Association of oral microbiome and pancreatic cancer: a systematic review and meta-analysis

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Abstract

Background: Oral microbiota reported to be associated with pancreatic diseases, including pancreatic cancer. However, the association of oral microbiome and pancreatic cancer has not been reviewed systematically.

Objectives: To systematically investigate the association between the oral microbiome and pancreatic cancer risk.

Design: A systematic review and meta-analysis.

Data Sources and Methods: Systemic searches were conducted using PubMed, Medline, Cochrane Library, and Embase databases without any language restriction from conception to August 29, 2020. The studies that evaluated the association of oral microbiome and pancreatic cancer risk were included in this meta-analysis.

Results: The six included studies encompassed a total of 863 pancreatic cancer cases and 906 controls. Four studies reported the overall oral microbiome in pancreatic cancer cases. A total of 12–17 species/clusters were correlated with pancreatic cancer. Three studies reported the odds ratios (ORs) or relative abundance of several oral microbiomes pieces/clusters, and the majority were associated with pancreatic cancer.

Conclusions: Overall, this study supports the hypothesis of associations of variations of patients' oral microbiota to pancreatic cancer. Nonetheless, due to all included studies were conducted in USA or Europe, additional original studies and meta-analysis particular studies from other countries are essential for an in-depth investigation into the role of oral bacteria in pancreatic cancer.

Keywords: oral microbiome, oral bacteria, pancreatic cancer, association, meta-analysis

Introduction

Cancer is a leading cause of death worldwide and the result of the interaction between a person's genetic factors. In the past decades, aging, heredity, daily diet, smoking, and inflammation are demonstrated to be typical risk factors of cancer.[1–3] Recent studies demonstrated pathogens as one of the risk factors, for example, in 1994, it was found that *Helicobacter pylori* was associated with the development of cancer and defined as a class I carcinogen.[4]

Oral bacteria are pathogens of several periodontal diseases that can lead to systemic inflammation and were associated with systemic disorders, such as diabetes, pulmonary diseases, and rheumatoid arthritis.[5–7] Accumulating evidence suggested the causal correlation between the oral microbiome and the development of malignant tumors.[8–10] Similar to the majority of cancers, heredity only accounts for about 10% of all pancreatic cancers and is mainly attributed to a few familial cancer syndromes.[11] Although the association of symbiosis and disease has not been completely understood, the data points are accumulated with respect to the effect on immune function, inflammation, the relative abundance of pathogenic bacteria, and host genetics. A previous study conducted by Farrell *et al*.[12] reported that oral microbiota is associated with pancreatic diseases, including pancreatic cancer. The correlation was also supported by a population-based nested

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case–control study.[13] However, the association of oral microbiome and pancreatic cancer has not been reviewed systematically. The previously published literature on this topic facilitates a robust and persuasive systematic review and meta-analysis that can provide specific evidence on the association of oral microbiome and pancreatic cancer. In this study, we systemically evaluated the association between the oral microbiome and pancreatic cancer risk by summarizing the relevant studies.

Methods

Literature search
To search the potential studies, PubMed, Medline, Cochrane Library, and Embase were employed without any language restriction from initiation to 29 August 2020. The individual and joint keywords used to search the potential literature were as follows: 'microbiota' OR 'microbiome' OR 'microbiome' AND 'pancreatic cancer' OR 'pancreatic carcinoma'. To include the literature, we also browsed the bibliographies of all relevant studies and reviews for additional eligible studies. Google Scholar was also searched for studies citing relevant articles. This current study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.[14]

Eligibility criteria
Studies that addressed the topic of the effects of the oral microbiome and pancreatic cancer were included. The inclusion criteria were as follows: (1) study population that was diagnosed as pancreatic cancer without restriction to histological types, such as adenocarcinoma, acinar cell carcinoma, intraductal papillary-mucinous carcinoma or anaplastic carcinoma, etc.; (2) cohort or case–control studies that focused on the association of oral microbiome and pancreatic cancer; (3) necessary data that could be extracted from original studies; (4) studies published in English; and (5) the study from the same institution providing detailed information or newly published article was selected if the study population was reported in duplicate.

Case reports, letters, reviews, comments, conference abstracts, and studies conducted in animal models or experiments *in vitro*, studies in languages other than English, and studies that were not available were excluded from this meta-analysis.

Data extraction
All studies retrieved from the above-mentioned datasets were evaluated independently by two authors (Zhimin Guo and Mengyao Yuan). Needed information was extracted by the two reviewers independently using a standardized form. The discrepancy was discussed with a third author (Ying Xu) and the consensus was reached on all the items. For all included studies, the following information was extracted: the name of first author, year of publication, and study design, characteristics of participants patient and/or control characteristics, disease characteristics, and results on the oral microbiome.

Quality scoring of studies
The quality of the included studies was assessed independently by two authors with the Quality Assessment and Validity Tool for Newcastle–Ottawa Scale (NOS), a procedure to independently assess the methodological quality of meta-analysis of observational studies.[15]

The NOS for grading observational studies was based on three factors: the selection of participants, comparability of each group, and exposure of factors. A study can be awarded 2–9 points. Studies awarded 0–2 points were defined as poor quality, 3–5 points as medium, and 6–9 as high quality.

Statistical analysis
Weighted mean correlations or odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were pooled using inverse variance methods with random effects. The standard heterogeneity was assessed using a I^2 statistic. For the $I^2 \geqslant 50\%$ and $< 50\%$,[16] the heterogeneity was deemed with and without significant heterogeneity, respectively. When significant heterogeneity was observed, we sequentially excluded the included studies to explore the source of the heterogeneity. The publication bias was assessed by Begg's rank correlation[17] and Egger's weighted regression methods.[18] Statistical analyses and the Begg's and Egger's tests were performed using Comprehensive Meta-Analysis (version 3.0, Biostat Inc.). *p* Values of < 0.05 indicated statistical significance.

Results

Study selection

The study selection flowchart is illustrated in Figure 1. The systematic literature search yielded 379 studies by the search strategy, and 172 were excluded due to duplication. Based on the above inclusion and exclusion criteria, 177 abstracts and titles were reviewed initially. It is worth noting that 13 studies were excluded due to necessary information cannot be extracted, which included authors assessed oral microbiome in multiple types of cancers and did not report exact information on pancreatic cancer. After retrieving 30 full-length manuscripts, ultimately, six articles[12,13,19–22] were included for data extraction and meta-analysis.

Study characteristics

The six studies encompassed a total of 863 pancreatic cancer cases and 906 controls. All the included studies were retrospective case–control studies, published between 2012 and 2019, and the sample size ranged from 30 to 911. 4/6 studies were conducted in the United States,[12,13,20,21] one in Sweden,[22] and one in other European countries (including 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom).[19] The controls were healthy individuals, and one study matched the case and control be age and sex.[19] The characteristics of the included studies are shown in Tables 1 and 2. Supplemental Table 1 presents microbes that were significant in each included study.

Quality assessment of studies

According to the scale of the published quality assessment and validity tool for correlational studies, three studies were assessed as moderate quality and 3 (7 points) as high quality (≥8 points). The detailed scores for each included study are shown in Table 3.

Assessment of oral microbiome

One study detected the antibody of the oral microbiome using plasma samples and the presence of antibodies using an immunoblot array with respect to 16S rRNA. Gene amplification and sequencing were used for the other five studies. Total bacterial 16S DNA gene copy number
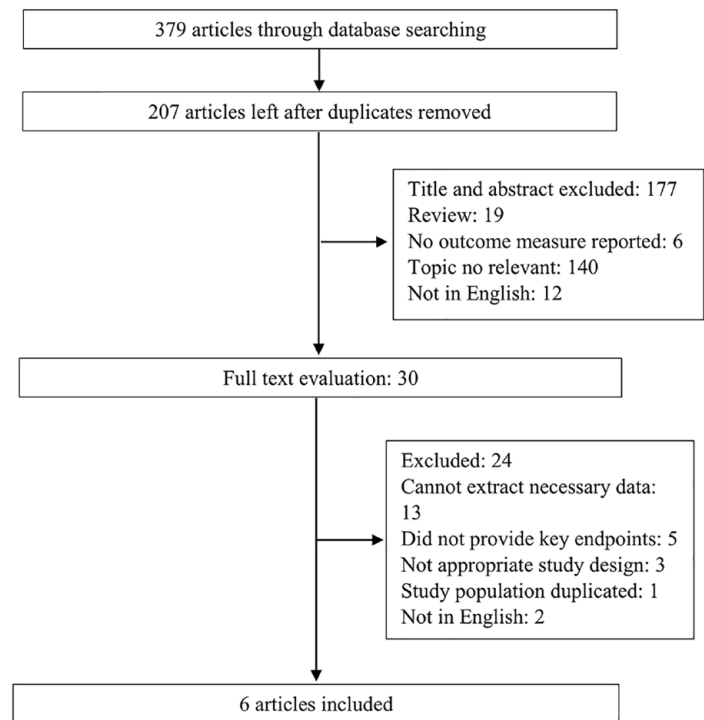
was quantified using the TaqMan quantitative polymerase chain reaction (qPCR) or real-time PCR.

Overall oral microbiome

Four studies reported the overall oral microbiome in pancreatic cancer cases. The study by Farrell *et al.*[12] observed 16 species/clusters, including *Streptococcus* (3 species/groups), *Prevotella* (4 species/groups), *Campylobacter* (4 species/groups), *Granulicatella* (2 species), *Atopobium* (1 species), and *Neisseria* (2 species). For the study conducted by Michaud *et al.*,[19] 25 preselected oral bacteria, including *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, had a two-fold higher risk of pancreatic cancer than individuals with lower levels of these antibodies (OR: 2.14; 95% CI: 1.05–4.36; >200 ng/ml *versus* ≤200 ng/ml). 12 and 17 bacterial phyla were observed for the studies by Torres *et al.*[20] and Fan *et al.*[21], respectively.

Oral microbiome and pancreatic cancer cases

Two of six included studies reported the correlation between the abundance of *Leptotrichia* and

Figure 1. Flowchart of the study design and literature selection.

Table 1. Characteristics of the included studies.

Study included	Country	Study design	PD cases			Controls				Tool for 16S sequences
			n	Age (means ± SD, years)	% of males	Selection of controls	n	Age (mean ± SD, years)	% of males	
Farrell et al.[12]	USA	Case–control	28	69.9 ± 11.6	60.70	Healthy controls	28	65.1 ± 10.1	64.28	QIIME
Michaud et al.[19]	Europe	Case–control	40	57.8 ± 8.0	48.40	Age- and sex-matched healthy controls	40	57.8 ± 7.9	47.80	QIIME
Torres et al.[20]	USA	Case–control	8	NA	0.75	Healthy controls	22	NA	54.55	QIIME
Olson et al.[21]	USA	Case–control	34	NA	0.52	Healthy controls	58	NA	39.66	MOTHUR
Fan et al.[13]	USA	Case–control	36	73.7	57.06	Healthy controls	37	63.8	57.14	QIIME
Gaiser et al.[22]	Sweden	Case–control	27	47 (30–77)	62.96	Healthy controls	21	71 (46–83)	4.76	QIIME

NA, not available; QIIME, the Quantitative Insights Into Microbial Ecology; SD, standard deviation; USA, United States of America.

Table 2. Characteristics of included pancreatic cancer cases.

Study included	Sample size of pancreatic cancer cases	Diagnosis of pancreatic cancer	Samples	Microbiology assessment
Farrell et al.[12]	28	Pathology	Saliva samples	16S rRNA gene and real-time quantitative PCR
Michaud et al.[19]	405	Pathology	Blood samples	Antibody
Torres et al.[20]	8	Pathology	Saliva samples	16S rRNA gene and quantitative PCR sequence analysis
Olson et al.[21]	34	Pathology	Saliva samples	16S rRNA gene and TaqMan quantitative PCR
Fan et al.[13]	361	Pathology	Saliva samples	16S rRNA gene and TaqMan quantitative PCR
Gaiser et al.[22]	27	Pathology	Saliva samples	16S rRNA gene and multiplexed and barcoded sequences

NA, not available; PCR, polymerase chain reaction.

Table 3. Summary of quality assessment.

Quality assessment scale	Farrell *et al.*[12]	Michaud *et al.*[19]	Torres *et al.*[20]	Olson *et al.*[21]	Fan *et al.*[13]	Gaiser *et al.*[22]
Selection						
Representativeness of the exposed cohort	*	*	*	*	*	*
Selection of non-exposed cohort	*	*	–	*	*	*
Ascertainment of antibiotic exposure	*	*	*	*	*	*
Demonstrated that outcome of interest was not present at start of study	–	*	–	*	–	–
Comparability of cohorts on basis of design, or analysis controlled for confounders (max 2 stars)	*	*	*	*	*	**
Outcome						
Assessment of outcome	*	*	*	*	*	*
Was follow-up long enough for outcomes to occur	*	*	*	*	*	*
Adequacy of follow-up of cohorts	*	*	*	*	*	*
Total (max 9)	7	8	7	8	7	8
Quality rating	Moderate	Good	Moderate	Good	Moderate	Good

*Starred according to the assessment criteria of The Newcastle-Ottawa Scale (NOS).

pancreatic cancer. When the results were pooled, the *r*-value for the correlation was 0.749, with the corresponding 95% CI as 0.197–0.940 with no significant heterogeneity ($I^2 = 22\%$). The forest plot is shown in Figure 2.

Three studies[11,13,20] reported the ORs or relative abundance of several oral microbiomes species/ clusters, such as *Firmicutes*, *Proteobacteria*, *Bacilli*, *Gammaproteobacteria*, *Betaproteobacteria*, *Lactobacillales*, *Pasteurellales*, *Neisseriales*, *Streptococcaceae*, *Pasteurellaceae*, *Neisseriaceae*, *Streptococcus*, *Hemophilus*, and *Neisseria*. As the results can be pooled when at least two studies reported one group of microbiome, we therefore summarized four groups of microbiomes, including *Fusobacteria*, *Bacteroidetes*, *Streptococcus*, and *Pasteurellaceae*. The pooled results of ORs for *Fusobacteria*, *Bacteroidetes*, *Streptococcus*, and *Pasteurellaceae* are presented in Figure 3.

Fusobacteria showed a slightly significant association with pooled OR as 0.94 (95% CI: 0.89–0.99). No heterogeneity was observed for each pooled process ($I^2 < 25\%$).

Of the included studies, one divided the samples into the identification and verification of bacterial candidates by real-time qPCR. When combining the two bacterial strains (*N. elongata* and *S. mitis*), an improved receiver operating characteristic plot area under the curve was seen as 0.90 (95% CI: 0.78–0.96, $p < 0.0001$) with sensitivity and specificity for distinguishing pancreatic cancer and healthy subjects as 96.4% and 82.1%, respectively.

Publication bias

No potential publication bias was detected among the included trials, according to Begg's
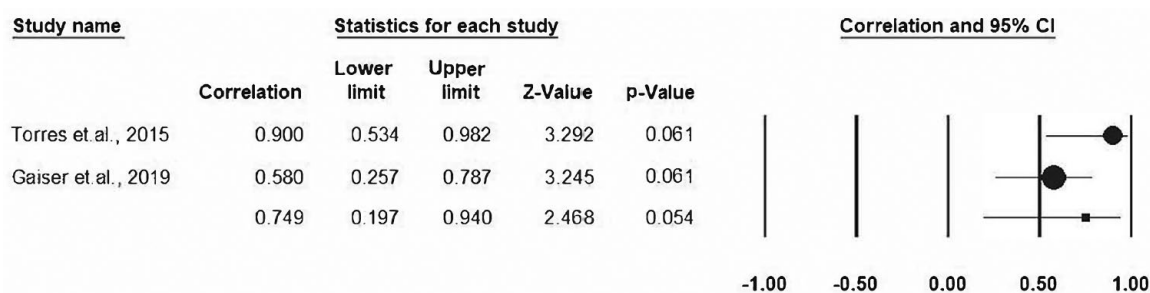
Study name		Statistics for each study				Correlation and 95% CI
	Correlation	Lower limit	Upper limit	Z-Value	p-Value	
Torres et.al., 2015	0.900	0.534	0.982	3.292	0.061	
Gaiser et.al., 2019	0.580	0.257	0.787	3.245	0.061	
	0.749	0.197	0.940	2.468	0.054	

Figure 2. Summarized correlations of abundance of *Leptotrichia* and pancreatic cancer.

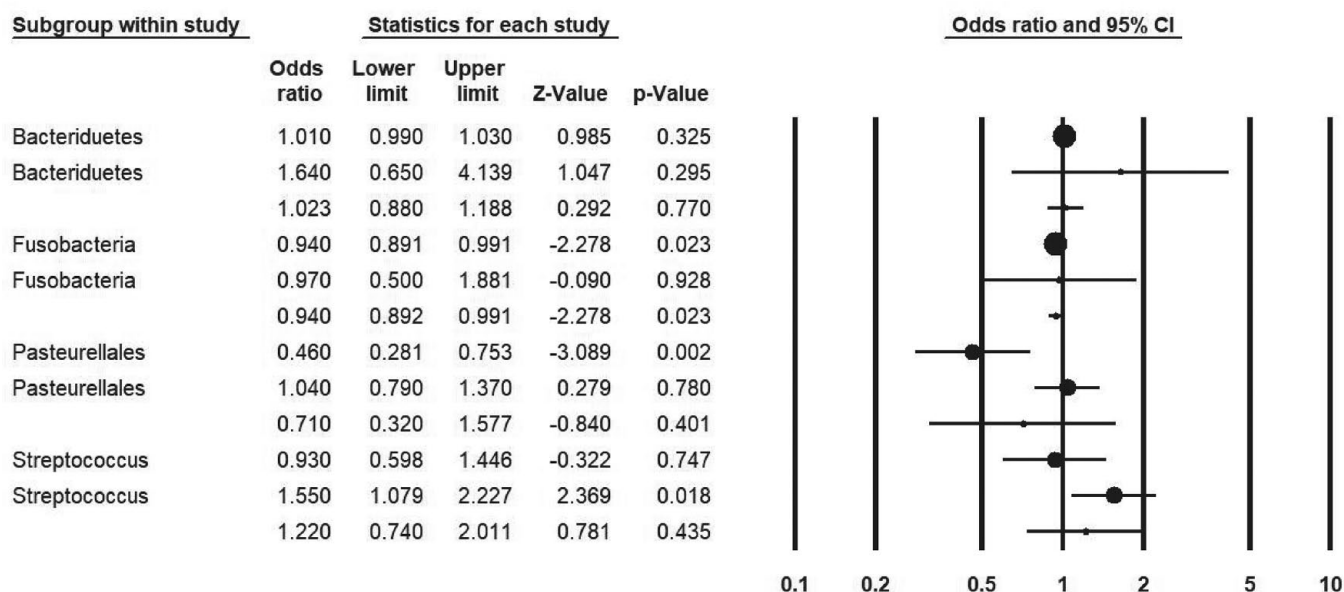| Subgroup within study	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Bacteriduetes	1.010	0.990	1.030	0.985	0.325	
Bacteriduetes	1.640	0.650	4.139	1.047	0.295	
	1.023	0.880	1.188	0.292	0.770	
Fusobacteria	0.940	0.891	0.991	-2.278	0.023	
Fusobacteria	0.970	0.500	1.881	-0.090	0.928	
	0.940	0.892	0.991	-2.278	0.023	
Pasteurellales	0.460	0.281	0.753	-3.089	0.002	
Pasteurellales	1.040	0.790	1.370	0.279	0.780	
	0.710	0.320	1.577	-0.840	0.401	
Streptococcus	0.930	0.598	1.446	-0.322	0.747	
Streptococcus	1.550	1.079	2.227	2.369	0.018	
	1.220	0.740	2.011	0.781	0.435	

Figure 3. Summarized ORs of increase or decrease in oral microbiome for pancreatic cancer.
ORs, odds ratio.

rank correlation analysis and Egger's weighted regression analysis (pooled process for the combination of Fusobacteria, n = 3, $p > 0.05$).

Discussion

To the best of our knowledge, although several reviews have been published in this topic,[23–26] the current study is the first meta-analysis on the association of pancreatic cancer and oral microbiome. In this meta-analysis, six studies with a total of 863 pancreatic cancer cases and 906 controls were included. This study supported the hypothesis of associations between variations of patients' oral microbiota and pancreatic cancer.

Previous study has reported the mechanism of microbiota-related tumor progression by two domains: inflammation and pro-tumorigenic immunomodulation in the tumor microenvironment. Chronic inflammation and infections are increasingly identified as a vital factor in the development of cancers.[27,28] A recent meta-analysis concluded that periodontitis was associated with pancreatic cancer, even after adjusting for several risk factors.[29] Several previous studies reported that gut microbiota dysbiosis, bacterial translocation, and inflammation were strongly linked with several pancreatic disorders, including pancreatic cancer.[30] Although this is the first meta-analysis to systemically analyze the association of oral

bacterial pathogens with pancreatic cancer risk, there is evidence supporting this finding. Some key pathogens among oral bacteria, such as the *P. gingivalis* and *A. actinomycetemcomitans*, are involved in the initiation of periodontal disease and tooth loss.[31] Recent studies also assessed the associations of oral microbiome with pancreatic cancer, such as the study conducted by Petrick et al.[32] which reported no associations were observed. Another study conducted in China[33] found *Leptotrichia* might be associated with pancreatic cancer specifically for patients in Sichuan Province, southwest China. A previous study observed the strong association between periodontal disease and tooth loss prospectively, also the association with increased risk of pancreatic cancer.[34] Five studies from the six included studies used saliva samples to perform gene sequencing analysis. One study[19] measured antibodies to oral bacteria in pre-diagnosis blood samples.

The bacterial assessment in pancreatic tumor development has been investigated by several approaches, including molecular and culture methods. The two approaches were seen similarities to oral microbiota.[35] Bacteria that has been demonstrated could reach pancreatic tissues by dissemination.[36] The study that used pre-diagnostic bloods were able to minimize reverse causation.[19] However, antibody levels might be influenced by drug use which may lead to lower sensitivity. Whether local oral microbiota infection without entering the bloodstream could potentially lead to systemic chronic inflammation or neoplasia is currently under intensive focus. The immune system of our bodies recognizes the microbiota infection by the overexpression of a family of membrane receptors, known as Toll-like receptors (TLRs).[37] The process of recognition of microbial components by TLRs can initiate signal transduction pathways. Thus, upregulated genes are launched in innate immune responses that effectuate the further development of antigen-specific acquired immunity.[38] In addition to the effects on immune cells, these TLRs also act on specific epithelial cells, including cancer cells, which promote their phenotypic transformation.[39] Besides the above-mentioned pathogenic mechanism, accumulating evidence also indicates 'mouth–gut axis' in the context of pathogenesis of gastrointestinal diseases.[40] Kitamoto et al. conducted a study on amassed oral pathobionts and reported that oral inflammation promotes gut inflammation by supplying the gut with both colitogenic pathobionts and pathogenic T cells.

In the past decades, various studies reported that moderate inflammatory reaction was protective against tumorigenesis[41] and excessive inflammatory response was reportedly to be a promoter to carcinogenesis in several types of cancers,[42] including pancreatic cancer.[43] In some cases, the tumorigenic process does not demonstrate the results of the activities of a specific organism but rather the result of an instability in the composition of the bacterial communities or dysbiosis. Recently, with the application of the next-generation sequencing, neoplastic inflammatory microenvironment also observed had effect in the oral microbiome.[44] Pushalkar et al.[44] reported enhanced the enrichments of some species and significantly decreased the abundance levels of some others.

In our study, both positive and negative associations of oral microbiota were seen with pancreatic cancer, which indicates that oral microbiota positively associated with pancreatic cancer may promote cancerization. Negative oral microbiota may be caused by wide genetic diversity, such as *Leptotrichia*.[45] The impact of *Leptotrichia* in human health remains unclear and was deemed as an opportunistic pathogen. Further studies are needed to investigate this relationship, and disentangle the complex role of immune response in pancreatic carcinogenesis. However, the observed association between pancreatic cancer and oral microbiome in our study may not prove causality. It is possible that the oral microbiome change is a consequence of pancreatic cancer occurrence, rather than be a factor for predisposing to pancreatic cancer. The conclusion that patients' oral microbiota is associated with pancreatic cancer which provides novel evidence to evaluate the specificity of microbial biomarkers. In clinical settings, the screening for pancreatic cancer is challenging. Early small pancreatic cancers, also known as PanIN stages, need to be detected.[46] Moreover, the phenotypically similar chronic pancreatitis, a benign pancreatic disease, needs to be differentiated from pancreatic cancer.[46] Thus, in future, a bacterial biomarker based on patients' oral microbiota might benefit pancreatic cancer cases.

When interrupting the findings of the current study, the limitations should be kept in mind. First, all included studies were conducted in the Western

countries and all the participants were Caucasian population. The representativeness of the study population might be weakened and therefore more studies from other countries are needed. Third, the limited number of included studies also reported various oral microbiome and statistical methods were employed. These could impede future investigations with respect to these studies. Fourth, in our study, we observed an association of oral microbiome and pancreatic cancer. However, due to the nature of the observed study design, the increase or decrease in oral microbiome may not causally related to pancreatic cancer. Fifth, none of the included studies provided stage of pancreatic cancer and that might be a potential source of bias. Sixth, potential language bias might exist because our literature searches only considered the articles published in English. Seventh, publishment bias cannot be assessed for all the analyses as a limited number of studies were included.

In conclusion, in the current meta-analysis, we first and systematically assessed the correlations between the oral microbiome and pancreatic cancer and the pooled results based on six studies from three different regions or countries. Next, we observed the slight correlation between the oral microbiome and pancreatic cancer. However, as all the six studies were conducted in western countries (the United States and Europe) and a weak scientific background of the correlation, additional studies are essential to validate and understand disease progression in pancreatic cancer. Limited by the small number of included studies, original studies and meta-analysis with a large sample size from different counties are needed to verify the current conclusion.

Declaration

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
Mengyao Yuan: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Ying Xu: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Zhimin Guo: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

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