional adjustment of HBV infection only			
0–10 teeth	28	100	Ref
11–32 teeth	84	169	1.95 (0.91–4.17)
Model with additional adjustment of HCV infection only			
0–10 teeth	28	100	Ref
11–32 teeth	84	169	1.94 (0.88–4.28)

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio.

^a Adjusted for age at baseline, education, body mass index, smoking pack-years, alcohol consumption and coffee consumption.