JAMA Oncology | Original Investigation

Oral Bacterial and Fungal Microbiome and Subsequent Risk for Pancreatic Cancer

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IMPORTANCE The oral microbiota may be involved in the development of pancreatic cancer, yet current evidence is largely limited to bacterial 16S amplicon sequencing and small retrospective case-control studies.

OBJECTIVE To test whether the oral bacterial and fungal microbiome is associated with the subsequent development of pancreatic cancer.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from 2 epidemiological cohorts: the American Cancer Society Cancer Prevention Study-II Nutrition Cohort and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Among cohort participants who provided oral samples, those who prospectively developed pancreatic cancer were identified during follow-up. Control participants who remained free of cancer were selected by 1:1 frequency matching on cohort, 5-year age band, sex, race and ethnicity, and time since oral sample collection. Data were collected from August 2023 to September 2024, and data were analyzed from August 2023 to January 2025.

EXPOSURES The oral bacterial and fungal microbiome were characterized via whole-genome shotgun sequencing and internal transcribed spacer (ITS) sequencing, respectively. The association of periodontal pathogens of the red complex (*Treponema denticola*, *Porphyromonas gingivalis*, and *Tannerella forsythia*) and orange complex (*Fusobacterium nucleatum*, *F periodonticum*, *Prevotella intermedia*, *P nigrescens*, *Parvimonas micra*, *Eubacterium nodatum*, *Campylobacter shower*, and *C gracilis*) with pancreatic cancer was tested via logistic regression. The association of the microbiome-wide bacterial and fungal taxa with pancreatic cancer was assessed by Analysis of Compositions of Microbiomes With Bias Correction 2 (ANCOM-BC2). Microbial risk scores (MRS) for pancreatic cancer were calculated from the risk-associated bacterial and fungal species.

MAIN OUTCOMES AND MEASURES Pancreatic cancer incidence.

RESULTS Of 122 000 cohort participants who provided samples, 445 developed pancreatic cancer over a median (IQR) follow-up of 8.8 (4.9-13.4) years and were matched with 445 controls. Of these 890 participants, 474 (53.3%) were male, and the mean (SD) age was 67.2 (7.5) years. Three oral bacterial periodontal pathogens—*P gingivalis*, *E nodatum*, and *P micra*—were associated with increased risk of pancreatic cancer. A bacteriome-wide scan revealed 8 oral bacteria associated with decreased and 13 oral bacteria associated with increased risk of pancreatic cancer (false discovery rate–adjusted Q statistic less than .05). Of the fungi, genus *Candida* was associated with increased risk of pancreatic cancer. The MRS, based on 27 oral species, was associated with an increase in pancreatic cancer risk (multivariate odds ratio per 1-SD increase in MRS, 3.44; 95% CI, 2.63-4.51).

CONCLUSIONS AND RELEVANCE In this cohort study, oral bacteria and fungi were significant risk factors for pancreatic cancer development. Oral microbiota hold promise as biomarkers to identify individuals at high risk of pancreatic cancer, potentially contributing to personalized prevention.

JAMA Oncol. doi:10.1001/jamaoncol.2025.3377
Published online September 18, 2025.

Multimedia

Supplemental content

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Pancreatic cancer is highly lethal; the 5-year survival is 13%.[1] Little is known about ways to prevent this cancer. Smoking, obesity, pancreatitis, and genetics are known risk factors, yet these factors explain less than 30% of all pancreatic cancer. To reduce the pancreatic cancer burden, there is a critical need to improve scientific knowledge on the specific causes of this disease and to provide guidance for preventive measures.

We hypothesize that the oral bacteria and fungi are associated with risk of pancreatic cancer. There is strong evidence that microbially related poor oral health,[2-4] and particularly periodontal disease,[5-9] are risk factors for pancreatic cancer. Consistent with a bacterial underpinning of these associations with pancreatic cancer, circulating antibody to *Porphyromonas gingivalis*, a periodontal pathogen, has been related to increased risk for orodigestive cancer[7] and specifically pancreatic cancer.[10] Using direct measurement of bacteria in oral samples by 16S ribosomal RNA amplicon sequencing, we previously showed that oral carriage of *P gingivalis* is related to increased risk for pancreatic cancer.[11] Detailed bacterial quantification[12] at the species level, based on whole-genome sequencing,[13] is needed to confirm these early findings.

The oral fungal microbiome is also a keystone component of the oral microbiome.[14] Clinical candidiasis has been associated with an elevated risk of pancreatic cancer in clinical cohort studies.[15] Fungi, as part of the oral microbiota, interact with bacterial communities, influencing the overall microbial balance and potentially driving carcinogenic processes.[16] While research has predominantly focused on the bacterial microbiome and pancreatic cancer, the relationship between oral fungi and subsequent pancreatic cancer risk remains largely unexplored.

We conducted a prospective study nested in 2 large well-established US cohorts to determine whether the oral bacterial and fungal microbiome is associated with subsequent risk of pancreatic cancer, involving the use of whole-genome shotgun sequencing for oral bacteria and internal transcribed spacer (ITS) sequencing for fungi. We assessed risk of pancreatic cancer associated with oral bacterial and fungal taxa and as summarized in a microbial risk score (MRS).[17]

Key Points

Question Is the prediagnostic oral bacterial and fungal microbiome associated with the subsequent development of pancreatic cancer?

Findings In this cohort study including 122 000 individuals, 3 oral bacterial periodontal pathogens, an additional 20 bacteria, and 4 fungi were identified, which together conferred a more than 3-fold increase in the risk for pancreatic cancer.

Meaning The oral fungal and bacterial microbiotas may serve as readily accessible, noninvasive biomarkers for subsequent pancreatic cancer risk to identify individuals at high risk of pancreatic cancer.

Methods

Study Populations

Parent Cohorts

This study is based on 2 well-established prospective US cohorts. The American Cancer Society Cancer Prevention Study-II Nutrition Cohort (CPS-II)[18] included more than 184 000 participants aged 50 to 74 years in 21 US states. Incident cancers were verified through medical records, state cancer registries, or death certificates. Oral wash samples were collected from 70 000 CPS-II participants from 2001 to 2002. Follow-up for incident cancers was conducted through June 2009. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) cohort[19] is a large population-based randomized clinical trial at 10 US screening centers that was conducted to examine the effect of screening on cancer mortality in approximately 155 000 participants aged 55 to 74 years. Incident cancers were verified through medical records or death certificates. Oral wash samples were collected from 52 000 participants in the PLCO trial control arm, between 2000 and 2003. Cancer follow-up was conducted through December 2010.

The study protocols were approved by the institutional review boards of the American Cancer Society (for CPS-II) and the National Cancer Institute (for PLCO). Written informed consent was obtained from all participants in both cohorts. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Nested Case-Control Study

This study included men and women diagnosed with pancreatic cancer and matched control participants (eTable 1 in Supplement 1). Participants with pancreatic cancer had histologically confirmed incident primary pancreatic adenocarcinoma (*Second Edition of the International Classification of Diseases for Oncology* codes C25.0 to C25.3 and C25.7 to 25.9). Cohort-nested control participants were selected by risk set sampling (1:1 frequency matched), by cohort, 5-year age band, sex, self-reported race and ethnicity (Asian, Black, Hispanic, White, or other race [including American Indian or Alaska Native, Native Hawaiian, Pacific Islander, multiracial, or other race]), year of birth, and time since oral wash sample collection. All participants had valid consent, oral wash samples (ie, before pancreatic cancer diagnosis for cases), and no prior personal history of any cancer.

Measurements

Demographic Information

At enrollment and follow-up periods, cohort participants completed structured questionnaires that included questions about age, sex, race and ethnicity, body mass index (BMI), smoking status, alcohol consumption, and history of diabetes. We used covariates from the questionnaire most closely preceding oral wash sample collection.

Oral Wash Sample Collection

Study participants from the 2 cohorts provided oral samples (Scope; Procter & Gamble), and aliquoting and DNA extraction were conducted at the central repository in each cohort,

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following similar collection and processing protocols.[18,19] The oral microbiome is highly stable over time[20-22] and shows much greater interindividual variation than intraindividual variation, indicating that oral sample collection at a single time is useful for assessing the oral microbiome in a cohort study.

Oral Bacterial and Fungal Microbiome Characterization

Whole-genome shotgun sequencing for oral bacterial microbiome and additional fungal-specific ITS1 sequencing were completed at NYU Langone Genome Technology Center, New York, New York. Sequencing data were processed using the SHOGUN pipeline, with detailed procedures for human read depletion, taxonomic assignment, and batch effect correction provided in the eMethods in Supplement 1. Both whole-genome shotgun sequencing and ITS assays yielded sufficient reads, capturing major bacterial and fungal phyla, with similar distributions across the 2 cohorts (eFigures 1 and 3 and eTable 2 in Supplement 1). The intraclass correlation coefficient for the blinded randomly repeated controls showed good agreement (0.96 for whole-genome shotgun sequencing and 0.80 for ITS; eFigure 2 in Supplement 1), with distinct clustering observed for the random quality control and positive control samples.

Statistical Analysis

We compared microbial taxa between participants with pancreatic cancer and control participants up to the species level via Analysis of Compositions of Microbiomes With Bias Correction 2,[23] including adjustments for covariates (matched pairs, age, BMI, diabetes, and smoking status). Final covariates were selected based on more than 10% change in effect size. The bacterial species were identified as noteworthy if the false discovery rate (FDR)-adjusted Q statistic was less than .05 and the *P* value for between-cohort heterogeneity greater than .05.[24] The fungal species were identified as noteworthy if the FDR-adjusted Q statistic was less than .10.[25]

We also examined the association with pancreatic cancer for bacterial periodontal pathogens selected a priori because of their established association with periodontal disease[26-28] (eTable 3 in Supplement 1). Specifically, we assessed the associations of the oral bacterial red complex (*Treponema denticola*, *P gingivalis*, and *Tannerella forsythia*), the orange complex (*Fusobacterium nucleatum*, *F periodonticum*, *Prevotella intermedia*, *P nigrescens*, *Parvimonas micra*, *Eubacterium nodatum*, *Campylobacter shower*, and *C gracilis*), and their combination (ie, red/orange complex) with the risk of developing pancreatic cancer. Taxonomic abundance was normalized via the bias-corrected log abundances after adding a pseudocount in microbiome data.[23]

Lastly, building on the concept of a polygenic risk score used productively in genomic research,[29] we constructed an MRS[17] to summarize the microbial profiles in relation to pancreatic cancer risk. Details are described in the eMethods in Supplement 1.

Statistical significance was set at $P < .05$, and all *P* values were 2-tailed. Analyses were conducted using R version 4.4.1 (The R Foundation), Python version 3.9.13 (Python Software Foundation), Trim Galore version 0.5.0, Samtools version 1.20 (Genome Research Limited), Bowtie2 version 2.5.3, and Miniconda3 version 4.6.14 (Anaconda). Data were collected from August 2023 to September 2024, and data were analyzed from August 2023 to January 2025.

Results

Participant Characteristics

Of 122 000 cohort participants who provided samples, 445 developed pancreatic cancer over a median (IQR) follow-up of 8.8 (4.9-13.4) years and were matched with 445 controls. Of these 890 participants, 416 (46.7%) were female and 474 (53.3%) were male, and the mean (SD) age was 67.2 (7.5) years. A total of 25 participants (2.8%) were Asian, 32 (3.6%) were Black, 12 (1.3%) were Hispanic, 2 (0.2%) were Pacific Islander, 817 (91.8%) were White, and 2 (0.2%) were another race or had missing data. The baseline characteristics of the study participants in both cohorts are presented in eTable 1 in Supplement 1. Matching factors, including age, sex, and race and ethnicity, did not differ by case-control status. As expected, family history of pancreatic cancer, smoking, and alcohol use tended to be higher in participants with pancreatic cancer.

Overall Microbiome Diversity and Risk of Pancreatic Cancer

Participants with pancreatic cancer did not differ significantly from matched controls in terms of oral bacterial α diversity, as assessed by species richness and evenness, or in overall microbiome composition (β diversity), as measured by 3 different distances (eFigures 5 and 6 in Supplement 1). Similarly, overall fungal α diversity and β diversity were not associated with pancreatic cancer (eFigure 7 in Supplement 1).

Oral Bacterial Taxa and Risk of Pancreatic Cancer

The periodontal disease pathogens *P gingivalis* in the red complex and *E nodatum* and *P micra* in the orange complex were associated with increased risk for pancreatic cancer (**Figure 1**; eFigure 4 in Supplement 1). In the oral microbiome-wide assessment of the 2 cohorts, we identified 21 novel oral bacterial species associated with the risk of pancreatic cancer, after correcting for multiple comparisons (FDR-adjusted Q statistic less than .05) (**Figure 2**A; eTable 4 in Supplement 1). The relative abundance of 3 bacterial species within *Proteobacteria*, 2 species in *Bacteroidetes*, and 2 species in *Actinobacteria* were related to a lower risk of developing pancreatic cancer. Conversely, 3 species within *Bacteroidetes*, 6 species within *Actinobacteria*, a *Fusobacterium*, and certain *Firmicutes* were associated with a greater risk of developing pancreatic cancer. The associations of these 21 bacterial species with pancreatic cancer risk tended to be consistent across the 2 cohorts (Figure 2B). These findings remained robust after excluding the first 3 years of follow-up and across stratified analyses by BMI, diabetes status, smoking status, and alcohol consumption (eFigures 8 to 10 in Supplement 1).

Oral Fungal Taxa and Risk of Pancreatic Cancer

Of the oral fungi identified by ITS1 sequencing, *Candida* was the most common genus (abundance, 47.6%; 95% CI, 44.7%-

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Figure 1. Bacterial Periodontal Disease Pathogenic Species and Risk of Pancreatic Cancer

Odds ratios (ORs) for the association of bacterial periodontal pathogenic species and risk of pancreatic cancer from random-effects meta-analysis of logistic regression estimates overall and for the 2 individual cohorts. Complete results for a priori selected pathogens are presented in eTable 3 in Supplement 1. ORs for pancreatic cancer for the periodontal pathogenic species/complexes represent changes per 1-SD increase in each species or complex as a continuous predictor. CPS-II indicates Cancer Prevention Study-II Nutrition Cohort; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

50.4%); greater oral abundance of this genus was significantly associated with increased risk for pancreatic cancer (**Figure 3**). Within this genus, the abundance of *Candida tropicalis* and unspecified *Candida* (*Candida spp*; abundance, 30.4%; 95% CI, 27.9%-33.0%) were associated with increased risk, while *C albicans* was associated with decreased risk. The second most common genus, *Malassezia* (abundance, 36.2%; 95% CI, 33.5%-38.9%), was not associated overall with pancreatic cancer risk, while *M globosa* was associated with decreased risk (Q statistic less than .10; eTables 5 and 6 in Supplement 1). These associations for the *Candida* and *Malassezia* species remained robust after excluding the first 3 years of follow-up (eFigure 11 in Supplement 1). The association of *Candida* with pancreatic cancer was particularly evident in study participants who had a history of tobacco use but showed no differentials with respect to BMI, diabetes, and alcohol consumption (eFigures 12 to 13 in Supplement 1). In an additional analysis comparing the oral and pancreatic fungal microbiomes in patients at NYU Langone, we found that members of the *Candida* genus present in the oral cavity were also present preferentially in pancreatic tumor tissue (eFigure 14 in Supplement 1). Other less common fungi (more than 1% abundance) were not associated with pancreatic cancer.

MRS and Risk of Pancreatic Cancer

Analyzing the microbial profile as a community can characterize more microbial information than analyzing microbes individually. We constructed summary MRSs consisting of risk-associated bacteria and fungi. In a 2-cohort meta-analysis, the MRSs derived for 3 a priori periodontal pathogens, 20 other bacterial species, and 4 fungal pathogens were associated with pancreatic cancer (multivariate odds ratio per 1-SD increase in MRS, 3.44; 95% CI, 2.63-4.51) (**Table**). There was also a strong degree of reproducibility between the PLCO and CPS-II cohorts and by Monte Carlo cross-validation (Table; eTable 7 in Supplement 1). Further examination of the association of the MRS with pancreatic cancer did not reveal substantial variability by follow-up period or in relation to BMI, diabetes, cigarette smoking, and alcohol use (eTable 8 in Supplement 1).

As an exploratory analysis, we examined the coabundance patterns among the 27 risk-associated taxa using Dirichlet multinomial mixture–based community clustering. This analysis revealed 3 distinct clusters (**Figure 4**A) that are differential for pancreatic cancer risk (k = 3; eTable 9 in Supplement 1): Cluster 1 was enriched for high-risk bacteria (Figure 4A) that link to high-risk carbohydrate and lipid metabolism modules (eFigure 15 in Supplement 1). Cluster 2 was characterized by enrichment of *Candida* and other fungal species, which are functionally linked to environmental processing and pathogenicity pathways (eFigure 15 in Supplement 1). Cluster 3 was enriched for *Prevotella* and *Propionibacterium*, which tended to be among the top-ranked taxa (Figure 4B; eTable 10 in Supplement 1) and are potentially associated with nucleotide and amino acid metabolism (eFigure 15 in Supplement 1).

Discussion

In 2 large, well-established cohorts, we showed that selected bacterial periodontal pathogens in the red and orange complexes were associated with greater risk of pancreatic cancer. In a bacteriome-wide metagenomic scan, we further identified 20 additional oral bacteria associated with this disease. In a mycobiome-wide scan for fungi, we found that greater

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Figure 2. Oral Microbiome-Wide Bacteria by Phylum and Risk of Pancreatic Cancer

Fold changes for the association between selected taxa and the risk of pancreatic cancer from random-effects meta-analysis of Analysis of Compositions of Microbiomes With Bias Correction 2 abundance estimates overall and for the 2 individual cohorts. Complete results for all bacteria are presented in eTable 4 in Supplement 1. Fold change values greater than 1 indicate enrichment in patients with cancer, while values less than 1 indicate enrichment in controls. CPS-II indicates Cancer Prevention Study-II Nutrition Cohort; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

abundance of 4 fungi, including *Candida*, is also associated with increased risk for pancreatic cancer. Finally, combined as an MRS, the 27 microbial agents were associated with a more than 3-fold increase in the risk for pancreatic cancer per 1-SD increase in the MRS. Our findings on oral microbiota are consistent for 2 cohort populations and are robust to evaluation by Monte Carlo cross-validation. The findings provide evidence that certain oral microbiota are linked to the subsequent development of pancreatic cancer.

Epidemiological studies have shown that clinical candidiasis (clinically defined oral *Candida* fungal infection)[15] is related to increased risk of pancreatic cancer. Patients with cancer are frequently infected by fungal *Candida*; however, this evidence is insufficient to distinguish *Candida* as a cause of cancer or as a sequela of the disease.[33] Early studies demonstrated that *C albicans*, the dominant oral *Candida*, can produce carcinogenic nitrosamines[34] and can act as a promoter of carcinogenesis in rats.[35] More recently, comprehensive profiling of the oral fungal microbiome has been made possible by sequencing the panfungal ITS1 gene from oral samples.[36] In, to our knowledge, the first study of the fungal microbiome using this method in a general population cohort, we prospectively demonstrate that increased oral *Candida* abundance is associated with a higher risk of pancreatic cancer. We further confirmed the presence of *Candida* in both tumor and normal tissue biospecimens from patients with cancer. In animal models, *Candida* has been reported to drive pancreas oncogenesis through modulation of tumor immunity.[37] Together, these findings support a potential mechanistic link between oral fungal dysbiosis and pancreatic cancer development, warranting further investigation into the role of *Candida* in oral-to-tumor translocation and pancreatic tumorigenesis.

At the mycobiome species level, we found that *C tropicalis* was related to increased risk and *C albicans* to decreased risk; however, caution is warranted in interpreting the species-

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Figure 3. Oral Microbiome-Wide Fungi and Risk of Pancreatic Cancer

Fold changes for the association between fungal taxa and the risk of pancreatic cancer from random-effects meta-analysis of Analysis of Compositions of Microbiomes With Bias Correction 2 abundance estimates overall and for the 2 individual cohorts. Complete results for all fungi are presented in eTable 5 in Supplement 1. Fold change values greater than 1 indicate enrichment in patients with cancer, while values less than 1 indicate enrichment in controls. The figure presents results for all *Candida* and *Malassezia* genera and species, as well as for other fungi with more than 1% abundance. CPS-II indicates Cancer Prevention Study-II Nutrition Cohort; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Table. Microbial Risk Score (MRS) and Risk of Pancreatic Cancer[a]

Characteristic	OR (95% CI)[b] CPS-II	PLCO	2-Cohort meta-analysis[c]	Monte Carlo cross-validation[d]
Bacteria[e]				
ANCOM-BC2 MRS	2.83 (1.90-4.20)	4.32 (3.10-6.02)	3.55 (2.34-5.37)	3.10 (2.68-3.52)
3-Pathogen MRS[f]	1.47 (1.04-2.07)	1.42 (1.08-1.88)	1.44 (1.16-1.79)	1.51 (1.28-1.75)
ANCOM-BC2 and 3-pathogen MRS[f]	3.02 (2.01-4.56)	3.87 (2.80-5.35)	3.52 (2.73-4.54)	3.04 (2.60-3.47)
Fungi[g]				
ANCOM-BC2 MRS	1.55 (1.10-2.19)	1.39 (1.02-1.89)	1.46 (1.16-1.83)	1.26 (1.10-1.43)
Bacteria and fungi[e,g]				
ANCOM-BC2 and 3-pathogen MRS[f]	3.88 (2.70-5.57)	2.96 (1.97-4.44)	3.44 (2.63-4.51)	3.57 (1.83-5.31)

Abbreviations: ANCOM-BC2, Analysis of Compositions of Microbiomes With Bias Correction 2 ; CPS-II, Cancer Prevention Study-II Nutrition Cohort; OR, odds ratio; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

[a] MRS was calculated as a weighted sum of the relative abundance of the bacterial and fungal species, with weights assigned according to their effect sizes determined via ANCOM-BC2. ANCOM-BC for the Monte Carlo cross-validation includes the 21 bacterial species or 4 fungal species associated with pancreatic cancer, as verified in the multiple comparisons (false discovery rate–adjusted *Q* statistic less than .05 for bacteria and Q statistic less than .10 for fungi) (eTables 4 and 5 in Supplement 1).

[b] Odds ratios for the MRS represent changes per 1 SD in the MRS, as a continuous predictor.

[c] Meta-analysis estimates were obtained from random-effects meta-analyses of cohort-specific logistic regression estimates. ANCOM-BC2 for each cohort and 2-cohort meta-analysis refers to the 21 bacterial species or 4 fungal species associated with pancreatic cancer.

[d] For the Monte Carlo cross-validation, data were split into a training set (80%) and test set (20%), with this process repeated 50 times to ensure robustness.

[e] Bacterial species included *Candidatus Burkholderia crenata*, *Propionibacterium sp oral taxon 192*, *Mannheimia hemolytica*, *Streptococcus porci*, *Campylobacter mucosalis*, *Actinomyces meyeri*, *Cryptobacterium curtum*, *Atopobium sp oral taxon 199*, *Prevotella oralis*, *Johnsonella ignava*, *Leptotrichia goodfellowii*, *P baroniae*, *Olsenella profusa*, *Slackia exigua*, *A timonensis*, *Eubacterium nodatume*, *P acidifaciens*, *Porphyromonas catoniae*, *Treponema putidum*, *P sp S7-1-8*, and *P multiformis*.

[f] The 3-pathogen analysis includes *P gingivalis*, *Parvimonas micra*, and *E nodatum* (eTable 3 in Supplement 1).

[g] Fungal species included *Candida albicans*, *C spp*, *C tropicalis*, and *Malassezia globosa*.

level findings, as a substantial proportion of *Candida* in the oral samples in our study (30.4%) could not be resolved to the species level, and abundance of these unresolved reads was also associated with increased risk for pancreatic cancer. *C*

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Figure 4. Overview of Microbial Community Clusters and Importance

A, Heatmap showing the clusters among oral pathogens, fungi, and bacteria in patients with pancreatic cancer and controls. The clustering was calculated to identify distinct groups based on the relative abundance of 3 periodontal pathogens, an additional 20 pancreatic cancer risk-associated bacteria, and 4 fungi. The color of the row strip indicates the group of Dirichlet multinomial mixtures (DMM) modeling clusters (k = 3).[30] B, Importance of the microbial taxa in XGBoost[31] and random forest[32] models. Complete results are presented in eTable 10 in Supplement 1.

tropicalis is reported to facilitate tumor immune evasion[38] and inflammasome activation.[39,40] *C albicans* has been studied for a broad spectrum of functions related to tumor development, including carcinogenic metabolism of alcohol and nitrosamines and induction of cell proliferation through candidalysin and macrophage IL7 pathways.[16] While our results suggest that *Candida* is etiologically involved in pancreatic cancer development, further work is needed to fully characterize the mycobiome at the species level and to better understand the mechanistic basis of our observed associations.

Periodontal disease, a chronic oral inflammatory condition of microbial origin, has been linked to pancreatic cancer in multiple epidemiologic studies.[5-9] Of the bacterial periodontal pathogens of the red and orange complexes associated with pancreatic cancer in our study, *P gingivalis* is the most extensively studied. This oral bacterium has been detected in human pancreatic cancer.[41] Recent investigations in mice by Saba et al[42] show migration of *P gingivalis* from the oral cavity to the pancreas, induction of pancreatic metaplasia by repetitive administration of this bacterium, and exposure-related ac-

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celerated progression from pancreatic intraepithelial neoplasia to adenocarcinoma. Several other oral bacteria associated with increased risk for pancreatic cancer in our study exhibit ecological signatures associated with poor oral hygiene[43] and periodontal disease,[44] including red complex *T forsythia*,[45,46] orange complex *E nodatum* and *P micra*,[46-48] and bacteria from the metagenomic screen, including *Slackia exigua*,[48] *Olsenella profuse*,[49] *Cryptobacterium curtum*,[50] *P baroniae*,[51] and *P catoniae*.[52]

Our evidence suggests a clustering tendency of the major newly identified oral bacterial species with the periodontal pathogens. These high-risk oral bacteria are also linked to high-risk modules in carbohydrate and lipid metabolism—which may drive de novo oncogenic mutations in pancreatic cells[53]—whereas low-risk species tend not to exhibit such modules, thereby supporting the proposition that metabolic profiles of the oral microbiome may relate to pancreas carcinogenesis.[54] In addition, we identified some previously unrecognized oral bacterial species linked to pancreatic cancer, as exemplified by *Leptotrichia goodfellowii*, which produces lactic acid and is primarily associated with infections in the immunocompromised.[55]

Emerging evidence systematically links oral pathogens to pancreatic carcinogenesis,[56] suggesting that poor oral health may be causally related to pancreatic cancer development. Moreover, the swallowing of oral periodontal pathogens can translocate to pancreatic cancer tissue,[42] resulting in strong shifts in the pancreatic microbiome[42] and dysbiosis that releases microbial toxins[57] and metabolites,[58] promoting pancreatic tumorigenesis by triggering an innate immune response[59] and thereby affecting phagocytic potential and inflammatory processes.[41] Collectively, the oral microbiome community may exert systemic effects on pancreatic cancer, with oral microbial dysbiosis contributing an etiological link between oral health status and pancreatic cancer development.[44] The associated MRS[17] summarizing the bacterial-associated and fungal-associated risks offers a promising tool to identify individuals at high risk of pancreatic cancer. Novel targeted methods for detecting microbial cell-free DNA are effective for detecting intracellular pathogens,[60] holding promise as valuable biomarkers in pancreatic cancer. These findings also underscore the potential importance of oral health interventions for prevention of pancreatic cancer.

Limitations and Strengths

Our study has several limitations. As an observational study, there is potential for confounding by unmeasured factors, including absence of dental history, and causality remains to be determined. To our knowledge, this study is the first to prospectively examine the association of the oral mycobiome with pancreatic cancer risk using ITS to characterize the mycobiome. Yet a current limitation is the incompleteness of the microbiome reference databases for fungal identification, which may have limited our findings at the species level for fungi.[16] Recognizing the limitations of our research, the findings warrant further investigation through experimental systems and human intervention studies, broadening to the complete oral microbiome.[42] Furthermore, our study involved a single collection of prediagnostic oral wash samples, which may limit our ability to capture the long-term dynamics of the oral microbiome; however, previous studies have demonstrated that a single measurement can reasonably capture the long-term variability.[61] Lastly, as our populations were predominantly White, the generalizability of our findings to other races and ethnicities may be limited.

The strengths of this study include the use of oral samples collected prior to pancreatic cancer development, nested in 2 large, well-established cohorts. This allows rigorous assessment of the microbe-disease temporal relationship, as the prediagnostic microbiome is not influenced by the cancer. We used comprehensive sequencing-based whole-genome shotgun sequencing and ITS assays, coupled with a novel analytic pipeline developed by our team.[62] This robust and unbiased approach is designed to characterize microbiota accurately,[63,64] supported by excellent quality control results.

Conclusions

In conclusion, this cohort study provides compelling evidence that oral microbiota, including bacteria and fungi, are risk factors for pancreatic cancer development, showing a greater than 3-fold increase in the risk of developing pancreatic cancer per 1-SD increase in the MRS. The oral microbiota holds promise as a biomarker to identify individuals at high risk of pancreatic cancer, potentially enabling personalized pancreatic cancer prevention.

ARTICLE INFORMATION

Accepted for Publication: July 5, 2025.

Published Online: September 18, 2025. doi:10.1001/jamaoncol.2025.3377

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Author Contributions: Drs Hayes and Ahn had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Meng, Hayes, Ahn.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Meng, Kwak, Wang, Usyk, Li.
Obtained funding: Hayes, Ahn.
Administrative, technical, or material support: Wu, Freedman, Um.
Supervision: Oberstein, Hayes, Ahn.

Conflict of Interest Disclosures: None reported.

Funding/Support: Research reported in this publication was supported in part by the National Institutes of Health under award numbers P20CA252728, R01CA159036, U01CA250186, P30CA016087, R01LM014085, and

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U24ES036002. Samples were sequenced at the NYU School of Medicine Genome Technology Center. The American Cancer Society funds the creation, maintenance, and updating of the American Cancer Society Cancer Prevention Study-II cohort.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We express sincere appreciation to all American Cancer Society Cancer Prevention Study-II participants and to each member of the study and biospecimen management group. We acknowledge the contribution to this study from central cancer registries supported through the US Centers for Disease Control and Prevention National Program of Cancer Registries and cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results Program. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, and contracts from the Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, and US Department of Health and Human Services. We thank the National Cancer Institute study management team, the screening center investigators, and staff at Information Management Services and Westat. Most importantly, we thank the study participants for their contributions that made this study possible.

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