Periodontal disease, edentulism, and pancreatic cancer: a meta-analysis

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Background: Periodontal disease (PD), now our commonest infectious disorder leads to tooth loss, and has been linked to various systemic diseases, including various types of cancer. The aim of this study is to provide a systematic review and a meta-analysis of the relationship between PD, edentulism, and pancreatic cancer (PC).

Patients and methods: From an initial review of 327 references we selected eight studies concerning periodontitis or edentulism with sufficient quantitative information to allow us to examine the risk of PC. We used relative risks (RRs), hazard ratios, or odds ratios to measure the association between periodontitis, edentulism, and PC. We employed random effects models to obtain summary risks, and we also provide measures of study differences and possible biases.

Results: The summary RR for periodontitis and PC was 1.74 [95% confidence interval (CI) 1.41–2.15] and 1.54 for edentulism (95% CI 1.16–2.05). There was no evidence of heterogeneity for either variable, and no evidence of publication bias. The studies included reports from three continents, suggesting that the association is generalizable. Most of the studies were adjusted for variables thought to be associated with PC, such as gender, smoking, BMI, diabetes, and alcohol.

Conclusions: Using meta-analysis, both periodontitis and edentulism appear to be associated with PC, even after adjusting for common risk factors. As yet, the mechanisms linking oral disease and PC are uncertain, but could be related to changes in the oral microbiome—an area of current research.

Key words: periodontal disease, periodontitis, edentulism, pancreas cancer, meta-analysis

Introduction

Pancreatic cancer (PC) is relatively infrequent, but ranks as the fourth most common cause of cancer death [1]. This is mainly due to its poor outcome, to late diagnosis, and to the lack of preventative measures. Because it is age-related, and since populations in most countries are ageing, the absolute number of PC cases is increasing; PC is anticipated to be the second leading cause of cancer death in the United States by 2020 [2, 3].

PC has been extensively studied and many risk factors, including tobacco smoking, heavy alcohol drinking, red meat, fruits and vegetables consumption, obesity, diabetes mellitus, metabolic syndrome, chronic pancreatitis, helicobacter pylori infection, ABO blood group, or allergy, have been identified and often confirmed by meta-analyses. Several of the identified risk factors are interrelated, indicative of common underlying etiological pathways such as insulin resistance [4], inflammation [5], DNA damage, immunity, or genetic susceptibility [6]; altogether they explain only a fraction of all PC cases [7]. Estimates of the fraction of PC attributable to known preventable risk factors range from 24% in China [8] or Japan [9] to 36% in the United Kingdom [10].

Periodontal disease (PD) and alterations in the oral microbiome, which are responsible for its development, have been linked to several forms of cancer including cancer of the oral cavity, head and neck, and cancer of the pancreas [11–13].
Periodontitis is an inflammation of the periodontium caused by a microbial biofilm that adheres to the tooth’s surface. It is characterized by a progressive loss of alveolar bone around the teeth, and, if untreated can lead to tooth loss. PD is a common chronic disease and a major health problem worldwide, affecting about half of adult populations. Globally, severe periodontitis and edentulism affect, respectively, 743 million and 158 million people worldwide [14–16].

The purpose of this study is to review the literature and to employ meta-analytic techniques to quantify the association between periodontitis, edentulism, and PC risk.

**Materials and methods**

**Search strategy, inclusion criteria, and data abstraction**

We carried out a systematic literature search using PubMed, without language or other restrictions, looking for papers referring to PD and PC. Only reports fulfilling the following inclusion criteria were included in the meta-analysis.

- Studies that contained the minimum information necessary to estimate the relative risk (RR) of PC associated with any measure of PD (i.e. periodontitis, tooth loss, gingivitis) and a corresponding measure of uncertainty (i.e. 95% confidence interval (CI), standard error, variance, or P value of the significance of the estimate).
- Case–control and cohort studies, published as original articles.
- Studies that were independent. In case of multiple reports on the same population or subpopulation, we considered the estimates from the most recent or most informative report.

When available, we used adjusted risk estimates and those based on population-based controls.


Titles and abstracts available in PubMed of all identified articles were screened to ascertain their relevance. The full text of 14 of the additional study reports identified from other sources (WEB of Science, Google scholar, and citations in reference lists of identified relevant articles or reviews on the topic) were also evaluated for inclusion in the meta-analysis. Selected articles were reviewed and data were extracted and crosschecked independently by two investigators (PM and ABL) and any disagreement was resolved by consensus among both of them. In the event of duplicate publications, the most recent or more complete publication was used. Fourteen were excluded: five were reviews or comments and did not contain original data, five contained pertinent information but could not be used in the meta-analysis, three did not provide measure of association between PD or tooth loss and PC and one study contained data reported in another report. In total eight studies satisfied the eligibility criteria and were included in the quantitative synthesis (Figure 1). No attempt was made to contact authors of the single report, out of the five which contained pertinent data that could possibly hold sufficient data to provide a risk estimate for our outcome of interest.

We carried out a second literature search in order to present credible measures of the magnitude of the association between a series of established potential confounders (tobacco smoking, alcohol drinking, overweight, diabetes mellitus, metabolic syndrome, or allergy) and PC, looking for recent meta-analyses, pooled analyses or review on the topic.

**Definitions of PD**

The definition and assessment of periodontal status varied across studies, being either self-reported, evaluated by dental examination or retrieved from health claim data. The conditions studied in the various reports also varied including gingivitis, periodontitis, other periodontal diseases, dental plaque, edentulism, or tooth number. In the meta-analysis, we summarized results for the two most frequently studied periodontal conditions, namely ‘Periodontitis’ and ‘Edentulism’ (being toothless to at least some degree). In the absence of specific risk estimates for ‘Periodontitis’ we used risk estimates reported for ‘any periodontal disease’, or ‘unacceptable dental plaque’ defined as a dental plaque covering more than one-third of the teeth. In absence of specific risk estimates for ‘Edentulism’ we used risk estimates reported for the lower category of remaining teeth. Studies reporting on non-sufficiently specific conditions (i.e. oral cavity disease) or related conditions (i.e. oral bacterial infection), studies providing risk estimates using peculiar reference group (i.e. gingivitis) or studies considering the effect of treatment of PD were used a supporting material but could not be included in the meta-analysis.

**Statistical analysis**

RRs or hazard ratios (cohort studies) and odds ratios (case–control studies) were used as a measure of the association between PD and PC. We used random effects models to estimate summary RRs in order to account for heterogeneity of the risk estimates and to provide more conservative risk estimates. Homogeneity of effects across studies was assessed using the $I^2$ statistic [17], which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance. Publication bias was graphically evaluated by funnel plots [18] and quantified by the test developed by Macaskill et al. [19] obtained by a regression of log (RR) on the sample size, weighted by the inverse of the variance. Meta-analysis was carried out using Review Manager software (RevMan) version 5.3.5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

**Results**

Table 1 provides detailed information about the eight studies (seven cohort studies and one case–control study) reporting risk
estimates for the association between periodontitis (six studies) and/or edentulism (four studies) and PC [20–28]. All risk estimates were adjusted at least for age and sex. Further adjustment for tobacco smoking was made in six studies [20, 21, 23, 25, 26, 28], for alcohol drinking in three studies [25–27], for diabetes in three studies [23, 26, 27], or for body mass index (BMI) in four studies [20, 23, 25, 26]. Information on dental status and PD were obtained by dental examination in three studies [20, 22, 28], were self-reported in four studies [21, 23, 25, 26], or were derived from a health claim database in one study [27].

The summary RR (SRR) and 95% CI, using random effect model for periodontitis and edentulism are, respectively, 1.74 (95% CI 1.41–2.15) and 1.54 (95% CI 1.16–2.05) with no evidence of heterogeneity (F = 0%) for either variables, or publication bias (Macaskill’s test P = 0.30 and P = 0.90, respectively) (Figures 2 and 3).

Risk estimates from single studies ranged from 1.55 (95% CI 1.02–2.33) to 4.56 (95% CI 0.93–22.3) for periodontitis and from 1.30 (95% CI 0.70–2.30) to 1.90 (95% CI 0.95–3.81) for edentulism. In two large cohort studies, the risk estimates for periodontitis were adjusted for all potential confounding factors (including age, sex, tobacco smoking, diabetes, and BMI). The risk estimate in these two studies: 1.64 (95% CI 1.19–2.26) in the Male Health Professional Study [23] and 2.06 (95% CI 1.14–3.75) in the Swedish Twin registry study [26] were very close to the SRR estimated from the meta-analysis. In a subset analysis, Michaud et al. [24] also confirmed the association between PD and PC among never smokers (RR 1.57; 95% CI 0.98–2.50).

Apart from the four studies reporting risk estimates for edentulism, Michaud et al. [23] reported risk estimate for tooth loss in the past 4 years, excluding edentulous participants at baseline. Although this risk estimate was not included in the meta-analysis its magnitude (RR, 1.61; 95% CI 1.13–2.31) is similar to the SRR estimated for edentulism.

Five other studies reported pertinent information on the association between oral health, periodontitis or microbiome and PC risk (Table 2) [29–33]. Ljung et al. [30] carried out a large nested case–control study based on data from National Swedish registries and found a modest but significant increased risk of PC (RR, 1.2; 95% CI 1.0–2.4) associated with disease of the oral cavity, which includes but is not limited to PD. Michaud et al. [29] also carried out a nested case–control study based on data from the European Prospective Investigation into Cancer and Nutrition study (EPIC) and found that individuals with high levels (>200 ng/ml) of antibodies against P. gingivalis had a twofold increased risk (OR, 2.14; 95% CI 1.05–4.36) of PC compared with individuals with lower levels. In a national cohort from Taiwan, Wen et al. [31] compared cancer risk among patients with periodontitis and gingivitis. The risk of PC was slightly higher (RR, 1.15; 95% CI 0.75–1.78) in the periodontitis group than in the gingivitis group, but the association was not statistically significant. A similar relation was found by Hujoel et al. [22] in the NHANES I epidemiologic follow-up study with higher risk of PC observed for periodontitis (RR, 1.77; 95% CI 0.85–3.67) than for gingivitis (RR, 1.44; 95% CI 0.67–3.11), corresponding to a 20% excess risk for periodontitis compared with gingivitis. In another cohort study from Taiwan, Hwang et al. [32] compared cancer incidence in treated versus untreated periodontitis patients. PD with treatment was associated with a significantly reduced risk of PC (HR, 0.55; 95% CI 0.35–0.85). Finally, a recent nested case–control study based on longitudinal data from two prospective cohort studies, the American Cancer Society Cancer Prevention Study II and the National Cancer Institute Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial revealed significant increased risk of PC with carriage of P. gingivalis (OR = 1.60; 95% CI 1.15–2.22) and Aggregatibacter actinomycetemcomitans (OR = 2.20; 95% CI 1.16–4.18) assessed from pre-diagnostic oral wash samples, using bacterial 16S ribosomal RNA (16S rRNA) gene sequencing [33].
<table>
<thead>
<tr>
<th>First author</th>
<th>Study design</th>
<th>Study population</th>
<th>Study period</th>
<th>Pancreas cancers</th>
<th>Controls</th>
<th>Dental status</th>
<th>Risk estimate (95% CI)</th>
<th>Adjustments</th>
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<tbody>
<tr>
<td>Stolzenberg-Solomon, 2003 [21]</td>
<td>Cohort</td>
<td>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, Finland</td>
<td>1985, 1997</td>
<td>174 cases</td>
<td>29,104 male smokers</td>
<td>Self-reported Missing teeth</td>
<td>1.00</td>
<td>Age, number of years of smoking, education, urban living, and height (by quintile trend variable)</td>
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<tr>
<td>Hujoel, 2003 [22]</td>
<td>Cohort</td>
<td>NHANES I Epidemiologic Follow-up Study, USA</td>
<td>1971, 1975, F-up 1992</td>
<td>12 cases with periodontitis, 11 gingivitis, 21 edentulism</td>
<td>11,328 persons</td>
<td>Dental examination Periodontal status</td>
<td>1.00, 1.44 (0.67–3.11), 1.77 (0.85–3.67), 1.90 (0.95–3.81)</td>
<td>Age, gender</td>
</tr>
<tr>
<td>Michaud, 2007 and 2016 [23, 24]</td>
<td>Cohort</td>
<td>Male health professionals study, USA</td>
<td>1986, Follow-up 2002, 1986, Follow-up 2012</td>
<td>216 cases</td>
<td>48,375 men, 19,933 never smokers</td>
<td>Self-reported Periodontal disease</td>
<td>1.00, 1.64 (1.19–2.26), 1.00, 1.57 (0.98–2.50)</td>
<td>Age, smoking history (pack-years, time since quit), profession, race, geographic location, physical activity, diabetes, BMI, height, cholecystectomy, NSAID use, multivitamin use, baseline teeth number, dietary factors, total calories</td>
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<td>Hiraki, 2008 [25]</td>
<td>Case–control</td>
<td>Aichi Cancer Center, Japan</td>
<td>2001–2005</td>
<td>178 cases</td>
<td>10,480 controls</td>
<td>Self-reported Remaining teeth</td>
<td>1.00, 1.33 (0.86–2.07), 0.60 (0.32–1.14), 1.33 (0.57–3.10)</td>
<td>Adjusted for age, sex, smoking and drinking status (never, former, current), vegetable and fruit intake, BMI, and regular exercise</td>
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<tr>
<td>Arora, 2010 [26]</td>
<td>Cohort</td>
<td>Swedish Twin Registry, Sweden</td>
<td>1963, F-up 2004</td>
<td>142 cases</td>
<td>15,333 Swedish twins</td>
<td>Self-reported Periodontal disease</td>
<td>1.00, 2.06 (1.14–3.75)</td>
<td>Sex, age, education, employment, number of siblings, smoking status, smoking status of partner, alcohol status, diabetes, and BMI</td>
</tr>
<tr>
<td>Chang, 2015 [27]</td>
<td>Cohort</td>
<td>National Health Insurance Research Database, Taiwan</td>
<td>1998–2005</td>
<td>107 cases</td>
<td>214,890 persons</td>
<td>Health claim data Periodontal disease</td>
<td>1.00, 1.67 (1.05–2.66), 1.42 (0.87–2.30), 1.55 (1.02–2.33)</td>
<td>Age, sex, diabetes, hyperlipidaemia, allergies, viral hepatitis, peptic ulcer,</td>
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</table>
We carried out a review of the literature and identified eight studies reporting on the association between PD or edentulism, a consequence of PD, and PC risk. In a meta-analysis, both conditions were associated with a significant increase risk of developing PC (respectively, +74% and +54% for PD and edentulism), with no evidence of heterogeneity across studies and no evidence of publication bias. Seven of the reports were based on either cohort studies, National health survey or National registry data which should be less subject to bias than case–control studies. Three studies were conducted in North America, three in Northern Europe and two in Asia, providing a good geographical representation and further supporting the generalizability of the association. All studies provided risk estimates adjusted at least for age and sex. In six studies risk estimates were also adjusted for tobacco smoking, in four for BMI, in four for alcohol consumption, in three for diabetes, which represent potential confounding factors.

PC and PD share many common risk factors including tobacco smoking, heavy alcohol drinking, obesity, the metabolic syndrome, diabetes, and allergy (Table 3). In a large meta-analysis of 47 case–control studies and 35 cohort studies, Iodice et al. [34] estimated that PC risk was increased by 74% (RR, 1.74; 95% CI 1.61–1.87) in current cigarette smokers compared with never smokers. Using data from the National Health and Nutrition Examination Survey (NHANES) 2009–2012, Vogtmann et al. [35] found a very similar risk between current cigarette smoking and PD (RR, 1.70; 95% CI 1.57–1.86). Heavy alcohol intake (≥30 grams/day or >3 drinks/day) has also been consistently associated with a modest increase risk of PC in pooled analyses of individual data from cohort studies (RR, 1.22; 95% CI 1.03–1.45) [36] and similarly from case–control studies (RR, 1.22; 95% CI 1.01–1.48) [37]. Da Silva Furtado Amaral et al. [38] carried out a systematic review of studies on alcohol drinking and PD; due to heterogeneity a meta-analysis could not be carried out. However, the authors concluded that alcohol consumption can be considered a ‘risk indicator’ for periodontitis. Obesity represents another common risk factor for PC and PD: In a pooled analysis of individual data from 14 cohort studies, Genkinger et al. [39] found that obese people had a 47% increased risk (95% CI 1.23–1.75) of developing PC compared with individuals of normal weight, a risk similar to that reported by Chaffee et al. [40] for PD (RR, 1.35; 95% CI 1.23–1.47) in a meta-analysis of 28 observational studies.

The association between diabetes and PC, whether as a risk factor or an early manifestation or a consequence of the cancer, has also been reviewed. In a huge pooled analysis of data from 97 prospective studies, the emerging risk factors collaborative group [41] estimated that diabetes was associated with a 51% (95% CI 1.24–1.83) excess risk of PC. In a meta-analysis, Ben et al. [42] found that long-term diabetes (more than 5 years) leads to an 83% increase risk of PC (95% CI 1.38–2.43). In other meta-analyses, Khader et al. [43] and Chávarry et al. [44] found that type 2 diabetes mellitus could also be considered a risk factor for PD and that diabetics had significantly higher severity of PD. The metabolic syndrome, which embraces a series of conditions including obesity, diabetes, dyslipidaemia, and hypertension, has also been associated with PC (RR, 1.55; 95% CI 1.19–2.01) and
PD (RR, 1.71; 95% CI 1.44–2.03) in two meta-analyses from Rosato et al. [45] and Nibali et al. [46], respectively.

Finally allergy has been consistently associated with a reduced risk of PD and in many reports protective against PD. In a meta-analysis of 10 case–control studies and four cohort studies, Gandini et al. [47] reported a 20% risk reduction of PC in allergic individuals (RR, 0.82; 95% CI 0.68–0.99). The inverse association was even stronger with atopic allergy (RR, 0.71; 95% CI 0.64–0.80). The same results were found in a more recent pooled analysis of individual data from 10 cases-control studies [48]. Arbes and Matsui [49] found an inverse association between allergy and oral pathogens or PD. Furthermore, allergy was associated with a risk reduction of PD ranging from 23% in a study by Friedrich [50] to about 50% in a study by Friedrich et al. [51].

Because the association between PD and PC could be subject to residual confounding from common risk factors, it is important to rely primarily on properly adjusted risk estimates. In several of the reports included in our meta-analysis, risk estimates were adjusted for most of these confounders: Michaud et al. [23] adjusted risk estimates for age, smoking history, diabetes, BMI in addition to a series of other variables. In an updated analysis of data from the same cohort but limited to never smokers, Michaud et al. [24] reported a risk of 1.57 (95% CI 0.98–2.50) for PD, which is similar to the risk reported for the whole cohort (RR, 1.64; 95% CI 1.19–2.26), but not subject to residual confounding by tobacco smoking. In the study by Arora et al. [26], the risk estimate for PD (RR, 2.06; 95% CI 1.14–3.75) was fully adjusted for sex, age, education, employment, number of siblings, smoking status, smoking status of partner, alcohol status, diabetes, and BMI and was again similar to the summary risk estimates obtained from our meta-analysis.

Since we observed no evidence of heterogeneity across studies, a thorough sensitivity analysis was not necessary. However, a subgroup analysis limited to studies in which dental status was assessed by clinical examination [20, 22, 28] showed similar results (SRR for PD 2.11; 95% CI 1.28–3.49; SRR for edentulism 1.51; 95% CI 0.96–2.37) than for studies in which dental status was self-reported or obtained from health claim databases (SRR for PD 1.67; 95% CI 1.32–2.10; SRR for edentulism 1.57; 95% CI 1.09–2.27). Limiting analysis to cohort studies, or excluding atypical studies such as the one by Chang which relied on health claim data [27] does not significantly change the results and conclusions (data not shown).

Our results are based on a relatively limited number of published reports but are supported by additional studies showing a significant increased risk of PC associated with carriage of known periodontopathic pathogens and with plasma level of Porphyromonas gingivalis (P. gingivalis) [33, 52, 29]. Porphyromonas gingivalis, a Gram-negative bacterium of the phylum Bacteroidetes has been implicated in the pathogenesis of human periodontitis. One investigation reported a threefold increased risk of orodigestive cancer, including PC, in relation to high levels of P. gingivalis antibodies, even in individuals without overtly expressed symptoms of PD [20]. Therefore, the role of the oral microbiota may not necessarily depend on oral disease. Although P. gingivalis is a well-described periodontal pathogen, it is also a normal inhabitant of the oral microflora, making it unclear whether the observed associations with this bacterium reflect proxy associations with other oral bacteria or perhaps a distinctly dysbiotic oral microbiota [53]. Either direct or indirect competitive exclusion of pathogens, indigenous and commensal oral bacteria may play a significant role in the risk of pancreatic oncogenesis [29]. An increasing number of studies have revealed
<table>
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<tr>
<th>First author</th>
<th>Study design</th>
<th>Study population</th>
<th>Study period</th>
<th>Number of patients</th>
<th>Condition</th>
<th>Risk estimate (95% CI)</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michaud, 2013 [29]</td>
<td>Nested case-control</td>
<td>Europe, EPIC cohort</td>
<td>1992–2000</td>
<td>405 pancreas cancer cases/416 controls</td>
<td>Plasma P. gingivalis High antibody titres against commensal (non-pathogenic) oral bacteria</td>
<td>2.14 (1.05–4.36)</td>
<td>0.55 (0.39–0.83)</td>
</tr>
<tr>
<td>Wen, 2014 [31]</td>
<td>Cohort</td>
<td>Taiwan</td>
<td>1997–2010</td>
<td>57191 patients with periodontitis and 96375 with gingivitis</td>
<td>Periodontitis vs Gingivitis</td>
<td>1.15 (0.75–1.78)</td>
<td>Sex, age and the presence of comorbidities</td>
</tr>
<tr>
<td>Hwang, 2014 [32]</td>
<td>Cohort</td>
<td>Taiwan</td>
<td>1997–2010</td>
<td>38 902 treated and 77804 untreated periodontitis patients</td>
<td>Treated vs Untreated</td>
<td>0.55 (0.35–0.85)</td>
<td>Age, sex, occupation, type 2 diabetes mellitus, hypertension and hyperlipidaemia</td>
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EPIC, European Prospective Investigation into Cancer and Nutrition study; CPSII, American Cancer Society Cancer Prevention Study II; PLCO, National Cancer Institute Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.
that the properties of the overall microbial community is the driver of health and disease [54, 55].

One small case–control study using 16S rRNA amplicon-based sequencing comparing salivary microbiota of PC patients with healthy patients revealed significant differences between the two groups [56]. However, since this study used saliva samples harvested after the onset of PC, it remains unclear whether observed characteristics of the microbiome preceded and contributed to carcinogenesis, or if they developed as a result of the cancer. More informative, the recently reported prospective CPS-II and PLCO cohort studies provides supportive evidence that oral microbiota may play a role in the etiology of PC, in particular since the association remained after exclusion of cases that developed within 2 years of sample collection [33].

There is also good evidence that the oral microbiome and PD are associated with other forms of cancer in particular oral [57], esophageal [58], gastric [58], and colorectal cancer [59].

The mechanism by which the oral microbiota might contribute to the development of PC is still evolving. The oral cavity is an obvious gateway for microbes, which could then enter the

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Pancreatic cancer</th>
<th>Periodontal disease</th>
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<tbody>
<tr>
<td></td>
<td>Meta-analysis of 47 case–control studies and 35 cohort studies (24,726 PC cases)</td>
<td>Prevalence of PD within categories of cigarette and tobacco use in the USA population aged 30 years and older, NHANES 2009–2012</td>
</tr>
<tr>
<td></td>
<td><strong>Current smokers 1.74 (1.61–1.87)</strong></td>
<td><strong>Current smokers 1.70 (1.57–1.86)</strong></td>
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<td></td>
<td>Pooled analysis of data from 14 cohort studies (2,187 PC cases)</td>
<td>Systematic review: due to heterogeneity, no meta-analysis was carried out</td>
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<td></td>
<td>≥30 grams/day 1.22 (1.03–1.45)</td>
<td>Alcohol consumption can be considered a risk indicator for periodontitis</td>
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<td></td>
<td>Lucenteforte, 2012 [38]</td>
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<td></td>
<td>Pooled-analysis of data from 10 case–control studies (5,585 PC cases)</td>
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<td></td>
<td>4–5 drinks/day 1.22 (1.01–1.48)</td>
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<td>6 drinks/day 1.46 (1.16–1.83)</td>
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<td></td>
<td>9 drinks/day 1.60 (1.16–1.22)</td>
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<td>Overweight obesity</td>
<td>Genkinger, 2011 [40]</td>
<td>Chaffee, 2010 [41]</td>
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<td></td>
<td>Pooled analysis of 14 cohort studies (2,135 PC cases)</td>
<td>Meta-analysis of 28 studies</td>
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<td></td>
<td><strong>Obesity 1.47 (1.23–1.75)</strong></td>
<td><strong>Obesity 1.35 (1.23–1.47)</strong></td>
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<td></td>
<td>Pooled analysis of data from 97 prospective studies (2,189 PC deaths)</td>
<td>meta-analysis</td>
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<td><strong>Diabetes 1.51 (1.24–1.83)</strong></td>
<td><strong>Diabetes had a significantly higher severity but the same extent of PD than non-diabetics</strong></td>
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<td></td>
<td>Meta-analysis of 35 cohort studies (20,410 PC cases)</td>
<td>meta-analysis</td>
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<td></td>
<td><strong>Diabetes 1.94 (1.66–2.27)</strong></td>
<td><strong>Type 2 DM can be considered a risk factor for periodontitis</strong></td>
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<td><strong>Diabetes &gt;5 yr 1.83 (1.38–2.43)</strong></td>
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<td></td>
<td>Meta-analysis of 1 case–control and 4 cohort studies (1,352 PC cases)</td>
<td>Meta-analysis of 20 observational studies</td>
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<td><strong>METs 1.55 (1.19–2.01)</strong></td>
<td><strong>METs 1.71 (1.44–2.03)</strong></td>
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<td></td>
<td>Meta-analysis of 10 case–control studies and 4 cohort studies (3,040 PC cases)</td>
<td><strong>Allergy 0.77 (0.58–1.00)</strong></td>
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<td></td>
<td><strong>Any allergy 0.82 (0.68–0.99)</strong></td>
<td>Friedrich, 2006 [52]</td>
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<tr>
<td></td>
<td><strong>Atopic allergy 0.71 (0.64–0.80)</strong></td>
<td><strong>Hay fever 0.53 (0.3–0.9)</strong></td>
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<td>Olson, 2013 [49]</td>
<td><strong>Mite allergy 0.39 (0.2–0.9)</strong></td>
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<td></td>
<td>Pooled analysis of data from 10 case–control studies (3,567 PC cases)</td>
<td><strong>Asthma 0.48 (0.2–1.0)</strong></td>
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<tr>
<td></td>
<td><strong>Any allergy 0.79 (0.62–1.00)</strong></td>
<td><strong>Many negative reports, see review by Arbes et al. [50]</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Hay fever 0.74 (0.56–0.96)</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>Animal allergy 0.62 (0.41–0.94)</strong></td>
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gastrointestinal system or the bloodstream and affect distant organs [60–63]. For example, Helicobacter pylori, one bacteria identifiable in the mouth, has been possibly associated with chronic pancreatitis as well as PC [64, 66]. Oral bacteria may play a role in triggering pancreatitis [67, 68]. The systemic dissemination of oral microbes and their toxins may also trigger systemic inflammatory and immune responses that could contribute to the risk of PC [61, 68–72]. Cancer, and more specifically, PC, is linked to chronic inflammatory states [72, 73]. Meanwhile, oral bacteria are increasingly being implicated in chronic, inflammatory-based systemic diseases [62, 74–76], that may degenerate in tumor development. For example, microbial activation of innate immune signaling via Toll-like receptors was found to inhibit apoptosis and stimulate tumor growth [53, 77, 78].

Oral bacteria play a role in producing carcinogenic metabolic byproducts from oral exposures. Both N-nitroso and acetaldehyde compounds are etiological exposures for PC [69, 79–81]. Oral bacteria convert ethanol to the carcinogen acetaldehyde; they also activate carcinogenic N-nitroso compounds present in tobacco smoke and some foods, and catalyse their endogenous formation from these and other sources [12, 69, 81–87]. Oral nitrate-reducing bacteria play a key role in the formation of carcinogenic N-nitroso compounds in the stomach: oral nitrate reduction is responsible for nearly 80% of one’s total nitrite exposure, and oral nitrate reduction and is directly correlated with urinary N-nitroso compound levels [83]. The endogenous formation of nitrosamines has been found to be substantially higher among individuals with poor oral hygiene than among those with good oral hygiene [88].

Major strengths of this meta-analysis are lack of heterogeneity of risk estimates across studies, the absence of evidence of publication bias and the presence studies supporting the role of microbiota in PC development. The main limitations include the relatively small number of published studies and use of different study designs and definitions of periodontal outcomes across studies.

In summary, available evidence points to an association between PD and subsequent tooth loss with PC. The potential link between oral disease and PC is unclear, but could be related to alterations in the oral microbiome.

**References**


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