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Periodontitis and cancer mortality: Register-based cohort study of 68,273 adults in 10-year follow-up

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Cancer Epidemiology

Periodontitis, a multifactorial infection-induced low-grade chronic inflammation, can influence the process of carcinogenesis. We studied with 10 years follow-up of 68,273 adults-based cohort the involvement of periodontitis as a risk factor for cancer mortality. Periodontal status was defined based on procedure codes of periodontal treatment. Rate ratios and absolute differences of overall and cancer mortality rates were assessed with respect to periodontal status using multiplicative and additive Poisson regression models, respectively. We adjusted for effect of age, sex, calendar time, socio-economic status, oral health, dental treatments and diabetes. Data about smoking or alcohol consumption were not available. Altogether 797 cancer deaths occurred during 664,020 person-years accumulated over a mean 10.1-year follow-up. Crude cancer mortality rate per 10,000 person-years for participants without and with periodontitis was 11.36 (95% CI 10.47–12.31) and 14.45 (95% CI 12.51–16.61), respectively. Crude rate ratios for periodontitis indicated an increased risk of overall (RR 1.27, 95% CI 1.08–1.39) and pancreatic cancer (RR 1.69, 95% CI 1.04–2.76) mortality. After adjustment, the results showed even stronger associations of periodontitis with increased overall (RR 1.33, 95% CI 1.10–1.58) and pancreatic cancer (RR 2.32, 95% CI 1.31–3.98) mortality. A higher pancreatic cancer mortality among individuals with periodontitis contributed considerably to the difference in overall cancer mortality, but this difference was not due to pancreatic cancer deaths alone.

Periodontitis, a multifactorial infection-induced inflammation, results in loss of connective tissue attachment and bone support of teeth and is a major cause of tooth loss in adults. Worldwide estimates for the prevalence of severe periodontal disease generally range from 10% to 15%.[1]

In addition to pathogenic microorganisms in the biofilm, genetic and environmental factors, including age, race, male sex, body mass index, tobacco, diabetes, nutrition, and populations with low socio-economic status and those with limited access to dental care, eventually contribute to the onset and course of periodontal diseases.[2] The impact of diabetes mellitus on periodontitis has been shown to be independent of the other major risk factors.[3]

In periodontitis, pathogenic microorganisms interact with host tissues and cells, causing the release of a broad array of inflammatory cytokines, chemokines, proteolytic enzymes, reactive oxygen species and other mediators that lead to local irreversible degeneration of the periodontal structures. The systemic dissemination of infectious agents and inflammatory mediators from the oral environment may cause an elevated and sustained systemic inflammatory condition, which may promote the pathogenesis of distal inflammatory processes such as the pathogenesis of cancer. Research in the field of periodontology has focused on the potential of this chronic low-grade inflammatory condition to contribute to the generation of a systemic inflammatory phenotype.[4] The importance of periodontal infections to systemic health is further strengthened by pilot intervention trials indicating that periodontal therapy can prevent and reverse systemic adverse events, for example, improving surrogate cardiovascular outcomes, such as endothelial function, and reducing proinflammatory biomarkers.[5]

Infection-driven inflammations have been estimated to be involved in the pathogenesis of ~15% of human tumors. Globally in 2012, an estimated 14 million new cancer cases

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Additional Supporting Information may be found in the online version of this article.

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What's new?

Periodontitis is characterized by infection-driven inflammation, a type of inflammation that is a factor in about 15% of human tumors. It remains unclear, however, whether periodontitis increases cancer risk or influences cancer mortality. In this study, long-term follow-up on a large cohort of dental patients in Finland suggests that periodontitis is associated with increased overall cancer mortality, especially increased mortality from pancreatic cancer. The findings suggest that the prevention and treatment of periodontitis can help reduce the risk of systemic adverse events, such as death, from cancer.

occurred, 2.2 million of which were attributable to carcinogenic infections.[6] In some types of cancer, inflammatory conditions are present before a malignant change occurs. Conversely, in other types of cancer, an oncogenic change induces an inflammatory microenvironment that promotes the development of tumours.[7] Several epidemiological studies have suggested a positive association between periodontal disease and carcinogenesis risk in different tissues, most notably in the mouth, upper gastrointestinal system, lung and pancreas, underpinned by immune-inflammatory mechanisms common to both entities.[8–10]

A few studies also exist on periodontitis and the morbidity and mortality associated with human cancers. Epidemiological studies have explored possible relationships between tooth loss/periodontitis and total mortality, all kinds of cancer and cancers of the oral cavity and pharynx, esophagus, stomach, pancreas, liver, colon, rectum, and anus, unadjusted or adjusted for age, gender, socio-economic status, smoking habits, vitamin A and C consumption and alcohol intake.[11–13]

Our aim was to investigate the relationship between periodontitis and cancer mortality by conducting a historic cohort study in a population of primary dental care patients. We utilized the high quality and coverage of the Finnish health care register data.

Methods

Study population

We used the data from the patient register of the Public Dental Service of the City of Helsinki to identify all individuals aged 29 years or more with at least one primary dental health care visit between 1 January 2001 and 31 December 2002. For these patients, follow-up data on deaths and causes of death were obtained from the register of deaths of Statistics Finland[14] through a computerized register linkage using the unique personal identification codes assigned to every resident in Finland. Along with the date of death, mortality data also included the cause of death coded according to the tenth revision of the International Classification of Diseases (ICD-10). In addition, data on socio-economic status and education were obtained from Statistics Finland. The dental care data were also linked to the Drug Reimbursement Register of the Finnish Social Insurance Institution (SII). These drug prescription records cover the entire study population, except for institutionalized patients. In Finland, patients with chronic or severe disease, such as diabetes, are granted special reimbursement rights for outpatient medical treatment based on a physician statement on their condition and need for medication.[15] The cancer diagnosis data, date of diagnosis and ICD-O-3 code[16] were obtained from the Finnish Cancer Registry (FCR). The FCR database contains data on virtually all cancers diagnosed in Finland since 1953. The coverage and accuracy of the Finnish Cancer Registry data are excellent.[17,18]

Altogether 71,200 patients visited the Public Dental Service of Helsinki in 2001–2002. We restricted the study population to those who had no history of cancer at the first visit and who were alive two years after the first visit (Fig. 1). The size of the final study population was 68,273 individuals. The follow-up for mortality started two years after the first visit and continued until 31 December 2013 or death, whichever occurred first.

Outcomes

The outcomes of interest were mortality from any cancer and nine cancer types defined by topology (ICD-O-3): lung (C33–34), breast (C50), pancreas (C25), upper gastrointestinal (C15–17), esophageal (C15), gastric (C16), liver (C22), head and neck (C00–C14) and prostate (C61). Most of these outcomes were included based on current epidemiological evidence, while the mortality from lung or liver cancer was selected to check whether the relationship between periodontitis and cancer mortality could be confounded by smoking and/or use of alcohol, which are known to be associated with both periodontitis and risk of cancer, but data of these exposures are not available in the register data.

Measure of exposure and potential confounders

We utilized data from dental visits within a period starting 2 years after the first visit. Dentists use the classification of the Finnish Social Insurance Institution (KELA) to record treatment measures provided, and these codes were used here to detect periodontal disease. These data include procedure codes of dental treatment (gingivitis, periodontitis, caries, endodontic, surgery and prosthesis) and information on dental status presented by number of teeth, oral health indices, such as primary caries (I), number of decayed teeth (DT), decayed/missing/filled teeth (DMFT) and need for periodontal treatment due to periodontal pockets (CPI = the Community Periodontal Index). Exposure to periodontitis was

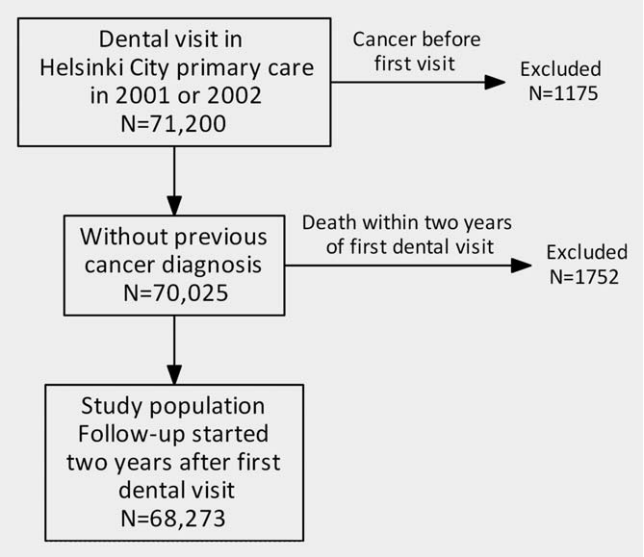

Figure 1. The flowchart of the study. Altogether 71,200 patients visited the Public Dental Service of Helsinki in 2001–2002. We restricted the study population to those who had no history of cancer at the first visit and who were alive for 2 years after the first visit. The size of the final study population was 68,273 individuals. The follow-up started 2 years after the first visit and continued until 31 December 2013 or death, whichever occurred first.

defined as a binary variable (no/yes) based on periodontitis treatment procedure codes.[19,20]

Among potential confounders in this study were socio-demographic characteristics, such as age, sex and socio-economic status, which were available for the entire study population. We used age (<40, 40–50, 50–60, 60–70, >70) and calendar time (<2006, 2006–2009, ≥2010) as time-dependent covariates. Data on profession obtained from Statistics Finland were categorized into eight broader categories (lower-level employees, upper-level employees, manual workers, pensioners, students, self-employed or employers, unemployed and unknown) to represent socio-economic status. In addition, we used prescription data to identify patients with diabetes, which is known to affect the risk for both periodontitis and cancer. We defined diabetes as use of any anti-diabetic medication (ATC-codes beginning with A10) based on prescription before the start of follow-up. To account for dental status other than periodontitis, we used number of teeth (0–23, 24–27, 28–32), indices I (0, 1–2, 3–4, ≥5), DT (0, 1–2, 3–4, ≥5), DMFT (0–13, 14–18, 19–23, ≥24 according to quartiles) and CPI (0–1, 2, 3–4), number of healthy sextants (0, 1, 2–4, 5–6), number of toothless sextants (0, 1–6), and indicators of different dental treatments (yes/no).[19,20] I, DT, DMFT and CPI indices were defined by taking the maximum value of those recorded during the dental visits within two years after the first visit. Number of healthy sextants was specified according to that of the first visit, and number of toothless sextants by selecting the minimum value. For part of the study population, however, information on health indices was not available because it is not routinely recorded at every visit; these appointments were defined as follow-up visits. Thus, we defined these covariates included a missing data category.

Statistical analyses

The individual follow-up period was split into the smaller bands using Lexis tabulation in R programming language.[21,22] For each outcome of interest, we calculated the crude mortality rates (MRs) as number of cases divided by person-time at risk along with exact confidence intervals based on Poisson rates. We also assessed age-standardized mortality rates (ASMRs) using weights according to the World Standard Population (1960).

For each outcome of interest, we calculated both absolute and relative differences to compare the MR between individuals with and without periodontitis. Mortality rate ratios (MRRs) and 95% confidence intervals (CIs) were estimated by fitting a multiplicative Poisson regression model to the numbers of events using the logarithm of person-years as an offset. Absolute rate differences (ARDs) along with 95% CIs were calculated by applying an additive Poisson regression model to the incidence rates with person-years as weights.[23] In these analyses, death from causes other than the cancer of interest were treated as censored. Crude and adjusted differences were evaluated using univariate and multivariate Poisson models, respectively. Through adjustment, we controlled in Model 1 for the effect of socio-demographic factors (period, age, sex and occupational status), and in Model 2, additionally, for number of teeth, oral health indices (I, D, DMF), need for periodontal treatment and diabetes.

In addition, by using the fully adjusted estimates of ARD, we calculated number-needed-to-harm (NNH), which is an inverse of ARD and indicates the number of patients on average needing to be exposed to periodontitis to cause the death of one patient who would otherwise have stayed alive.

Sensitivity analyses

Robustness of results was checked by performing sensitivity analysis. In the primary analysis, we analyzed the entire cohort, which included also individuals with missing observations for some covariates. To check whether the differences in mortality rates were similar among individuals with complete observations (i.e., data missing at random), we analyzed individuals with complete data. We also investigated whether the change in the definition of periodontitis affects the results. In addition to periodontitis procedure codes, which were used in the main analysis to define periodontal status, a periodontal pocket depth of >3 mm was also interpreted as periodontitis. We then evaluated the effect of this new exposure variable on mortality rates. We used the version 3.2.2 of R[21] and the *Epi*[24] package to perform all analyses.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in

recruitment, design or implementation of the study. Patients were not asked to interpret or disseminate results.

Results

The study population included 68,273 patients who had cumulated 664,020 person-years (PYs) over a median follow-up of 10.1 years (Table 1). The mean age of the population at baseline was 43 years, and the slight majority was females (58%). The mean number of teeth was 27.6, but that information was not available for 19,633 patients (28.8%). The reason for missing information is that the whole oral health status is not always routinely checked when a patient visits the dentist because of an accident or emergency. Endodontic treatment was the most common procedure, affecting 70.3% of all patients, whereas only 40.6% were treated for gingivitis and 20.5% for periodontitis.

During the 10-year follow-up, 797 cancer deaths occurred. The total number of deaths was 5,434; thus, deaths due to cancer comprised 14.7% of all deaths. Of all cancer deaths, 199 (25%) were observed in patients with periodontitis, for which the crude cancer MR was 14.45 per 10000 person-years (95% CI 12.51–16.61), while for patients without periodontitis, the crude MR was 11.36 (95% CI 10.47–12.31). Lung cancer was the most common diagnosis in cancer mortality, with a crude MR of 2.42 (95% CI 2.06–2.83), followed by cancers of the breast (crude MR = 1.89, 95% CI 1.48–2.37), pancreas (1.13, 95% CI 0.89–1.42) and prostate (0.95, 95% CI 0.62–1.40).

Age-standardized cancer mortality rates in our study were similar to the rates for the general population of Helsinki reported by the FCR for the period 2008–2012 (Table 2). The absolute and relative differences in cancer mortality rates between individuals with and without periodontitis are presented in Table 3. Based on both absolute and relative rate differences, a significantly increased overall cancer mortality was associated with periodontitis. Comparison of MRs on the relative scale yielded a crude MRR of 1.27 (95% CI 1.08–1.86), while a crude ARD of 3.01/10,000 person-years (0.89, 5.30) was observed when comparing mortality rates on the absolute scale. These differences remained significant after adjustment for the available demographic risk factors (Model 1) and further adjustment for diabetes and oral health indices (Model 2), yielding MRR of 1.32 (1.10, 1.58) and ARD of 6.54 (2.48, 10.61) in this fully adjusted model. When comparing site-specific cancer mortality rates among patients with and without periodontitis, the results indicated a twofold risk of death due to pancreatic cancer on the relative scale (Model 2: MRR 2.28, 95% CI 1.31–3.98), but no significant difference on the absolute scale (Table 3).

For other cancer types, no significant differences were found on either the absolute or the relative scale, when performing comparisons of mortality rates by periodontal status. The adjusted ARD in overall cancer mortality between people with and without periodontitis was 6.54 (2.48–10.61) per 10000 person-years, which gives number-needed-to-harm (NNH = 1/ADR) of 1529 (942–4,032) for periodontitis.

The results of the main analysis were robust across the sensitivity analyses performed (Supporting Information, Table/Data not shown). After exclusion of individuals with missing observations (29%), the association between periodontitis and excess overall (fully adjusted MRR 1.26, 95% CI 1.03–1.55) and pancreatic (2.05, 95% CI 1.05–3.99) cancer mortality persisted. After expanding the periodontitis status to incorporate also gum pockets of a depth of >3 mm, a total of 20,269 individuals were interpreted as having periodontitis. Comparisons of mortality rates performed according to this division yielded similar results for overall (1.36, 1.09–1.71) and pancreatic cancer (2.32, 95% CI 1.24–4.37) mortality.

Discussion

Our study with a long follow-up (10 years) of a large population-based cohort ($n = 68,273$) showed a clear positive association between periodontitis and cancer mortality, especially pancreatic cancer mortality.

Strengths and limitations of this study

Strengths of our study are the large, relatively unselected population and the long follow-up time. The study population consisted of patients with at least one visit to dental health care of the City of Helsinki, that is, individuals without any of the aforementioned dental visits were not eligible for the study. In principle, this noneligible population includes people without any dental visits and those utilizing only the private sector dental health care. Usage of private health care may have caused some selection of the study population because about 36% of dental care was covered by it in the study period.[25] On the other hand, observed standardized mortality rates in our study were quite similar to the rates of the entire City of Helsinki population. This means that it is not very probable that population selection would have had a large impact on study results.

The strength of the exposure data in our study is that it contained detailed clinical information about oral health and dental procedures. On the other hand, a limitation of our data is that a large proportion of dental status data is missing, that is, for 28% of the study population, the number of teeth was not known. In statistical analyses, missing information was treated as a separate category that was probably adequate for adjusting purposes. Our primary exposure—periodontal status—was determined by procedure codes, which means that the number of false positives is very low. Connected to this, there are many false negatives, that is, people with periodontitis who were not treated. However, it is reasonable to assume that these false negatives tend to have less severe periodontitis, and thus, the potential bias caused by false negatives can be considered to be relatively small.

Table 1. Basic characteristics of the study population of 68,273 patients

	Periodontitis treatment, $N = 14,021$	No periodontitis treatment, $N = 54,252$
Sex, male *N* (%)	6,461 (46.1)	21,719 (40.0)
Age, mean (SD), years	43.6 (9.8)	43.0 (12.1)
Age groups, *N* (%)		
30–39	7,483 (53.4)	34,372 (63.4)
40–49	4,043 (28.8)	11,315 (20.8)
50–59	1,922 (13.7)	4,546 (8.4)
60–69	224 (1.6)	1,191 (2.2)
≥70	349 (2.5)	2,828 (5.2)
Median follow-up time (IQR)	10.0 (9.6, 10.6)	10.1 (9.5, 10.7)
Person-years (1/10,000)	13.8	52.6
Socio-economic status, *N* (%)		
Lower level employees	4,199 (29.9)	16,358 (30.1)
Upper level employees	2,382 (17.0)	11,022 (20.3)
Manual workers	2,869 (20.5)	9,409 (17.3)
Pensioners	1,376 (9.8)	6,104 (11.3)
Students	399 (2.9)	1,774 (3.3)
Self-employed or employers	457 (3.3)	1,576 (2.9)
Unemployed	1,545 (11.0)	4,971 (9.2)
Unknown	794 (5.6)	3,038 (5.6)
Number of teeth, mean (*SD*)	27.7 (3.9)	27.5 (5.1)
Number of teeth, *N* (%)		
28–32	8,307 (59.3)	25,819 (47.6)
24–27	2,902 (20.1)	6,708 (12.4)
0–23	1,302 (9.3)	3,602 (6.6)
Missing	1,510 (10.8)	18,123 (33.4)
Treatment, *N* (%)		
Caries	3,034 (21.6)	8,854 (16.3)
Endodontic	11,226 (80.1)	36,758 (67.8)
Gingivitis	5,042 (36.0)	22,672 (41.8)
Prosthesis	712 (5.1)	2,359 (4.4)
Surgery	3,846 (27.4)	11,259 (20.8)
I index,[1] *N* (%)		
0	2,942 (21.0)	9,983 (18.4)
1–2	3,811 (27.2)	11,118 (20.5)
3–4	2,428 (17.3)	6,504 (12.0)
≥5	3,336 (23.8)	8,584 (15.8)
Missing	1,504 (10.7)	18,063 (33.3)
D index,[1] *N* (%)		
0	3,970 (28.3)	15,072 (27.8)
1–2	4,666 (33.3)	12,695 (23.4)
3–4	2,029 (14.5)	4,471 (8.2)
≥5	1,859 (13.2)	3,977 (7.3)
Missing	1,497 (10.7)	18,037 (33.3)
DMF index,[1] *N* (%)		
0–13	2,992 (21.3)	10,629 (19.6)

Table 1. Basic characteristics of the study population of 68,273 patients (Continued)

	Periodontitis treatment, $N = 14,021$	No periodontitis treatment, $N = 54,252$
14–18	2,911 (20.8)	8,960 (16.5)
19–23	3,305 (23.6)	8,260 (15.2)
≥24	3,317 (23.6)	8,354 (15.4)
Missing	1,496 (10.7)	18,049 (33.3)
CPI[1]		
0–1	227 (1.6)	6,198 (11.4)
2	7,206 (51.4)	23,981 (44.2)
3–4	5,199 (37.1)	6,248 (11.5)
Missing	1,389 (9.9)	17,825 (32.9)
Number of healthy sextants[2]		
0	9,850 (70.3)	17,896 (33.0)
1	1,597 (11.4)	5,227 (9.6)
2–4	897 (6.4)	7,387 (13.6)
5–6	288 (2.1)	5,917 (10.9)
Missing	1,389 (9.9)	17,825 (32.9)
Number of toothless sextants[3]		
0	11,640 (83.0)	33,305 (61.4)
1–6	992 (7.1)	3,122 (5.7)
Missing	1,389 (9.9)	17,825 (32.9)
Diabetes, *N* (%)	703 (5.0)	1,842 (3.4)

Abbreviations: N, number of individuals; SD, standard deviation; I index, initial caries; D index, decayed teeth; DMF, decayed-missing-filled teeth; CPI, need of periodontal treatment.
[1]Maximum value.
[2]Value at first visit.
[3]Minimum value.
Data from the patient register of the Public Dental Service of the City of Helsinki, individuals aged 29 years or more with at least one primary dental health care visit between 1 January 2001 and 31 December 2002.

Studies investigating the association between periodontal disease and cancer have used a variety of measures to define periodontal disease and the manner in which disease progression is ascertained. There is no standardized definition or clinical criteria for periodontal disease in periodontal epidemiological research, hindering comparisons of studies examining the association between periodontal disease and cancer.[26] Periodontal disease is generally diagnosed by probing and measuring alveolar bone height with radiographs. As periodontitis is a primary cause of tooth loss in adults, the number of lost adult teeth has also been used as a marker of periodontal disease in epidemiological literature. Tooth loss at an older age is more likely to be caused by chronic periodontal disease, while tooth loss at younger ages is probably the result of dental caries.[27] Assessing the presence of periodontal disease by extent of tooth loss alone may be inadequate to examine the link between periodontal disease and cancer; studies in this area may, however, provide some insights into the overall role of oral health in cancer. Tooth loss appears to be a better indicator than probing as a marker of lifetime oral health. Tooth loss or missing teeth has been hypothesized to reflect an individual's lifetime accumulation of oral inflammation.[28] In our study, we used reported history of dental status represented by number of teeth, oral health indices, initial caries, decayed/missing/filled teeth and need for periodontal treatment according to the involvement of gingival pockets. Furthermore, we defined periodontitis as a binary variable (no/yes) based on the procedure codes of periodontitis treatment in the years 2001 and 2002, when we collected data on patients' oral health status. All the collected data support the association between periodontitis and all-cancer mortality, especially pancreatic cancer.

The main potential confounding factors between periodontitis and cancer are tobacco, alcohol, socio-economic status, diabetes, age, gender and ethnicity, along with genetic and dietary factors.[20] Among the potential confounders in this study were socio-demographic characteristics, such as age, sex and socio-economic status, which were available for the entire study population. In addition, we used prescription data to identify patients with diabetes, which is known to affect the risk for both periodontitis and cancer. The study was limited by the lack of information on smoking and alcohol use, which may confound the findings because both are known risk factors of pancreatic cancer. We found a strong

Table 2. Cancer mortality: number of deaths, person-time, crude mortality rates along with 95% confidence intervals and age-standardized mortality rates for any cancer and by specific sites

	Number of deaths	Person-time, 10,000 PY	Crude MR/10,000 PY (95% CI)	ASMR/10,000 PY	General population ASMR[1]/10,000 PY
Lung cancer					
Men	89	27.24	3.27 (2.62–4.02)	2.79	2.95
Women	72	39.16	1.84 (1.44–2.32)	1.63	1.46
Pancreatic cancer					
Men	35	27.24	1.28 (0.89–1.79)	1.30	1.05
Women	40	39.16	1.02 (0.73–1.39)	0.90	0.71
Upper gastric cancer					
Men	38	27.24	1.39 (0.99–1.91)	1.20	2.22
Women	26	39.16	0.66 (0.43–0.97)	0.35	0.92
Esophageal cancer					
Men	18	27.24	0.66 (0.39–1.04)	0.51	0.36
Women	5	39.16	0.13 (0.04–0.30)	0.07	0.11
Gastric cancer					
Men	20	27.24	0.73 (0.45–1.13)	0.69	0.45
Women	18	39.16	0.46 (0.27–0.73)	0.24	0.27
Liver cancer					
Men	20	27.24	0.73 (0.45–1.13)	0.69	0.74
Women	18	39.16	0.46 (0.27–0.73)	0.32	0.21
Head and neck cancer					
Men	12	27.24	0.44 (0.23–0.77)	0.17	0.34
Women	9	39.16	0.23 (0.11–0.44)	0.05	0.09
Breast cancer (women)	74	39.16	1.89 (1.48–2.37)	1.12	1.51
Prostate cancer	26	27.24	0.95 (0.62–1.40)	0.73	1.18
Any cancer					
Men	353	27.24	12.96 (11.64–14.38)	11.10	11.80
Women	444	39.16	11.34 (10.31–12.44)	8.69	8.37

Abbreviations: PY, person-years; CI, confidence intervals; MR, mortality rate; ASMR, age-standardized mortality rate with weights according to the World Standard Population.
[1]Based on cancer statistics from the Finnish Cancer Registry for 2008–2012 for Helsinki area.

positive association between periodontitis at baseline and subsequent risk of fatal pancreatic cancer. However, at the same time, we did not detect any association between periodontitis and lung cancer, which may be interpreted to indicate that confounding by smoking is probably not strong. Altogether, additional studies are needed with more detailed measurements of confounders such as smoking and alcohol use in order to confirm these results.

Comparisons with other studies

Although the NNH of periodontitis for any cancer death (1529) was relatively high, the commonness of periodontitis makes it a risk factor with high public health relevance. In Finland, the population segment aged 30 years and over was 3.6 million in 2015. Using the above-reported NNH figures and assuming a 20% prevalence of periodontitis, we can estimate that 470 cancer deaths occur every year due to periodontitis. Between the years 2009 and 2013, there was on average 11 743 cancer deaths per year in Finland, 1,004 of these due to pancreas cancer. Using these assumptions, we may calculate that about 4% of all cancer deaths are due to periodontitis. In the European Union with ca. 377 million people aged over 25 years, this means about 49,000 cancer deaths using the above assumptions.

In USA, >50,000 people will be diagnosed with pancreatic cancer this year, and because the disease is often not diagnosed until an advanced stage, <10% of those diagnosed will still be alive in 5 years.[29] In Finland, the number of pancreatic cancer cases was 577 in females and 539 in males in the year 2013.[30] The corresponding numbers of deaths for the same year were 526 and 499. Pancreatic cancer is extremely difficult to treat and little is known about its risk factors.

Table 3. Crude overall and site-specific cancer mortality rates, and crude and adjusted mortality rate ratios and absolute rate differences along with 95% confidence intervals in patients with periodontitis compared with patients without periodontitis

Cancer type	Periodontitis (PY, 10,000)	Cancer cases, *N*	Crude MR/ 10,000 PY (95% CI)	Crude ARD/10,000 PY (95% CI)	Crude MRR (95% CI)	Adjusted MRR[1] (95% CI)	Adjusted MRR[2] (95% CI)	Adjusted ARD[2]/ 10,000 PY (95% CI)
Lung cancer	No	120 (52.63)	2.28 (1.89, 2.73)	ref	ref	ref	ref	ref
	Yes	41 (13.77)	2.98 (2.14, 4.04)	0.70 (−0.30, 1.70)	1.31 (0.92, 1.86)	1.08 (0.76, 1.55)	1.20 (0.81, 1.80)	2.64 (−0.11,5.39)
Pancreatic cancer	No	52 (52.63)	0.99 (0.74, 1.30)	ref	ref	ref	ref	ref
	Yes	23 (13.77)	1.67 (1.06, 2.51)	0.68 (−0.05, 1.42)	1.69 (1.04, 2.76)	1.66 (1.01, 2.74)	2.28 (1.31, 3.98)	0.76 (−0.27, 1.79)
Upper gastric cancer	No	47 (52.63)	0.89 (0.66, 1.19)	ref	ref	ref	ref	ref
	Yes	17 (13.77)	1.23 (0.72, 1.98)	0.34 (−0.30, 0.98)	1.38 (0.79, 2.41)	1.18 (0.68, 2.07)	1.23 (0.67, 2.27)	0.47 (−0.54,1.48)
Esophageal cancer	No	17 (52.63)	0.32 (0.19, 0.52)	ref	ref	ref	ref	ref
	Yes	6 (13.77)	0.44 (0.16, 0.95)	0.11 (−0.27, 0.49)	1.35 (0.53, 3.42)	1.06 (0.41, 2.70)	1.04 (0.38, 2.84)	0.29 (−0.67,1.26)
Gastric cancer	No	27 (52.63)	0.51 (0.34, 0.75)	ref	ref	ref	ref	ref
	Yes	11 (13.77)	0.80 (0.40, 1.43)	0.29 (−0.22, 0.80)	1.56 (0.77, 3.14)	1.39 (0.68, 2.81)	1.60 (0.73, 3.52)	0.51 (−0.47,1.49)
Liver cancer	No	29 (52.63)	0.55 (0.37, 0.79)	ref	ref	ref	ref	ref
	Yes	9 (13.77)	0.65 (0.30, 1.24)	0.10 (−0.37, 0.57)	1.19 (0.56, 2.51)	0.96 (0.45, 2.05)	1.26 (0.55, 2.90)	0.29 (−0.62,1.20)
Head and neck cancer	No	14 (52.63)	0.27 (0.15, 0.45)	ref	ref	ref	ref	ref
	Yes	7 (13.77)	0.51 (0.20, 1.05)	0.24 (−0.16, 0.64)	1.91 (0.77, 4.74)	1.65 (0.66, 4.12)	1.66 (0.60, 4.64)	0.28 (−0.46 to 1.03)
Breast	No	56 (31.69)	1.77 (1.34, 2.29)	ref	ref	ref	ref	ref
	Yes	18 (7.47)	2.41 (1.43, 3.81)		1.36 (0.80, 2.32)	1.27 (0.74, 2.17)	1.19 (0.66, 2.12)	1.32 (−1.24 to 3.89)
Prostate	No	20 (20.94)	0.95 (0.58, 1.47)	ref	ref	ref	ref	ref
	Yes	6 (6.30)	0.95 (0.35, 2.07)		1.00 (0.40, 2.49)	1.12 (0.44, 2.80)	1.75 (0.63, 4.87)	3.99 (−1.24 to 3.89)
Any cancer	No	598 (52.63)	11.36 (10.47, 12.31)	ref	ref	ref	ref	ref
	Yes	199 (13.77)	14.45 (12.52, 16.61)	3.01 (0.89, 5.30)	1.27 (1.08, 1.86)	1.18 (1.01, 1.39)	1.32 (1.10, 1.58)	6.54 (2.48, 10.61)

Abbreviations: N, number of cancer deaths; PY, person-year; CI, confidence interval; MR, mortality rate; ARD, absolute rate difference; MRR, mortality rate ratio.
[1]Model 1: adjusted for calendar time, age, sex (except breast and prostate cancers) and socio-economic status.
[2]Model 2: Model 1 additionally adjusted for number of teeth, dental treatments (gingivitis, caries, endodontic caries, surgery and prosthesis), oral health indices (I, D, DMF), need of periodontal treatment and diabetes.

Recognition of periodontitis as an important risk factor is therefore of great importance.

Studies to date indicate a positive correlation between periodontitis and several forms of cancers and include some assessment of potential confounding factors in different populations. The most consistent increased risk was noted between oral and esophageal cancers and periodontitis. Gastric and pancreatic cancers showed an association in most but not all studies. Lung, prostate, hematological and other cancers were less consistently associated with periodontitis or insufficient studies were conducted to determine a predictable pattern.[31]

A few reports exist on the relationship between periodontal disease and cancer mortality, with limited findings. Abnet *et al.* explored the association between tooth loss and total and cause-specific mortality, and found higher upper GI cancer mortality (RR 1.35, 1.14–1.59) in cohort of nearly 29,000 individuals over a follow-up period of 15 years.[32] In addition, a difference in the effect of tooth loss on upper GI cancer mortality was noted between smokers and nonsmokers; the risk of upper GI cancer associated with increased tooth loss among male never-smokers was actually higher than that observed in male ever-smokers. In this population, esophageal, gastric cardia and noncardia cancers were responsible for 51%, 23% and 10% of total cancer deaths, respectively.[33] We did not detect association between periodontitis and esophageal cancer. One reason may be low number of cases ($N = 23$) that makes inference uncertain.

Cabrera *et al.* examined the relation between tooth loss and cancer mortality in a prospective cohort of 1,462 women in western Sweden over a 24-year follow-up. There was no significant association between tooth loss and all-site cancer morbidity or mortality in this study. It should be noted that no association was reported between tooth loss and C-reactive protein in this study.[34] In a cohort study, rural Chinese tooth loss (which occurs through poor dental hygiene) was significantly associated with increased risk for total death from cancer and from upper GI cancer.[33] Hujoel *et al.* showed an increased risk for 884 cancer deaths in 11,328 individuals with periodontitis.[35] By contrast, in the cohort study ($n = 12\ 223$) of Tu *et al.*, there was no significantly enhanced risk between cancer deaths ($n = 549$) and increased number of missing teeth in Scotland. In addition, no evidence of an association between lung cancer and tooth loss was found, with or without adjustment for smoking.[36] In the male cohort study ($n = 48{,}375$) by Michaud *et al.* with a median follow-up of 17.7 years and 5,720 incident cancer cases, periodontal disease was associated with a small but significant increase in overall cancer incidence and mortality, and this increase persisted among never-smokers.[37]

A Japanese 12-year prospective study with 656 subjects aged 80 years found an association between tooth loss and increased orodigestive (including oral cavity and pharynx, esophagus, stomach, pancreas, liver, colon, rectum and anus) cancer mortality (HR: 1.06, 95% CI: 1.01–1.13) after adjustment for sex and smoking status, although the causality remains unclear.[11]

In the following cohort, studies suggest that periodontal disease is a risk factor for pancreatic cancer mortality and may play a role in the development of pancreatic cancer, independent of other known risk factors such as smoking. Hujoel *et al.* also observed an increased risk for 49 pancreatic cancer deaths in 11,328 individuals with periodontitis in the NHANES I population cancer association.[35] In Finland, a significant association between tooth loss and pancreatic cancer (174 cases) was reported in a cohort study (between 1985 and 1997) of male smokers ($n = 29{,}104$).[38] Michaud *et al.* found an association between pancreatic cancer (216 cases) and history of periodontal disease (48,375 males), with the association being higher among nonsmokers after adjustment for age, smoking, diabetes, body mass index and several dietary factors.[39] Ahn *et al.* using the NHANES III data ($n = 12{,}605$), reported a fourfold increase in risk of pancreatic cancer among those with severe periodontitis. In the same study, elevated antibodies to the periodontitis pathogen *Porphyromonas gingivalis* were associated with a threefold increase risk of orodigestive cancer mortality, but a separate examination of this periodontitis pathogen with pancreatic cancer mortality could not be conducted due to insufficient case numbers. Their study suggests *P. gingivalis* as a potential etiological agent.[12] The findings of Michaud *et al.* support this study, and they showed in a large European prospective cohort study ($n = 821$) that individuals with high levels of antibodies against *P. gingivalis* had a twofold higher risk of pancreatic cancer than individuals with lower levels of these antibodies.[40] Furthermore, a recent study determined that people with periodontitis-causing oral pathogens have a greater risk of subsequently developing pancreatic cancer, showing that oral microbiome dysbiosis preceded the development of pancreatic cancer instead of developing after onset of cancer.[41] All these studies are in line with our results. Relative to these cohort studies, our study provides more detailed information on oral health and a more generalizable study population, including both sexes and a wider age range.

Established risk factors in pancreatic cancer are type 2 diabetes, insulin resistance, cigarette smoking and obesity.[39] The impact of diabetes mellitus on periodontitis has been found to be independent of the major risk factor. Periodontitis and related systemic inflammation have an additive effect on the development of diabetic complications, probably via exacerbation of insulin resistance.[42] In our study, after further adjustment for diabetes, the results showed an even stronger association of periodontitis with increased risk of mortality from pancreatic cancer and any cancer.

The associations between oral diseases and general health have recently attracted much attention, and the World Health Organization has recognized the importance of oral health care in preventing fatal chronic diseases.[43]

Although validation by further prospective studies is essential, early diagnosis of initial periodontal disease

associated with preventive treatment of periodontal inflammation[44] may have a significant impact on reducing overall incidence and prevalence of human cancers. Prevention and treatment of periodontitis may thus have substantial implications for public health in terms of prevention and early diagnosis, reducing the morbidity and mortality associated with human cancers.

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