Evidence Accumulates Indicating Periodontal Disease as a Risk Factor for Colorectal Cancer or Lymphoma

Two recent reports have found that periodontal disease may be a risk factor for the development of colorectal cancer (Int J Cancer. 2017;140:646-652) and non-Hodgkin lymphoma (NHL) (Int J Cancer. 2017;140:1020-1026). Periodontal disease is a chronic inflammatory condition of the supporting tissue of the teeth and has been linked to several chronic diseases, including cardiovascular disease, diabetes, stroke, and cancer. The authors of the current reports state that previous studies have found associations between periodontal disease and various cancers, including those of the oral cavity, lung, pancreas, breast, and upper gastrointestinal tract. However, colorectal cancer and NHL have been studied less frequently. The current analyses examined the potential link between periodontal disease and these 2 malignancies as a part of 2 large population-based studies.

Nurses’ Health Study
The Nurses’ Health Study is an ongoing, large, prospective cohort study of 121,700 female nurses from 11 different states. Since its initiation, participants have completed medical history and lifestyle questionnaires every 2 years, with a 90% rate of follow-up. Information regarding periodontal disease (defined as a history of periodontal bone loss) first was assessed in 1998 and then again in 2000. Each survey has collected information concerning various colorectal cancer risk factors, screening history, and the development of colorectal cancer. In addition, in 1992, the survey asked participants about the number of natural teeth still present (none, 1-10, 11-16, 17-24, and 25-32 natural teeth).

In the study regarding the risk of colorectal cancer, a Cox proportional hazards model was used to calculate multivariable hazard ratios (HRs) after adjusting for smoking and other known risk factors for colorectal cancer. The number of teeth and history of periodontal bone loss were assessed separately. Compared with women with 25 to 32 natural teeth, women with fewer than 17 natural teeth were found to have an increased risk of colorectal cancer, with an HR of 1.2 (95% confidence interval [95% CI], 1.04-1.39). Significant associations also were observed for proximal colon cancer (HR, 1.23) and rectal cancer (HR, 1.48), but not for distal colon cancer.

When analyzing the data regarding periodontal bone loss, the authors found that there was no significant association with colorectal cancer risk overall or cancer at any subsite. Compared with women without periodontal bone loss, there was a suggestion (albeit not statistically significant) of a higher risk of colorectal cancer among those with moderate to severe periodontal disease (HR, 1.22; 95% CI, 0.91-1.63).

In summary, women with fewer natural teeth (0-16 teeth), and possibly those who have moderate or severe periodontal bone loss, might be at a modestly increased risk of developing colorectal cancer.

“Oral health might biologically increase systemic inflammation, lead to immune dysregulation, and alter gut microbiota, thereby possibly influencing colorectal carcinogenesis. Our study supports this possibility,” says Xuehong Zhang, MD, ScD, the study’s corresponding author and associate epidemiologist at Brigham and Women’s Hospital as well as assistant epidemiologist at the Harvard School of Public Health.

KEY POINTS
- Periodontal disease is associated with an increased risk of colorectal cancer and NHL.
- Research to determine whether periodontal disease is causal and to identify the mechanism is needed.
- More communication between dental and medical professionals is indicated.
professor of medicine at Harvard Medical School, both in Boston. “However, epidemiological data on oral health and colorectal cancer risk are scarce. Future study should confirm our observation and evaluate the potential mechanisms behind this association (if not due to chance).”

Health Professionals Follow-Up Study

In a previous analysis of the Health Professionals Follow-Up Study, a 31% higher risk of NHL was observed for those participants who reported having periodontal disease with bone loss at baseline. The current study by Bertrand et al provides 8 additional years of follow-up and analysis by NHL subtype.

The Health Professionals Follow-Up Study is a prospective cohort study that includes 51,529 men who completed a self-administered baseline questionnaire in 1986. Participants are sent questionnaires every 2 years regarding demographic factors, lifestyle habits, and medical history. Patients with any missing pertinent data or with a previous history of cancer before study entry were excluded from the current analysis. Among the 46,147 men with complete data who were included in these analyses, 875 incident diagnoses of NHL made between 1986 and 2012 were identified. Participants reported their number of natural teeth at baseline, and a history of periodontal disease with bone loss was assessed at baseline as well as on each biennial questionnaire. A Cox proportional hazards model to calculate multivariable HRs also was used in this study.

In multivariable analyses adjusting for age, tooth loss, and other potential confounders, men with a history of periodontal disease with bone loss at baseline were found to have an increased risk of developing NHL overall (all subtypes considered together) compared with men without a history of periodontal disease (HR, 1.26; 95% CI, 1.06-1.49). In the analyses of NHL subtypes, significantly increased risks were observed for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (HR, 1.41) and diffuse large B-cell lymphoma (DLBCL) (HR, 1.35), but not for follicular lymphoma. Similar results were observed with the updated periodontal disease status (HR for NHL overall, 1.30; 95% CI, 1.11-1.51).

Tooth loss was found to be inversely associated with periodontal disease after adjustment for periodontal disease status. The authors indicate that one potential explanation for this finding could be that the tooth loss alleviated the chronic inflammation, but they note that this hypothesis would need further study.

“We found that men with a history of periodontal disease had up to a 30% increased risk of developing NHL (higher in the subsets of CLL/SLL and DLBCL) compared with those who did not have periodontal disease,” says Kimberly Bertrand, ScD, assistant professor of medicine and an epidemiologist at the Slone Epidemiology Center at Boston University. “This is significant because the causes of NHL are poorly understood and most people with NHL have no known risk factors. Our study provides the first strong evidence that periodontal disease may be a novel risk factor for NHL.”

Implications

These studies add to the epidemiologic data that implicate periodontal disease as a risk factor for cancer, specifically colorectal cancer and NHL. Although the limitations inherent to observational population studies exist, the study size and length of follow-up add strength to the findings. Although the authors of both studies acknowledge that these are not definitive studies, they also note the biologic plausibility given the systemic chronic inflammation and possible immune dysregulation in the setting of periodontal disease.

Cesar Migliorati, DDS, MS, PhD, chair of the department of diagnostic sciences and oral medicine at the University of Tennessee in Memphis, is an advocate for the collaboration between medical and dental professionals. He says he has been interested in identifying the underlying cause of an increased cancer risk with periodontal disease.

“A new concept of parainflammation—a low-grade process identified with a gene signature—described in a recent study by Aran and colleagues (Genome Biol. 2016;17:145) could be involved,” says Dr. Migliorati, who was not involved with either study. “This process was found in a quarter of human cancers in this preclinical study, and given that periodontal disease is a chronic low-grade process, it is a plausible cause.”

“Further research is needed to determine whether the association we observed is causal and to identify the causal mechanism,” adds Dr. Bertrand. “Regardless of these uncertainties, there are immediate clinical implications: our findings highlight the importance of maintaining good oral health, including brushing and flossing teeth and seeing a dentist regularly, to prevent gum disease and possibly cancer as well.”

Dr. Migliorati notes that physicians and dental professionals tend to treat and follow their patients in an isolated manner without reference to the other’s discipline. “However, the oral cavity is part of the whole body—as are the heart, lungs, and brain—and should be included in cancer management,” he says.

doi: 10.3322/caac.21367