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Associations Between Poor Oral Hygiene and Risk of Pancreatic Cancer

A Meta-analysis of Observational Studies

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Objectives: Epidemiological studies have reported the association of poor oral hygiene, especially periodontal disease, and tooth loss with the risk of pancreatic cancer (PC). However, these studies have yielded inconsistent results. Therefore, this systematic review and meta-analysis aimed to investigate the relationship between oral disease and PC.

Methods: We systematically searched the PubMed, Embase, and Cochrane Library databases for English literature since inception through May 2021. We used relative risks, hazard ratios, or odds ratios to measure the association between oral disease and PC. A fixed- or random-effects model was applied to evaluate pooled risk estimates, and sensitivity and subgroup analyses were performed to identify sources of heterogeneity and pooled estimation.

Results: We identified 17 relevant observational studies involving 1,352,256 participants. Notably, oral disease correlated significantly with PC (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.13–1.54). In subgroup analyses, subjects with periodontal disease (HR, 1.38; 95% CI, 1.12–1.71) had a higher risk of developing PC than those with tooth loss (HR, 1.19; 95% CI, 0.97–1.46).

Conclusions: The results suggest that subjects with oral disease may face a significant and independent risk of PC. However, the mechanisms linking oral disease and PC are uncertain, and additional investigations of this correlation are warranted.

Key Words: pancreatic cancer, oral hygiene, periodontal disease, meta-analysis

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Pancreatic cancer (PC) is a fatal malignant tumor with an overall 5-year survival rate of approximately 5%, with very poor prognosis.[1] Pancreatic cancer ranks as the fourth leading cause of cancer-related deaths in the United States and seventh leading cause of cancer deaths worldwide.[2] The latest data from the Global Cancer Observatory showed that PC accounted for almost as many deaths (466,000) as cases (496,000) in 185 countries in 2020,[3] with the highest incidence rates in Europe and North America. Although advancements in treatment, such as chemotherapy, radiation, and immunotherapy, have improved the overall short-term survival, the long-term survival and prognosis remain poor. This is mainly attributable to the fact that most patients with PC are diagnosed at a later stage of disease because of the lack of specific symptoms, which otherwise prompt an early investigation.[4] Pancreatic cancer is extremely difficult to treat, and little is known about its risk factors; therefore, further studies are warranted for better understanding of its etiology and pathogenesis.

It is reported that some modifiable factors, including smoking, alcohol abuse, obesity, as well as diet,[5–7] and some nonmodifiable factors, such as genetics, diabetes mellitus, and age, can increase the risk of PC.[8,9] Accordingly, other risk factors, such as conditions related to oral disease, are thought to correlate with an increased risk of PC.[10–12] Oral hygiene might potentially affect nutritional status and microbial flora. In addition, emerging evidence suggests that the mechanism of periodontal disease (PD) in the pathogenesis of PC is associated with a chronic inflammatory process.[13] For instance, the bacteria involved in PD stimulate the production of inflammatory mediators and secretion of various cytokines, ultimately promoting cell proliferation, mutagenesis, oncogene activation, and angiogenesis,[14] indicating that PD may be a considered a high-risk factor for PC.[15–17] However, conclusions from the abovementioned studies are inconsistent and, in some cases, contradictory. Therefore, a better understanding of the etiology of PC, interactions between risk factors, and new approaches to prevention and treatment are required to improve the outcomes of this disease.

A meta-analysis involving the systematic summarization of existing data may provide more credible evidence than a relatively small sample from a single study. For this reason, we used a meta-analysis to comprehensively summarize the existing relevant data and investigate the hypothesis that oral disease may be an independent predictor of PC. In addition, this report aimed to discuss the important role of chronic periodontal inflammation in the development of PC.

MATERIALS AND METHODS

Search Strategy

The literature search strategy was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18] The PubMed, Embase, and Cochrane Library databases were searched systematically to identify relevant studies from the earliest available data until May 2021. The following Medical Subject Headings terms and key words were used as search terms: oral disease, oral hygiene, periodontal disease, periodontitis, tooth loss, tooth miss, alveolar bone loss, periodontal pocket, clinical attachment loss, pancreatic cancer, pancreatic neoplasms, pancreas cancer, and pancreas neoplasms (Supplemental Table 1,

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http://links.lww.com/MPA/A978). The search was restricted to studies conducted on human subjects and those published in English.

Eligibility Criteria

Studies were considered eligible for analysis if they met the following criteria: (1) an observational study design, including cross-sectional, case-control, and cohort studies and (2) studies that contained the minimum information necessary to estimate the relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs) to measure the association between oral disease and PC. In cases of multiple reports on the same population or subpopulation, either the most recently published study or the study with the longest follow-up period was included.

Data Extraction

Two independent reviewers (S.X. and H.L.W.) selected the studies for inclusion and extracted the data. Any discrepancies or uncertainties were resolved by consensus after rechecking the source and discussing with a third reviewer (G.Z.). The following information was extracted from all included publications: first author, publication year, country, study design, sample size, sex, age, follow-up duration (in years), exposure assessment, PC criterion, adjusted HR/RR values and corresponding 95% confidence intervals (CIs), covariates in the fully adjusted model, and study quality.

Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale was used to evaluate the quality of the retrieved case-control and prospective studies.[19] These comprehensive tools have been partially validated as measures of the quality of observational studies in meta-analyses. Both tools yield scores according to the following system: low quality, 0–4; moderate quality, 5–7; and high quality, 8–11.[20] A higher score indicates better methodological quality.

Statistical Analysis

Relative risks or HRs and ORs were used as the measure of the association between oral disease and PC. Statistical heterogeneity among studies was evaluated using Cochran Q test and quantified using the I^2 metric. This parameter was used to establish whether it was reasonable to assume a consistent estimate of HR across studies.[21] For the Q statistic, a P value less than 0.10 was considered to indicate statistically significant heterogeneity. For the I^2 statistic, the following cutoff points were used: less than 30% (little or no heterogeneity), 30% to 75% (moderate heterogeneity), and more than 75% (high heterogeneity).[22] When the heterogeneity among studies was high, a random-effects model was used to calculate the pooled estimates. Otherwise, a fixed-effects model was applied. Forest plots were produced to visually assess the HR estimates and corresponding 95% CIs across studies; this was done for individual studies as well as for all studies combined.

To explore the potential causes of and test possible associations for heterogeneity, subgroup analyses based on the adjusted HR/RRs were conducted according to geographical region, study design, sample size, sex, exposure assessment, length of follow-up, and methodological quality. Furthermore, potential publication bias was assessed using Begg rank correlation test and Egger linear regression method.[23,24] Funnel plots were also generated to assess the publication bias. In cases of possible publication bias, a trim-and-fill algorithm strategy was used to correct the asymmetry of the funnel plot.[25] Finally, a sensitivity analysis was performed by sequentially eliminating one individual study from the meta-analysis at a time using the Metaninf algorithm in STATA software (version 12.0; STATA Corporation, College Station, Tex). All reported P values were 2-tailed, and a P value less than 0.05 was considered statistically significant.

RESULTS

Literature Screening

A detailed illustration of the study selection process is presented in Figure 1. Briefly, the preliminary literature search identified 937 potentially relevant articles. After evaluating the titles and abstracts, 366 studies were selected for a full-text review. Finally, 17 articles containing data from 1,352,256 participants were included in this meta-analysis.

Study Characteristics

The characteristics and adjusted covariates of each study are listed in Table 1. All analyzed studies were published between 2003 and 2020 and contained analyzed data collected from studies conducted between 1963 and 2016. The reports included 1 case-control study[29] and 16 prospective cohort studies.[12,17,26–28,30–40] Across all studies, the reported ages of participants ranged from 18 to 86 years. Seven, 6, and 4 studies were primarily conducted in the United States, Asia, and Europe, respectively. All studies reported adjusted HR/RR/OR values, and only one study did not adjust the analysis for potential confounders. All cases of PC had been pathologically or cytologically confirmed. An association of PD with PC was reported in 14 studies, whereas 3 demonstrated an association of tooth loss with PC. The parameters of PD exposure varied among studies and included the gingival bleeding index, alveolar bone loss, and clinical attachment loss. The overall quality of the studies was high, with no remarkable limitations (Supplemental Table 2, http://links.lww.com/MPA/A978).

Meta-analysis

The adjusted HR/RR/ORs from the 17 studies were pooled and analyzed as presented in Figure 2. Overall, oral disease exhibited a statistically significant correlation with PC (HR, 1.32; 95% CI, 1.13–1.54) and remained an independent risk factor for PC even after adjusting for confounders such as smoking, alcohol consumption, age, and sex. In other words, our analysis strongly suggests that participants with tooth loss or PD face a significantly increased risk of PC.

As we detected moderate statistical heterogeneity among the studies ($P = 0.001$, $I^2 = 60.6\%$), we used the random-effects model to merge HR values. In addition, Begg test ($P = 0.537$), Egger test ($P = 0.002$), and a funnel plot revealed minor publication bias (Fig. 3). Therefore, we applied the trim-and-fill method to re-evaluate the pooled risk estimates, which yielded a result of "no trimming performed; data unchanged." Sensitivity analyses conducted during the sequential elimination of each study did not alter the overall risk estimate, which ranged from 1.13 (95% CI, 1.09–1.29) to 1.54 (95% CI, 1.45–1.63; Fig. 4). These sensitivity analyses indicate that the results of this meta-analysis are stable and reliable.

Subgroup Analysis

To examine the stability of the studies, we conducted subgroup analyses based on several factors. When we stratified subjects by poor oral hygiene condition, we found that those with PD (HR, 1.38; 95% CI, 1.12–1.71) faced a slightly higher risk of developing PC compared with those with tooth loss (HR, 1.19; 95% CI, 0.97–1.46; Table 2). In a sex-specific subgroup analysis, we found that 4 male-pooled studies demonstrated an increased risk of PC

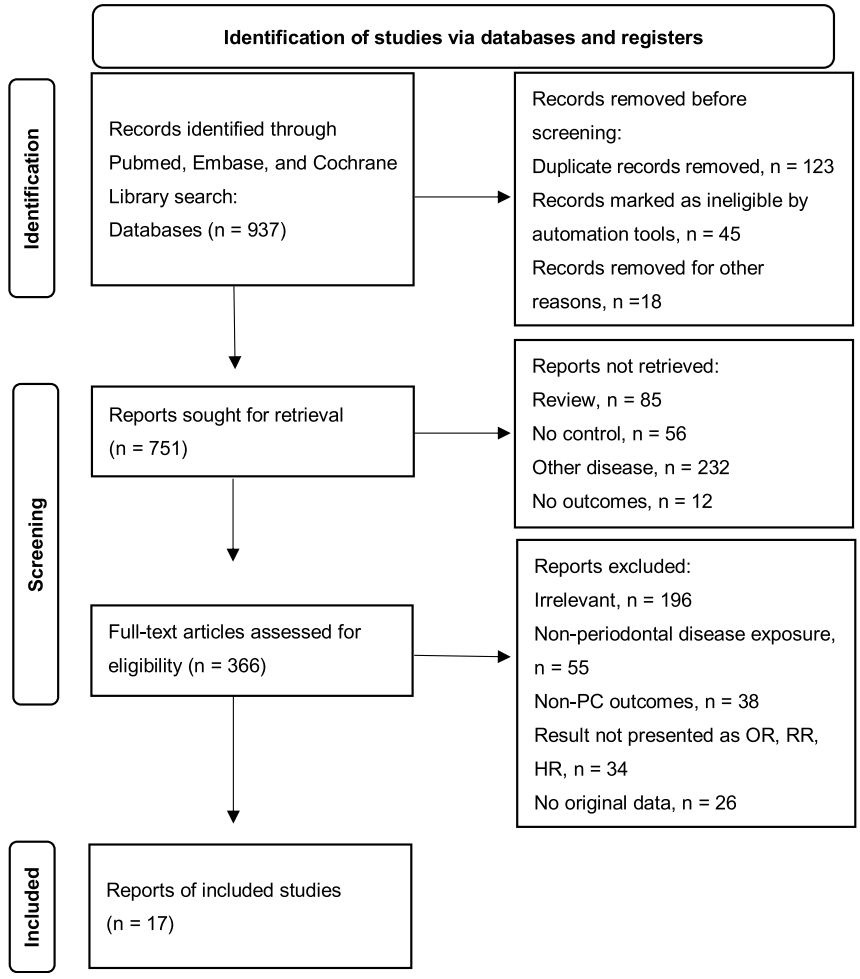

FIGURE 1. Flowchart demonstrating the process from the identification of eligible studies to their final inclusion.

(HR, 1.53; 95% CI, 1.29–1.82), whereas 2 female-pooled studies showed only a marginally increased risk of PC (HR, 1.00; 95% CI, 0.60–1.66). In terms of geographical distribution, the incidence rate of PC in European countries is significantly higher (HR, 1.76; 95% CI, 1.36–2.27) than that of the United States (HR, 1.40; 95% CI, 1.07–1.82) and Asia (HR, 1.02; 95% CI, 0.91–1.14). Overall, our subgroup analyses based on various factors revealed that subjects with either tooth loss or PD have a high risk of developing PC.

DISCUSSION

We reviewed the literature and identified 17 studies reporting the association between PD and PC risk. Our results showed that oral disease is associated with an increased risk of PC (HR, 1.32; 95% CI, 1.13–1.5), with no evidence of heterogeneity across studies and no evidence of publication bias. Even after adjusting the results for smoking, alcohol, sex, age, and education, subjects with tooth loss or PD had a significantly increased risk of PC.

Our results concurred with those of previous studies that support a positive association between PD and PC risk.[41,42] Maisonneuve et al[42] pooled 8 studies in a meta-analysis and reported that PD (HR, 1.74; 95% CI, 1.41–2.15) and edentulism (HR, 1.54; 95% CI, 1.16–2.05) seem to be associated with PC, even after adjusting for common risk factors. In the updated Health Professionals Follow-up Study analyses, PD was associated with PC in smoking-adjusted multivariable models (HR, 1.54; 95% CI, 1.16–2.04) and for smoking-related cancers among nonsmokers that included an elevated risk of PC (HR, 1.57; 95% CI, 0.98–2.50).[36] In a study by Arora et al,[30] the risk estimate for PD (RR, 2.06; 95% CI, 1.14–3.75) was fully adjusted for known risk factors and was also similar to the summary risk estimates obtained from our meta-analysis.

Pancreatic cancer and PD share many common risk factors, including tobacco smoking, heavy alcohol drinking, obesity, metabolic syndrome, diabetes, and allergy. Smoking has been considered the most important environmental risk factor for PC.[43] In Finland, a significant association between tooth loss and PC (174 cases) was reported in a cohort study (between 1985 and 1997) of male smokers (n = 529,104).[12] Michaud et al[27] found an association between PC (216 cases) and history of PD (48,375 males), with the association being higher among nonsmokers after adjustment for age, smoking, diabetes, body mass index, and several dietary factors. Moreover, excessive alcohol consumption is considered the main cause of chronic pancreatitis, which is a known risk factor for PC.[44] For instance, the most recent meta-analysis found that low and moderate alcohol consumption was not associated with PC risk; however, in those with high alcohol consumption, there was a 15% increased risk of PC.[45] After extensive adjustment for recognized confounders (age, sex, race, alcohol, education), our

TABLE 1. Characteristics of the Observational Studies on Oral Hygiene and PC Included in This Meta-analysis

Study, Year	Country	Study Design	n	Sex	Age, y	Followed	Oral Disease Criterion	Dental Status	Pancreatic Criterion	Risk Estimates (95% CI)	Adjustments	Quality
Hujoel et al,[26] 2003	United States	Cohort study	11,328 adults	M: 4469 F: 6859	25–74	1971, 1975 F-up 1992	A medical and dental examination with a periodontal pocket and attachment loss	PD	Diagnosed with pancreas obtained (*ICD-9* 157.0–157.9)	OR, 1.77 (0.85–3.67)	Age, sex	High
Stolzenberg et al,[12] 2003	Finland	Prospective cohort study	29,104 males	M: 29,104	50–69	1985–1997	Questionnaires	Tooth loss	Diagnosed with pancreas obtained coded *ICD-9* 157	HR, 1.63 (1.09–2.46)	Age, smoking history, education, urban living, and height	Low
Michaud et al,[27] 2007	United States	Prospective cohort study	51,529 White males	M: 51,529	40–75	1986 to January 31, 2002	Questionnaire	PD	Diagnoses of PC were confirmed with medical records (95%)	RR, 1.64 (1.19–2.26)	Age, smoking history, profession, race, geographic location, physical activity, diabetes, BMI, height, history of cholecystectomy, nonsteroidal anti-inflammatory drug use, multivitamin use, dietary intake of fruits and vegetables, vitamin D, calcium, sucrose, and total calories	Low
Michaud et al,[28] 2008	United States	Prospective cohort study	48,375 males	M: 48,375	40–75	1986 to January 31, 2004	Radiographs examined to assess bone loss in all posterior teeth present	PD	Medical records or pathology reports	HR, 1.54 (1.16–2.04)	Age, race, physical activity, history of diabetes, alcohol, body mass index, geographic location, height, calcium intake, total caloric intake red meat intake, fruit and vegetable intake, and vitamin D score, smoking history	Low
Hiraki et al,[29] 2008	Japan	Case-control study	5240 cancer and 10,480 noncancer	Case: F: 2541 M: 2699; Control: F: 5082 M: 5398	18–79	January 2001 to November 2005	A self-administered questionnaire	Tooth loss	Cancers were defined according to the *ICD*, pancreas (C25)	OR, 1.33 (0.57–3.10)	Age, sex, smoking and drinking status, vegetable and fruit intake, BMI, and regular exercise	High
Arora et al,[30] 2010	Swedish	Prospective cohort study	15,333 twins	F: 55% M: 45%	38–77	1963–2004	Questionnaire	PD	Physician and pathologist reports	HR, 2.06 (1.14–3.75)	Sex, age, education, employment, number of siblings, smoking status, smoking status of partner, alcohol status, diabetes, and BMI	High
Ahn et al,[31] 2012	United States	Prospective cohort study	12,605 periodontitis	M: 6046 F: 6559	17 and older	1988 to 2006	Periodontal attachment loss and pocket depth	PD	Pancreatic cancer coded by the *ICD-10-C25*	RR, 4.56 (0.93–22.29)	Age, sex, smoking status, education, race/ethnicity, and BMI	High
Ansai et al,[32] 2013	Japan	Prospective cohort study	657	M: 277 F: 420	80	1998–2010	A medical questionnaire	Tooth loss	Cancer deaths coded by the *ICD-10*	HR, 0.96 (0.83–1.11)	Sex and smoking status, total cholesterol, serum albumin, fasting serum glucose, BMI, physical activity, place of residence	High

Wen et al,[33] 2014	China	Nationwide cohort study	51,791 periodontitis and 96,375 gingivitis patients	M: 73,810 F: 71,086	Older than 20	January 1, 1997 to December 31, 2010	Diagnosed with periodontitis (*ICD-9-CM* codes 523.3 and 523.4)	PD	Cancer diagnosis (*ICD-9-CM* codes 140–194, 200–208)	HR, 1.15 (0.75–1.78)	Sex, age, and the presence of comorbidities	High
Huang et al,[34] 2016	Sweden	Cohort study	19,924	M: 9862 F: 10,062	≥15	1973–1974 to 2012	Clinical examination of dental plaque	PD	PC of death register (*ICD-7* to *ICD-9*: 157; *ICD-10*: C25)	HR, 1.30 (0.70–2.30)	Age, sex, and attained calendar period in 10-year-intervals, tobacco use, alcohol consumption, and area of residence	High
Chang et al,[35] 2016	Taiwan	Retrospective cohort study	139,805 with PD and 75,085 without PD	PD: M: 63,958 F: 75,847 Without PD: M: 38,515 F: 36,570	Mean age, 39.4 vs 46.7	1998–2005	Diagnosis of PD (*ICD-9-CM* code: 523)	PD	Diagnosis issued by the hospital with confirmation by laboratory results, histology, and/or diagnostic imaging	HR, 1.55 (1.02–2.33)	Age, sex, diabetes, hypelipidemia, allergies, viral hepatitis, peptic ulcer, pancreatitis, COPD, and alcohol-related conditions	High
Michaud et al,[36] 2016	United States	Prospective cohort study	19,933 males	M: 19,933	40–75	1986 to 2012	Questionnaire	PD	Medical records were obtained from physicians/hospitals	HR, 1.26 (0.82–1.93)	Age, race, alcohol use, physical activity, history of diabetes, body mass index, geographical location, height, NSAID use	Low
Nwizu et al,[37] 2017	United States	Prospective cohort study	65,869 females	F: 65,869	54–86	1999 and 2003 to September 2013	Questionnaire	PD	*International Classification of Diseases for Oncology* (*ICD-O-2*)	HR, 0.89 (0.67–1.18)	None	Low
Chou et al,[38] 2018	China	Retrospective cohort	67,672 with PD	M: 34,395 F: 33,277	≥18	January 1, 2001, to December 31, 2010	A diagnostic code of periodontitis (*ICD-9*, 5234 and 5235)	PD	Pancreatic cancer was diagnosed using the *ICD for Oncology* (C25)	HR, 0.90 (0.47–1.75)	Age, sex, comorbidities, Charlson Comorbidity Index score, medication, and socioeconomic status	High
Heikkilä et al,[39] 2018	Finland	Cohort study	68,273	F: 58% M: 42%	Mean age, 43	January 1, 2001, and December 31, 2002, continued until December 31, 2013, or death	Data from dental visits within a period starting 2 y after the first visit	PD	Cancer defined by topology (*ICD-O-3*): pancreas (C25)	RR, 2.28 (1.31–3.98)	Calendar time, age, sex, and socioeconomic status, number of teeth, dental treatments, oral health indices, need of periodontal treatment, and diabetes	High
Gerlovin et al,[40] 2019	United States	Prospective cohort study	3088	F: 3088	33–81	2007–2016	Questionnaire	PD	Pancreatic adenocarcinoma (*ICD-10* codes C25.0–25.9, histology code 8140).	HR, 1.77 (0.57–5.49)	Age, smoking status, pack-years of smoking, alcohol consumption, BMI, and type 2 diabetes	Low
Lee et al,[17] 2020	Korea	Prospective cohort study	150,774	M: 91,855 F: 58,919	40–79	January 2002 to December 2015	A medical health examination program	PD	Pancreatic cancer coded by the *ICD-10* classification (C25)	HR, 0.98 (0.85–1.14)	Age, smoking history, profession, race, geographic location, physical activity, history of diabetes, BMI, height, history of cholecystectomy, nonsteroidal anti-inflammatory drug use, multivitamin use	High

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; F-up, follow-up; *ICD*, *International Classification of Diseases*; NSAID, nonsteroidal anti-inflammatory drug.

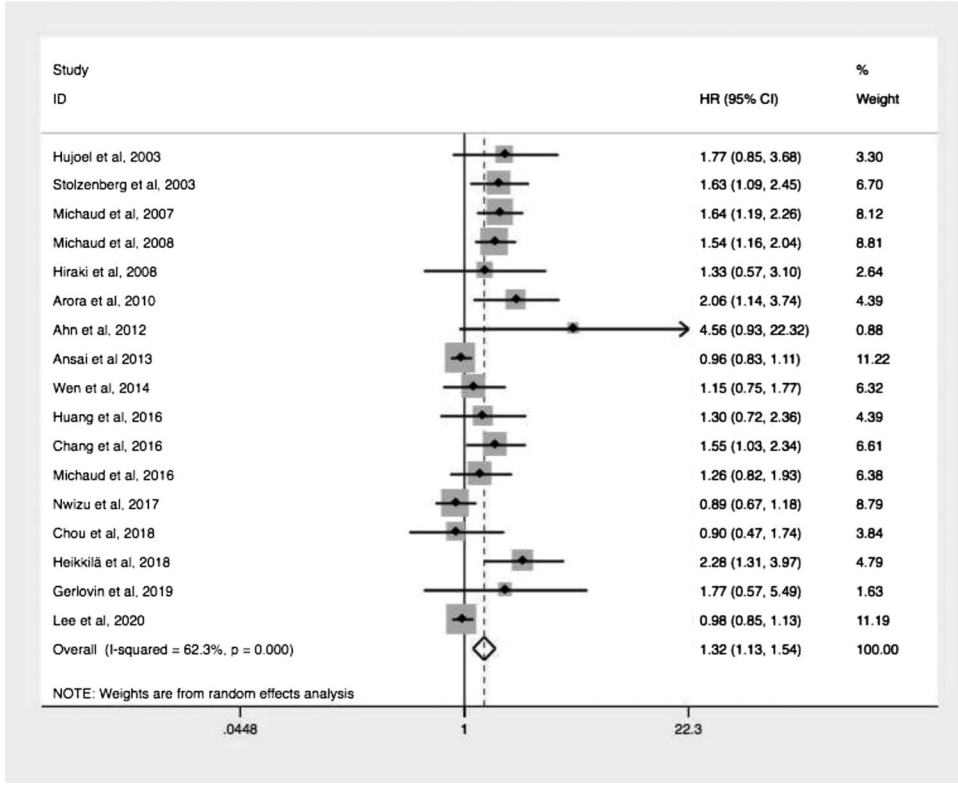

FIGURE 2. Meta-analysis of observational studies on oral hygiene and PC in a random-effects model. The horizontal lines correspond to the study-specific HR/RR/OR and 95% CI. The areas of the squares reflect the study-specific weights.

meta-analysis results suggest that PD is a risk factor for PC mortality and may play a role in the development of PC, independent of other known risk factors.

How can PD, which occurs in the oral cavity, be linked to cancer development at a distant site such as the pancreas? Periodontal disease is a chronic inflammatory disease affecting the supporting structures of the teeth, which is induced by pathogenic bacteria.[10] Several possible mechanisms have been proposed. Oral infection may result in inflammation at distant sites, and chronic inflammation is known to induce carcinogenesis.[35] Given the lack of strong evidence that specific pathogenic oral bacteria are found in the pancreatic tumor tissue or tumor microenvironment, it is likely that the oral microbiome influences PC risk through systemic impact on immune function and inflammation, which is plausible, given the association between inflammation and PC. Several biological mechanisms could explain the link between periodontitis and cancer risk, including systemic inflammation, immune dysregulation due to chronic periodontitis, and alteration of cancer signaling pathways by oral pathogens. Elevated systemic markers of inflammation in patients with chronic periodontitis include interleukin 6, tumor necrosis factor α, and fibrinogen. In addition, periodontopathogenic bacteria may enter circulation and induce inflammatory response at distant sites.

Alternatively, emerging evidence suggests that the host's immunity and inflammatory responses to oral bacteria, rather than the bacteria themselves, cause PD.[46] Oral bacteria is involved in producing carcinogenic metabolic by-products from oral exposures. Both N-nitroso and acetaldehyde compounds are etiological

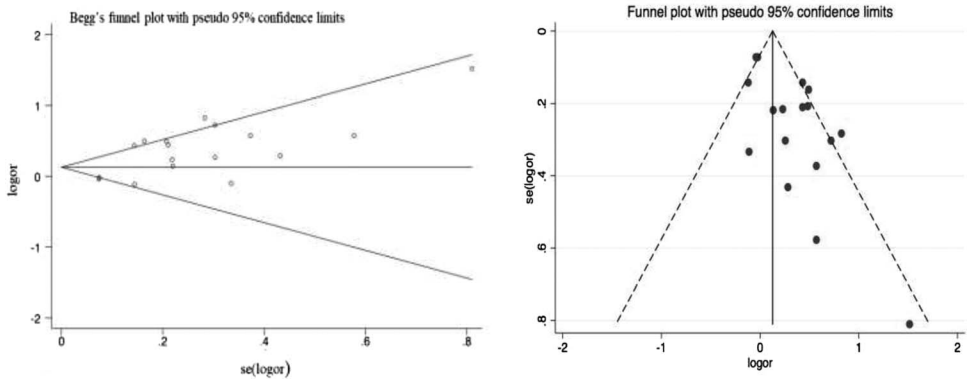

FIGURE 3. Begg funnel plot of publication bias in the included studies. Funnel plot of the included studies for publication bias. Each point represents a separate study for the indicated association.

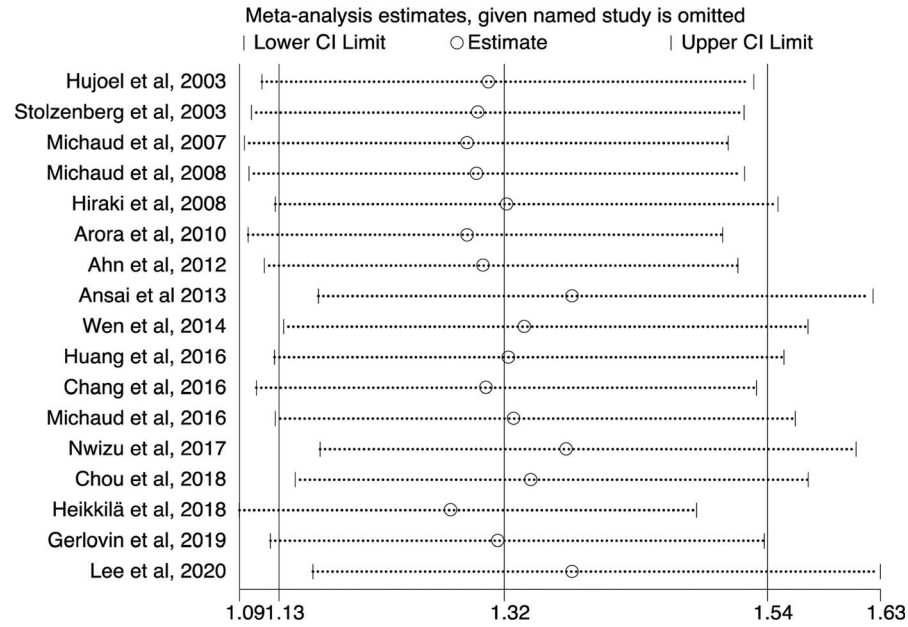

FIGURE 4. Sensitivity analysis of the meta-analysis of the correlation between oral hygiene and PC. The HR/RR/OR and 95% CI were determined by omitting each study from the pool of eligible studies concerning the link between oral hygiene and PC.

factors for PC. Oral bacteria convert ethanol to acetaldehyde, a carcinogen; they also activate carcinogenic N-nitroso compounds present in tobacco smoke and some foods and catalyze their endogenous formation from these and other sources. Moreover, 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 the total nitrite exposure by an individual; it is also directly correlated with urinary N-nitroso compound levels.[47] 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. The importance of periodontal infections to PC is further strengthened by pilot intervention trials indicating that periodontal therapy can prevent and reverse cancer adverse events, for example,

TABLE 2. Results of Subgroup Analyses Included in This Meta-analysis

Group	No. Studies	Pooled HR (95% CI)	*P* (Heterogeneity)	I^2, %
All studies	17	1.32 (1.13–1.54)	0.000	62.3
Assessment				
Periodontal disease	14	1.36 (1.13–1.63)	0.002	60.8
Missing tooth	3	1.21 (0.81–1.82)	0.047	67.4
Study design				
Prospective cohort study	16	1.32 (1.12–1.54)	0.000	64.6
Case-control study	1	1.33 (0.57–3.10)	0.000	0.0
Location				
America	7	1.40 (1.07–1.82)	0.034	55.9
Europe	4	1.76 (1.36–2.27)	0.525	0.0
Asian	6	1.02 (0.91–1.14)	0.344	11.1
Sex				
Male	4	1.53 (1.29–1.82)	0.786	0.0
Female	2	1.00 (0.60–1.66)	0.248	25.0
No. participants				
>10,000	15	1.37 (1.15–1.62)	0.002	59.9
<10,000	2	1.00 (0.75–1.33)	0.294	9.3
Length of follow-up, y				
>10	13	1.27 (1.07–1.50)	0.001	64.3
<10	4	1.51 (1.13–2.01)	0.292	19.7
Study quality				
High	11	1.28 (1.05–1.55)	0.007	59.1
Low and moderate	6	1.36 (1.07–1.73)	0.039	57.2

reducing the pathogenesis of distal inflammatory processes, such as the pathogenesis of cancer.

In addition to inducing inflammation, some oral bacteria have been shown to activate carcinogens contained in alcohol and cigarettes. For example, studies have shown the capability of nonpathogenic *Neisseria* and streptococci, which are both commonly present in the mouth, in converting ethanol into acetaldehyde, which is an established carcinogen.[48,49] Furthermore, certain common oral bacteria, including *Streptococcus mitis* and *Veillonella dispar*, were found to activate nitrosamine in cigarette smoke.[50] Although some mechanisms have been proposed, the cause of PC in relation to periodontitis remains unclear. Therefore, further studies are required to confirm the relationship between periodontitis and PC in future investigations.

In addition to PD, tooth loss has been considered a potential risk factor for PC. For instance, a meta-analysis that pooled four studies on edentulism suggested that edentulism is associated with PC, even after adjusting for common risk factors (RR, 1.54; 95% CI, 1.16–2.05).[51] In this regard, tooth loss is of notable interest because it can be an indicator of severe periodontitis. However, it can also be related to several other conditions or factors; thus, tooth loss may not be an accurate or appropriate measure of periodontitis/PD. Furthermore, tooth loss may be a surrogate measure of high bacterial load on teeth because of poor dental hygiene practices and a possible marker for the presence of gastrointestinal flora, which may be related to the risk of PC.[52] In a large cohort study, a statistically significant 2-fold increase in the risk of PC was observed for those who had dental plaque covering more than one-third of the tooth surface versus no dental plaque at the baseline examination among those with at least 10 teeth remaining.[34] In addition, it was reported that as edentulous and dentate individuals with missing teeth change their eating habits,[53] they may avoid certain nutritious foods because of the difficulty in chewing and would opt for high-calorie, high-fat foods instead.[54] Because there is a reduced ability to pulverize foods to small particle sizes during the masticatory process, deglutition and digestion of larger particles may take longer durations, which might adversely affect the intestinal absorption of nutrients and increase the risk of PC.[55] Ultimately, the changes in eating habits due to tooth loss and consequent chronic malnutrition predispose these individuals to an increased risk of death. For instance, Hujoel et al[26] showed that edentulous individuals had an elevated risk of death from PC (OR, 1.90; 95% CI, 0.95–3.81). However, Michaud et al[27] found that the association between incident tooth loss and PC was further attenuated when PD was added to the model, suggesting that tooth loss may not be an independent risk factor. The results of this meta-analysis showed that tooth loss has a slight association with the increased risk of PC, after analyzing 3 large cohort studies (OR, 1.21; 95% CI, 0.81–1.82). The findings from studies that evaluated tooth loss were less consistent, with only a few of the associated risk estimates reaching statistical significance, and had no general evidence of a trend in risks related to the number of teeth lost.

In addition, incidence rates of PC are higher in high Human Development Index countries especially in Europe and North America.[3] Understanding the geographic distribution of PC is important in assessing disease burden and in identifying high-risk populations. Differences in incidence rates are strikingly apparent and as high as 20-fold between the populations with the highest rate of 9.7 per 100,000 in Europe and the lowest rate with a reported incidence of 0.5 per 100,000 in South Asia. A further study showed that it ranges from 7.3 to 7.4 per 100,000 population in North America and Western Europe to 1.0 per 100,000 population in Middle Africa and South Central Asia.[56] In this meta-analysis, 7 studies were conducted in the United States, 4 in Europe, and 6 in Asia, providing a good geographical representation and further supporting the generalizability of the association. The result suggests that the United States (HR, 1.40; 95% CI, 1.07–1.82) and Europe (HR, 1.78; 95% CI, 1.36–2.27) have a higher risk of PC than Asia (HR, 1.02; 95% CI, 0.91–1.14). Therefore, providing support and confirming previous studies that Europe and North America have higher incidence rates of PC. With regard to geographic distribution, future studies should therefore assess the relationship of health behaviors and the impact of the physical environment with the spatial distribution of PC.

Despite its strengths, our study has several limitations of note. First, our meta-analysis was based on observational studies. Although typical and major risk factors, such as smoking and alcohol consumption, were considered in most included studies with adjusted groups, it is difficult to control for these confounding factors in epidemiological studies. Second, although all PC cases were histopathologically confirmed, information about the stage or severity or detailed kinds of PC was not available. Third, heterogeneity was detected among the studies included in our meta-analysis. This factor should not be ignored even if it is a common limitation among meta-analyses of general association studies. In our case, the heterogeneity remained even when we performed subgroup analyses to verify the data. Fourth, the assessment tools used to identify PD differed among the included studies. Fifth, the numbers of remaining teeth were examined in subjects after the occurrence of cancer. Although it is unlikely that cancer caused tooth loss, this limitation should be considered when interpreting the results. Thus, the abovementioned limitations may affect our conclusions.

In summary, the available evidence points to an association between PD and subsequent tooth loss with PC. 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 PC. The potential link between oral disease and PC remains unclear but could be related to alterations in the oral microbiome. Further studies are warranted to confirm such association and investigate potential underlying mechanisms, such as identifying the pathogenic bacteria and/or fungi, or other unmeasured factors related to dental plaque and oral mucosal lesions.

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