LETTER

Periodontal disease, tooth loss, and risk of oesophageal and gastric adenocarcinoma: a prospective study

We read with great interest the study by Coker *et al*[1] that provided supportive evidence for the role of oral microbiota in gastric cancer. A few studies also highlighted the possible link with oesophageal cancer.[2–4] However, there is a lack of robust epidemiologic data on whether periodontal disease and tooth loss, indicators of oral microbial dysbiosis, are associated with these two cancers.

Here, we prospectively examined the association of history of periodontal disease and tooth loss with the risk of oesophageal and gastric adenocarcinoma in 98 459 women from the Nurses' Health Study (1992–2014) and 49 685 men from the Health Professionals Follow-up Study (1988–2016). Dental measures, demographics, lifestyle, and diet were assessed using validated follow-up questionnaires. Self-reported cancer diagnosis was confirmed by review of medical records. We used Cox proportional hazards models to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). We also examined the independent association of history of periodontal disease and tooth loss in a joint analysis.

Over 22–28 years of follow-up, we documented 199 cases of oesophageal adenocarcinoma and 238 cases of gastric adenocarcinoma. History of periodontal disease was associated with a 43% and 52% increased risk of oesophageal adenocarcinoma (multivariable-adjusted HR (aHR) 1.43, 95% CI 1.05 to 1.96) and gastric adenocarcinoma (aHR 1.52, 95% CI 1.13 to 2.04) (table 1). Compared to individuals with no tooth loss, the risks of oesophageal and gastric adenocarcinoma for those who lost ≥2 teeth were also modestly increased (aHR 1.42, 95% CI 1.00 to 2.03 [p_{trend} 0.05] and aHR 1.33, 95% CI 0.95 to 1.86 [p_{trend} 0.09], respectively). Among individuals with a history of periodontal disease, no tooth loss and losing ≥1 tooth were equally associated with a 59% increased risk of oesophageal adenocarcinoma (aHR 1.59, 95% CI 1.04 to 2.41 and aHR 1.59, 95% CI 1.04 to 2.44, respectively) compared to those with no history of periodontal disease and no tooth loss. Similarly, the same group of individuals had 50% and 68% greater risk of gastric adenocarcinoma (aHR 1.50, 95% CI 1.01 to 2.23 and aHR 1.68, 95% CI 1.13 to 2.50, respectively) (figure 1).

Prior findings on the relationship of periodontal disease and tooth loss with oesophageal and gastric cancer have been inconsistent.[5] This is in part due to great variation in study design, exposure ascertainment, and confounding adjustment. Compared with prior studies, our analysis has the advantage of prospective design, long term follow-up, examination of validated periodontal disease, a more specific marker for dysbiotic oral microbiome, in conjunction with tooth loss, as well as detailed covariate assessment that allowed us to control vigorously for confounding factors, especially smoking. Increasing evidence has highlighted the strong scientific rationale for a link between oral microbiome and oesophageal and gastric cancer. *Tannerella forsythia* and *Porphyromonas gingivalis*, as members of the 'red complex' of periodontal pathogens,[6] have been associated with the presence or risk of oesophageal cancer.[2–4] Coker *et al*[1] observed an over-representation of *Tannerella forsythia*, along with *Peptostreptococcus stomatis and Streptococcus anginosus*, among other oral microbes, in gastric cancer compared with other precancerous stages. From a mechanistic standpoint, *Porphyromonas gingivalis* may modulate the risk of oesophageal cancer through anergy of activated T cells,[7] inhibition of apoptosis,[8] and dehydrogenation

Table 1 Age-adjusted and multivariable associations of history of periodontal disease and tooth loss with oesophageal and gastric adenocarcinoma

	History of periodontal disease			No of teeth lost			
	No	Yes	P value	0	1	≥2	P_{trend}*
Oesophageal adenocarcinoma							
No of cases	134	65		123	25	51	
Person-years	11 033 730	997 259		10 205 784	1 037 319	787 886	
Age-adjusted HR (95% CI)†	1 (reference)	1.72 (1.27–2.33)	0.0005	1 (reference)	1.26 (0.81–1.95)	1.72 (1.22–2.42)	0.002
Multivariable-adjusted HR (95% CI)‡	1 (reference)	1.64 (1.21–2.24)	0.002	1 (reference)	1.24 (0.80–1.94)	1.64 (1.16–2.33)	0.005
Multivariable+smoking-adjusted HR (95% CI)§	1 (reference)	1.43 (1.05–1.96)	0.02	1 (reference)	1.16 (0.74–1.81)	1.42 (1.00–2.03)	0.05
Gastric adenocarcinoma							
No of cases	169	69		156	30	52	
Person-years	11 033 734	997 265		10 205 789	1 037 326	787 884	
Age-adjusted HR (95% CI)†	1 (reference)	1.63 (1.22–2.18)	0.001	1 (reference)	1.14 (0.76–1.69)	1.43 (1.03–1.99)	0.03
Multivariable-adjusted HR (95% CI)‡	1 (reference)	1.60 (1.19–2.14)	0.002	1 (reference)	1.13 (0.76–1.69)	1.40 (1.00–1.94)	0.05
Multivariable+smoking-adjusted HR (95% CI)§	1 (reference)	1.52 (1.13–2.04)	0.006	1 (reference)	1.12 (0.75–1.67)	1.33 (0.95–1.86)	0.09

*Calculated by using the median number of teeth lost in each category as an ordinal variable.
†Cox proportional hazards model stratified by age (continuous, month), cohort (Nurses' Health Study, Health Professionals Follow-up Study), and study period (in 2-year intervals).
‡Further adjusted for race (white, non-white), history of diabetes mellitus (no, yes), body mass index (<20, 20–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2), physical activity (in quintiles, metabolic equivalent of task-hour/week), fruits (in quintiles, serving/day), vegetables (in quintiles, serving/day), red/processed meat (in quintiles, serving/day), alcohol (women: never, <3.5, 3.5–6.9, ≥7.0 g/day; men: never, <7.0, 7.0–13.9, ≥14.0 g/day), regular aspirin use (no, yes), antacid medication (no, yes), menopausal hormonal therapy (premenopause, postmenopausal never user/men, postmenopausal past user, postmenopausal current user), and physical examination within the past 2 years (no, yes).
§Further adjusted for smoking status (never smoker, past smoker, current smoker) and smoking intensity (continuous, pack-year).

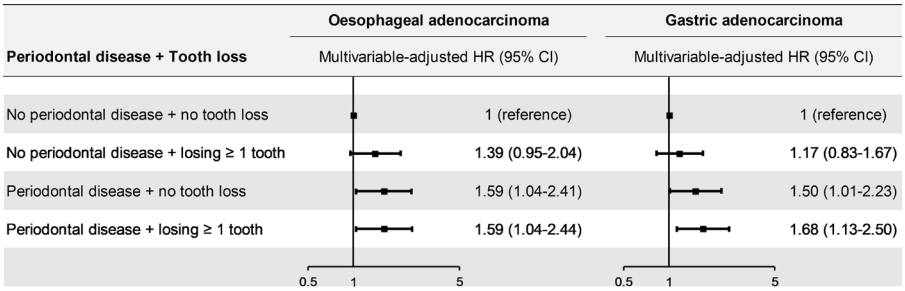

Figure 1 Multivariable-adjusted hazard ratios (HRs) of oesophageal and gastric adenocarcinoma for a history of periodontal disease and tooth loss. Cox proportional hazards models were stratified by age (continuous, month), cohort (Nurses' Health Study, Health Professionals Follow-up Study), and study period (in 2-year intervals), and adjusted for the same covariates as the full model in table 1. The p value for interaction between history of periodontal disease and tooth loss was calculated by including a cross-product interaction term between history of periodontal disease and tooth loss in the model and estimating the significance using the likelihood ratio test.

of ethanol to acetaldehyde, causing DNA damage, mutation, and excessive proliferation of epithelial cells.[9] Poor oral hygiene and periodontal disease could also promote the formation of endogenous nitrosamines known to cause gastric cancer through nitrate-reducing bacteria.[10]

Together, these data support the importance of oral microbiome in oesophageal and gastric cancer. Further prospective studies that directly assess oral microbiome are warranted to identify specific oral bacteria responsible for this relationship. The additional findings may serve as readily accessible, non-invasive biomarkers and help identify individuals at high risk for these cancers.

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