An Exploration of Shared Genetic Risk Factors Between Periodontal Disease and Cancers: A Prospective Co-Twin Study

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Biologic mechanisms underlying associations of periodontal disease with cancers remain unknown. The authors propose that both conditions share common genetic risk factors. They analyzed associations between baseline periodontal disease, measured by questionnaire-recorded tooth mobility, and incident cancers, identified by linkage with national registries, between 1963 and 2004 in 15,333 Swedish twins. The authors used co-twin analyses to control for familial factors and undertook analyses restricted to monozygotic twins to further control for confounding by genetic factors. They observed 4,361 cancer cases over 548,913 person-years. After adjustment for covariates, baseline periodontal disease was associated with increased risk of several cancers ranging from 15% for total cancer (proportional hazard ratio (HR) = 1.15, 95% confidence interval (CI): 1.01, 1.32) to 120% for corpus uterine cancer (HR = 2.20, 95% CI: 1.16, 4.18). Periodontal disease was also associated with increased risk of colorectal (HR = 1.62, 95% CI: 1.13, 2.33), pancreatic (HR = 2.06, 95% CI: 1.14, 3.75), and prostate (HR = 1.47, 95% CI: 1.04, 2.07) cancers. In co-twin analyses, dizygotic twins with baseline periodontal disease showed a 50% increase in total cancer risk (HR = 1.50, 95% CI: 1.04, 2.17), but in monozygotic twins this association was markedly attenuated (HR = 1.07, 95% CI: 0.63, 1.81). Similar patterns emerged for digestive tract cancers, suggesting that shared genetic risk factors may partially explain associations between periodontal disease and cancers.

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

Emerging evidence suggests that periodontal disease, a common chronic inflammatory condition, may be associated with an increased risk of total and site-specific cancer (1–3). Periodontal disease results from colonization by predominantly Gram-negative bacteria that stimulate an inflammatory response that, in some individuals, results in the breakdown of the connective tissue surrounding teeth (4). The inflammatory response to periodontal infection extends beyond the oral cavity and leads to elevated levels of circulating inflammatory markers (5). Of importance to the relation between periodontal disease and cancer is the proposition that chronic inflammation increases the risk of several cancers (6–9). This link is supported by the higher incidence of cancers in persons with chronic inflammatory conditions (6) and the efficacy of antiinflammatory medications in preventing some cancers (10). The latter finding, however, has not been corroborated in all studies (11, 12).

Increases in systemic inflammation resulting from periodontal disease may, therefore, offer one pathway by which this oral disease increases the risk of various cancers. Other mechanisms, including a compromised immunologic system and carcinogenic byproducts of periodontal pathogens, have also been proposed as possible links (13). Alternatively, underlying genetic risk factors may increase susceptibility to both conditions or may modify the relation of environmental risk factors, for example, tobacco smoke, with periodontal disease and cancers. Most epidemiologic studies of periodontal disease and cancer have extensively controlled for possible environmental confounders. The role...
of common genetic risk factors between the 2 conditions, however, remains largely unexplored.

In the present study, we aim to evaluate the role of underlying genetic factors in the relation of periodontal disease to total and site-specific cancer using a co-twin approach. Co-twin analyses offer the advantages of controlling for shared genetic factors within twin pairs and controlling for prenatal and early life environmental exposures and familial factors (14). Such methods have proven successful in identifying the impact of genetic factors on the development of a number of diseases including cardiovascular disease and cancers (15, 16). To address our study aim, we examined the association between periodontal disease and incident cancer in a population-based cohort of more than 15,000 Swedish twins followed prospectively over a period of 41 years.

MATERIALS AND METHODS

Study population

The Swedish Twin Registry, currently the largest population-based twin registry in the world, was established in the late 1950s to study the role of environmental and genetic factors in cancer and cardiovascular disease (14). In 1963, all like-sexed twin pairs aged 38 years or older completed a written questionnaire on health outcomes, including oral health, and a number of risk factors. Zygosity was also determined via questionnaire where twins indicated that they were "as similar as peas in a pod" or "no more alike than siblings in general." Validation studies showed a high degree of accuracy (>95% agreement) using this method (14). The 1963 questionnaire was completed by 18,634 twins. Of these, we excluded those participants who did not respond to the item on periodontal disease (n = 2,742). We also excluded those with prevalent cancer or a cancer diagnosis earlier than 1963 (n = 326) and those with deaths prior to 1963 (n = 88). Participants who reported denture use were classified separately (n = 174). Overall, we included data on 15,333 participants in our study. The Swedish Twin Registry received approval from the Karolinska Institutet ethics committee, and informed consent was obtained from the twins prior to enrollment in the study.

Periodontal disease ascertainment

Twins were asked to respond to the question, "Have you noticed that some of your own teeth have come loose or fallen out on their own?". Twins were classified as having periodontal disease if at least half of their teeth had mobility, which is indicative of advanced disease. Participants who reported having a few loose teeth were categorized separately as having minor disease. In a recent systematic review evaluating the validity of self-reported indicators of periodontal disease, self-reported tooth mobility was found to be one of the most valid measures of periodontal disease when compared with clinical examination (17). Notably, in one study, self-reported mobility showed a specificity of 92% to predict periodontal disease on examination (18). Because tooth mobility is a sign of advanced disease, the sensitivity of this measure is generally lower (18, 19), presumably because of limited detection of mild to moderate periodontal disease. In our study, measurement accuracy of periodontal disease is unlikely to have varied by cancer diagnosis and, therefore, any misclassification would lead to a bias toward the null rather than an overestimation of any association between periodontal disease and cancer.

Identification of cancer cases and deaths due to cancer

We identified incident cancer in the cohort by linkage to data in the Swedish National Cancer Register using unique national identification numbers assigned to all Swedish residents. This registry was established by the National Board of Health and Welfare in 1958, and Swedish law mandates that physicians and pathologists report every newly diagnosed malignant tumor. Case reporting is essentially 100% complete (20), with all reports being verified at 1 of 6 regional registries in Sweden. All cancer diagnoses are classified according to the International Classification of Diseases.

Information on all-cause and cancer-specific mortality was available from the National Cause of Death Register, which includes the date and cause of death obtained from death certificates, which are coded using International Classification of Diseases' standards. Medical certification is carried out by the attending physician or coroner, using both clinical records and autopsy reports (21). This registry, which was established in 1961, maintains death records for more than 99% of the Swedish population who died after this year.

Assessment of smoking and other risk factors

Participants reported their smoking history on a questionnaire, and we used a combination of packs of cigarettes smoked per day and smoking status in our analyses. To further control for potential exposure to tobacco smoke, we also included the smoking status of the participant's partner. We calculated body mass index at baseline from self-reported height and weight (weight (kg)/height (m)²). Data on other important covariates including diabetes, alcohol intake, education, employment, number of siblings, age, and sex were also recorded by using questionnaires.

Statistical analysis

We examined the distribution of periodontal disease status within key participant characteristics. Subsequently, we analyzed the association between periodontal disease and incident cancer using time-to-event analyses. Person-time was calculated from the date of entry into the cohort (January 1, 1963) until the date of first cancer diagnosis, death due to cancer, or censoring on account of death due to other causes or the end of the observation period (December 31, 2004). We estimated Kaplan-Meier survival curves within categories of periodontal disease status (none, minor mobility, periodontal disease) and compared the estimates using the Mantel-Haenszel log-rank statistic. We computed hazard ratios and 95% confidence intervals using
Cox proportional hazard regression models (Proc PHREG software; SAS Institute, Inc., Cary, North Carolina). For the latter analyses, we used 3 approaches. First, we adjusted for individual-level cancer risk factors and potential confounders. These included sex (males vs. females), age (years), education (none above obligatory school, junior secondary, senior secondary, vocational, other), employment (yes, no, housewife, pensioner, other), number of siblings (ordinal), smoking status (current ≥ 1 pack/day, current <1 pack/day, former ≥ 1 pack/day, former <1 pack/day, never), smoking status of partner (current, former, never), alcohol status (current, former, never), body mass index (<20, 20–24.9, 25–29.9, ≥30 kg/m²), and diabetes (yes, no). Because tooth loss at an early age may be due to causes other than periodontal disease, for example, dental caries, we undertook additional analyses stratified by age to check if the association between periodontal disease and cancers varies in different age groups. We compared the association of periodontal disease with cancers among those who were younger than 51 years (the median age of our study population) and those who were 51 years or older.

In our second approach, to address our main hypothesis on genetic factors common to periodontal disease and cancer, we used a co-twin design where we conducted stratified proportional hazard analyses in which each stratum comprised a twin pair. The co-twin control method takes advantage of the fact that monozygotic and dizygotic twins share different degrees of genetic relatedness and also have shared prenatal and early life environmental exposures. It should be noted that the co-twin–control method may entail control of factors in the biologic pathway between exposure and disease, which may cause an underestimation of the risk posed by the exposure under study (14). In our study, we have compared cancer incidence in exposure-discordant pairs (i.e., pairs discordant for periodontal disease).

In our final set of analyses, we undertook co-twin analyses restricted to monozygotic pairs. Because monozygotic twins share 100% of their genes, these analyses further controlled for unmeasured confounding by genetic factors. We used contrasts in the hazard ratios from the co-twin and unstratified analyses as an indication of confounding by familial effects of the association between periodontal disease and cancer. Furthermore, the extent to which hazard ratios differed when analyses were restricted to monozygotic pairs provided a measure of the degree of residual confounding by genetic factors. To ensure that our co-twin results were not driven by differences in cancer rates among our control groups (those who were periodontal disease free), we compared the distribution of cancer events and the mean time to cancer diagnoses in monozygotic and dizygotic twin controls with those of controls in the whole cohort.

We were concerned that the results of our co-twin analyses would be confounded by exposure to tobacco smoke, and we had intended to undertake parallel analyses restricted to low tobacco-exposed participants (nonsmoking participants whose partners were also nonsmokers). However, among low tobacco-exposed participants, only 10 monozygotic twin pairs with baseline periodontal disease developed any cancer during the follow-up period. This small sample prevented us from undertaking co-twin analyses limited to low tobacco-exposed participants. For an alternate approach to evaluating the confounding effect of smoking, we compared our stratified Cox proportional hazard models that adjusted for smoking variables with those that excluded all smoking variables. A substantial change in hazard ratios between these models would indicate that smoking was an important confounder in our analyses.

RESULTS

Our participants had a median age at baseline of 51 years (range, 38–77 years), and 55% were female. They contributed 548,913 person-years to our study during a median follow-up period of 27 years (range, 1–41 years). In all, 4,361 cases of incident cancer were documented. Almost 6% of the participants had advanced periodontal disease, as determined by self-reported tooth mobility, and an additional 12% of participants reported minor tooth mobility. Participants with periodontal disease were more likely to be male and of older age, and they were less likely to have received education beyond compulsory schooling or to be current consumers of alcohol (Table 1). We observed that the proportion of current smokers was higher among those with periodontal disease, but only in participants who were in the first and second tertile of age (<56 years). In older participants, this trend was not clear. In this cohort, those with periodontal disease were less likely to have a partner who was a current smoker at the start of the study. No differences in body mass index were observed across the 3 disease groups.

In analyses not accounting for genetic factors, participants with advanced periodontal disease at baseline had a higher incidence of total cancer compared with those without periodontal disease (hazard ratio (HR) = 1.48, 95% confidence interval (CI): 1.30, 1.69). After adjustment for individual-level factors (Table 2), including smoking, the association of periodontal disease and total cancer was reduced but remained significant (HR = 1.15, 95% CI: 1.01, 1.32). We observed significant associations between periodontal disease and cancers of the digestive tract as a whole, as well as with colorectal and pancreatic cancers. Periodontal disease was also significantly associated with an increased risk of prostate cancer in men and with cancer of the corpus uteri in women. Individuals with periodontal disease had an increased risk of lung cancer; however, after adjustment for smoking and other risk factors, this association was no longer statistically significant. Periodontal disease was associated with an increased risk of bladder cancer and female breast cancer, but these associations were not statistically significant. We were unable to investigate the relation between periodontal disease and other cancer types because of the small number of cancer cases. In analyses stratified by age, we observed that the association of periodontal disease and total cancer was stronger in those aged 51 years or more (HR = 1.22, 95% CI: 1.04, 1.42). In participants younger than 51 years, the association between periodontal disease and cancers was not significant (HR = 0.95, 95% CI: 0.72, 1.24. We observed a similar pattern for digestive tract, prostate, and colorectal cancers (data not shown).
In our co-twin analyses, we found that the crude association between periodontal disease and total cancer incidence was not statistically significant (HR = 1.27, 95% CI: 0.96, 1.70) (Table 3). Furthermore, adjustment for individual-level risk factors did not produce any appreciable change in the hazard ratios from the unadjusted crude stratified analysis (HR = 1.32, 95% CI: 0.98, 1.77). This was in contrast to the unstratified analyses where adjustment for individual-level factors produced a substantial change in the association of periodontal disease and cancer. When we restricted our stratified analysis to monozygotic twins, which further adjusted for confounding by genetic factors, the association between periodontal disease and cancer was essentially absent (HR = 1.07, 95% CI: 0.63, 1.81). However, a significant association remained in dizygotic twins (HR = 1.50, 95% CI: 1.04, 2.17).

We observed a similar pattern when examining digestive tract cancers. Compared with unstratified analyses, stratified analyses by twin pair showed that the crude association between periodontal disease and digestive tract cancers was smaller (HR = 1.21, 95% CI: 0.74, 1.99). When we adjusted for individual-level risk factors, including smoking, the association between periodontal disease and digestive tract cancers showed little change (HR = 1.25, 95% CI: 0.74, 2.10). In monozygotic twins, this association was substantially attenuated (HR = 1.06, 95% CI: 0.39, 2.88), while being stronger in dizygotic pairs (HR = 1.39, 95% CI: 0.73, 2.65) (Table 3). Because of the limited number of cases, we were unable to confirm these findings in other cancer types.

We investigated whether our co-twin results may be affected by underlying differences in cancer risk between the periodontal disease-free controls of the whole cohort and the controls of the monozygotic and dizygotic twin groups. However, we observed no significant differences in either the proportion of cancer events or the mean time to cancer diagnoses between these groups (data not shown).

Finally, in co-twin analyses where we excluded all tobacco-related variables, the hazard ratios showed little meaningful change from the fully adjusted models that included participants’ smoking habits and also their partner’s smoking status. In these analyses, participants with periodontal disease at baseline had a 33% increase in risk of all cancers (HR = 1.33, 95% CI: 0.98, 1.78). As with the tobacco-exposure–adjusted results, the association was effectively absent among monozygotic twins (HR = 1.05, 95% CI: 0.62, 1.77). Similarly, participants with baseline periodontal disease showed a 23% increase in risk of digestive tract cancers (HR = 1.23, 95% CI: 0.73, 2.05) with this association being absent in monozygotic twins (HR = 0.94, 95% CI: 0.35, 2.55).

**DISCUSSION**

The results of this large prospective study, undertaken among Swedish twins, suggest that shared genetic risk factors may partially explain the association between
periodontal disease and cancers. Participants with periodontal disease at baseline, as determined by self-report of tooth mobility, experienced a higher incidence of total cancers, but this association was markedly reduced and no longer significant in stratified analyses limited to monozygotic twins. We were able to further confirm this finding in analysis of cancers of the digestive tract. In contrast, when we restricted our analyses to dizygotic twins, the association of periodontal disease with total and digestive tract cancers was stronger than that observed in monozygotic twins, supporting our hypothesis that shared genetic factors may affect the association between these 2 conditions.

Our findings are supported by the increasing body of evidence that has linked polymorphisms in genes coding for inflammatory mediators with increased risk of periodontal disease. A recent systematic review confirmed the association of the interleukin 1 gene, IL1, polymorphisms, specifically IL1A C[-889]T and IL1B C[3953/4]T polymorphisms, with chronic periodontal disease (22). Gene polymorphisms in other cytokines and cytokine receptors, including IL2, IL6, and IL10, as well as the tumor necrosis factor gene, TNF, polymorphisms TNFA, TNFB, and TNFR2, have also been linked with periodontal disease (23–27). However, these associations have not been confirmed in all studies on this topic (27).

Inflammation may play a role in some cancers (6, 7), and it is possible that polymorphisms associated with increased risk of periodontal disease are also important in cancer. For example, genetic polymorphisms in IL1 have been associated with increased risk of gastric cancer (28). At present, however, the associations between cytokine polymorphisms and other cancer sites are inconsistent (29), and it is, therefore, not possible to identify specific genetic factors that may be causally associated to both periodontal disease and specific cancer types.

Our other findings agree with earlier published literature on the association between periodontal disease and cancer. We observed that participants with periodontal disease at baseline had a 15% increase in cancer risk, which is similar to that reported in a prospective study of US male health professionals (3). Because our study included both males and females, we were able to examine associations with female-specific cancers. We observed that females with periodontal disease had a statistically significant increase in risk of cancer of the corpus uteri but not of cancer of the cervix uteri (data not shown). Although periodontal disease was also associated with increased risk of breast cancer, this was not statistically significant.

We used self-reported tooth mobility as an indicator of periodontal disease. Although it has been shown that tooth mobility is among the most valid self-reported measures to detect advanced periodontal disease and has high specificity compared with clinical diagnosis (17, 18), it is possible that mild or moderate cases of periodontal disease were not detected. It is also possible that participants without periodontal disease at baseline developed this condition at a later stage. However, any misclassification due to these reasons would underestimate the association between periodontal disease and cancer, and so it is possible that the cancer risk associated with periodontal disease is stronger than what we see.
have reported. Because tooth loss in younger age groups may be due to causes other than periodontal disease, we stratified our analyses by age and found that the association between periodontal disease and incident cancer was stronger in those 51 years or older; further suggesting that self-reported tooth mobility and tooth loss were a useful marker of periodontal disease in our study.

Even though we had over 15,000 participants in our study, with an average follow-up of 27 years, there were insufficient cancer cases to undertake co-twin analyses for all cancer types. Therefore, in our analyses of monozygotic twins, we were restricted to studying the association of periodontal disease with total and digestive tract cancers. Combining several cancers together in this manner may have distorted our results as risk factors vary between different cancer types, and it is possible that periodontal disease shares genetic risk factors with only some cancers. Furthermore, the lack of association between periodontal disease and cancers in monozygotic twins may be due to limited statistical power to evaluate the association in this subgroup.

We were unable to undertake co-twin analyses within low tobacco-exposed participants; however, we observed that excluding the smoking variable from our co-twin models did not substantially change the association of periodontal disease with total or digestive tract cancers, indicating that residual confounding by smoking is unlikely to have exerted a large effect on the results of our co-twin analyses. Although the association of smoking status and periodontal disease was clear among participants younger than 56 years, it was less evident in older participants (Table 1). This may indicate that older survivors of this cohort were less susceptible to the effects of smoking on periodontal tissues, or that measurement error in one or both of these variables was greater in the older age group. It is similarly possible that other unmeasured or mismeasured variables may have affected the association observed between periodontal disease and cancers.

Our study is strengthened by its prospective design and a large sample of participants that included both males and females. All diagnoses of cancer were made by a medical health professional, and the cancer registry covers over 99% of the Swedish population, making it unlikely that cancer cases were misclassified or lost to follow-up. Notably, our study population comprised twins with well-established zygosity measured using a highly valid method (14). This allowed us to adjust for confounding by common underlying genetic factors using a co-twin design.

Overall, our results suggest that there may exist shared underlying genetic factors that increase the risk of both periodontal disease and cancers. However, this requires further confirmation with prospective studies that overcome the limitations of our work. If a genetic link between periodontal disease and cancer does exist, identification of the specific genetic polymorphisms that are linked to both conditions may prove relevant in identifying at-risk individuals and developing preventive strategies.

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Table 3. Co-Twin Analyses for the Association of Periodontal Disease With Total and Digestive Tract Cancers, the Swedish Twin Registry, 1963–2004 (n = 14,367)*

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<td>Digestive tract</td>
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<tr>
<td>No disease</td>
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* Participants whose zygosity could not be confirmed were excluded from co-twin analysis.

b Cox proportional hazard ratios were stratified by twin pair. Stratifying by twin pair inherently adjusts for age, sex, early environmental exposures, and familial factors. Additional covariates were not included in this model.

c Cox proportional hazard ratios were stratified by twin pair. Analyses were adjusted for education (none above obligatory school, junior secondary, senior secondary, vocational, other), employment (yes, no, housewife, pensioner, other), number of siblings (ordinal), smoking status (current < 1 pack/day, former < 1 pack/day), former smoking status of partner (current, former, never), alcohol status (current, former, never), diabetes (yes, no), and body mass index (< 20, 20–24.9, 25–29.9, ≥ 30 kg/m²).
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