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INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

January 26, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Could there be an interplay between periodontal changes and pancreatic malignancies?

Bogdan Silviu Ungureanu, Dorin Nicolae Gheorghe, Flavia Mirela Nicolae, Sandu Râmboiu, Petru Adrian Radu, Valeriu Marin Şurlin, Victor Dan Eugen Strâmbu, Dan Ionut Gheonea, Alexandra Roman, Petra Şurlin

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ksiazek M, Poland; Sun SY, China

Received: November 18, 2022

Peer-review started: November 18, 2022

First decision: December 10, 2022

Revised: December 19, 2022

Accepted: January 10, 2023

Article in press: January 10, 2023

Published online: January 26, 2023



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Abstract

The term "periodontal disease" refers to a group of chronic inflammatory illnesses caused by specific microorganisms from subgingival biofilm, that affect the tooth-supporting tissues. Recent research has also shown that periodontal infection plays a role in aggravating systemic disease states at distal sites, reinforcing the significance of the oral cavity for general health. Additionally, it has been suggested that gastroenterological malignancies may be promoted by hematogenous, enteral or lymphatic translocation of periopathogens. In the past 25 years, the global burden of pancreatic cancer (PC) has more than doubled, making it one of the major causes of cancer-related mortality. Periodontitis has been linked to at least 50% increased risk of PC and it could be considered a risk factor for this malignancy. A recent study performed on 59000 African American women with a follow up of 21 years showed that participants who had poor dental health had higher chances of PC. The findings, according to researchers, might be related to the inflammation that some oral bacteria trigger. Regarding the mortality of PC, periodontitis considerably raises the chance of dying from PC. Microbiome

alterations in the gut, oral cavity and pancreatic tissues of PC patients occur when compared to healthy flora, demonstrating a link between PC and microecology. Inflammation may also contribute to PC development, although the underlying pathway is not yet known. The function of the microbiome in PC risk has drawn more focus over the last decade. Future risk of PC has been linked to the oral microbiome, specifically increased levels of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* and decreased relative abundance of *Leptotrichia* and *Fusobacteria*, suggesting that it may have an impact on the inflammatory condition by expanding, altering, and regulating the commensal microbiome. Patients who received periodontal treatment had significantly decreased incidence rate ratios for PC. By analyzing patterns in the microbiome composition throughout PC development and establishing strategies to enhance the cancer-associated microbial system, we can increase the efficacy of therapy and eventually find an application for the microbial system. The development of immunogenomics and gut microgenomics in the life sciences will result in a significant advancement in our understanding of how microbial systems and immunotherapy interact, and it may also have intriguing therapeutic implications for extending the lifetime of PC patients.

Key Words: Periodontal disease; Pancreatic cancer; Microbiome; Periodontitis; Periopathogens; Periodontal medicine

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Core Tip: It has been suggested that gastroenterological malignancies may be promoted by hematogenous, enteral or lymphatic translocation of periopathogens. Periodontitis has been linked to at least 50% increased risk of pancreatic cancer (PC) and it could be considered a risk factor for this malignancy. Future risk of PC has been linked to the oral microbiome, specifically increased levels of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* and decreased relative abundance of *Leptotrichia* and *Fusobacteria*. By analyzing patterns in the microbiome composition throughout PC development and establishing strategies to enhance the cancer-associated microbial system, we can increase the efficacy of therapy.

Citation: Ungureanu BS, Gheorghe DN, Nicolae FM, Râmboiu S, Radu PA, Șurlin VM, Strâmbu VDE, Gheonea DI, Roman A, Șurlin P. Could there be an interplay between periodontal changes and pancreatic malignancies? *World J Clin Cases* 2023; 11(3): 545-555

URL: <https://www.wjgnet.com/2307-8960/full/v11/i3/545.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v11.i3.545>

INTRODUCTION

The term "periodontal disease" refers to a group of inflammatory illnesses that affect the tooth-supporting tissues, ultimately leading to tooth loss and even resulting in systemic inflammation. Up to 90% of people worldwide are affected by the two most common periodontal disorders, gingivitis and periodontitis[1]. The cornerstone of avoiding periodontitis is the treatment of gingivitis, a reversible inflammation of the gingiva that takes place before periodontitis. By gradually destroying the alveolar bone and periodontal ligament, periodontitis-which is typically caused by Gram-negative bacteria-can result in recession, increased probing depth, or both[1].

Periodontal disease is initiated and progresses due to a dysbiosis of the commensal oral microbiota, which subsequently interacts with the host's immune system[2,3]. Diverse bacteria (or certain gene combinations within the community) may be capable of having various functions within the periodontal ecosystem that collaborate to generate and establish a microbiota that promotes disease. Numerous microbial species were found in the oral cavity, but most of them are commensal bacteria such as *Streptococcus*, *Capnocytophaga*, *Eikenella corrodens* and *Veillonella parvula*; nevertheless, in condition of some imbalances, they could also become pathogens for the tooth supporting tissues[4]. One of the crucial requirements for the development of a potentially pathogenic community is the ability of certain species to modify host responses in ways that compromise immune surveillance and tip the balance from homeostasis to dysbiosis[5]. *Porphyromonas gingivalis* (*P. gingivalis*), *Treponema denticola* and *Tannerella forsythia*, Gram-negative and anaerobic bacteria, possess a higher virulence and aggressiveness and are also involved in periopathogenesis[4].

Numerous mechanisms, including the systemic dissemination of periodontal pathogens and the systemic leakage of local inflammatory mediators, have been involved in the strong association between periodontitis and a number of systemic disorders[6]. Periodontal and systemic diseases have a two-way relationship; periodontal disease can have negative effects on the overall systemic health, and some systemic conditions increase the risk of periodontal disease onset[6,7]. Recent research has also shown that periodontal infection plays a role in aggravating systemic disease states at distal sites, including cardiovascular disease, adverse pregnancy outcomes, diabetes mellitus, Alzheimer's disease, inflammatory bowel diseases, and various cancer types, reinforcing the significance of the oral cavity for general health[6-9]. Additionally, it has been suggested that gastroenterological malignancies may be promoted by hematogenous (oral-blood axis *via* the perturbed periodontal tissues), enteral (oral-gut axis *via* saliva) or lymphatic (*via* the lymphatic drainage system) translocation of periopathogens[10-12].

In the past 25 years, the global burden of pancreatic cancer (PC) has more than doubled, making it one of the major causes of cancer-related mortality[13]. It comprises for almost 2% of all malignancies and is linked to 5% of deaths caused by cancer[14]. North America, Europe, and Australia have the highest incidence rates of PC[14,15]. While the ageing process of the global population could increase the incidence, other major risk factor, specifically smoking, obesity, diabetes and drinking alcohol should be considered for their modifiable nature[13,15].

Only around 20% of patients are initially diagnosed with early-stage PC, which is surgically resectable, thus explaining the low survival rates[13]. Even after a potentially radical treatment, the majority of patients eventually relapse, and their 5-year survival rate is only 2%-9%[14]. During the initial stages of the disease and its progression to advanced pancreatic metastasis, when tumor cells are very invasive, the majority of patients don't exhibit any apparent symptoms. Considering that it is one of the life-threatening malignant tumors, early diagnosis is imperative[13-15]. Pancreatic ductal adenocarcinomas account for over 90% of pancreatic malignancies[13].

Viral infections have been shown to express a strong relationship with cancer, but also certain bacteria can stimulate or trigger uncontrolled cell development by escaping the immune system or preventing apoptosis. Since periodontitis is a chronic oral bacterial infection, a potential link between periodontitis and PC has been proposed[9].

AIM

The purpose of this current review is to update and organize the most recent data on periodontal disease and its implications in PC in order to highlight the fact that there is sufficient evidence to establish a connection between them, through the action of periodontal pathogens, taking into account that periopathogens are essential for the onset and progression of periodontal disease, and their involvement in various systemic disorders has already been proven. This would encourage more exploration into the negative impact of periodontal disease on the development of PC in individuals with both disorders. The findings of future studies may have significant implications for periodontal and gastroenterological practice. For instance, periodontal screening for patients with this type of cancer and periodontal therapy, when necessary, may help lower the risk of PC's adverse evolution while also improving the quality of life for these patients.

PERIODONTAL DISEASE AND PC: EPIDEMIOLOGIC DATA

Periodontitis has been linked to various malignancies, with risk ranging between 14% and 20%[16,17]. Periodontitis has been linked to at least 50% increased risk of PC and it could be considered a risk factor for this malignancy[1,16,17], whereas other studies reported no significant association between periodontal disease and PC[1,18]. Periodontal disease risk is linked to a number of variables that are known to increase the risk of PC, such as smoking, alcohol drinking, and diabetes. The oral microbiome is thus affected by these exposures and circumstances, leading to dysbiosis and a relative increase in the amount of oral pathogenic microorganisms[19,20].

A 10 years follow-up study showed that the risk of all or specific gastro-intestinal malignancies, including PC, was not significantly associated with the severity of chronic periodontitis. After sex and age stratification, this null connection remained consistent[21]. No associations were found between the risk of PC and the eight single nucleotide polymorphisms, which provide the strongest explanation for a genetic predisposition to developing chronic or aggressive periodontitis[22].

Patients with PC may exhibit increased bleeding on probing when exposed to minimal amounts of dental plaque, which could point to periodontitis' excessive activity, often known as a hyperactive phenotype. Although dysfunctions of the CD14 axis receptor, nuclear factor kappa B (NF- κ B) factors, and NOTCH pathway proteins are hypothesized, the source of high bleeding on probing index values at a relatively low plaque index rate is unknown at this time[23].

A cohort study that followed 5889441 individuals for a median of 7.2 years discovered that, compared to those with a healthy dental status, people with root canal infections, mild inflammation, and periodontitis in the under-50 age group had a 58% higher risk of developing PC, while those with periodontitis had a 56% higher risk. Only the subgroup of those with periodontitis exhibited a 20% elevated risk in the 50–70 age range. In all age categories, people with fewer teeth seemed to be at a higher risk[12]. Another study found that having periodontal disease was linked to a higher risk of developing PC in people 65 years of age or older, but not in people under 65[24].

A recent study performed on 59000 African American women with a follow up of 21 years showed that participants who had poor dental health had higher chances of PC[25]. Participants who reported both gum disease and tooth loss had a 58% higher chance of receiving a PC diagnosis[25]. Furthermore, compared to women who had neither periodontal disease nor tooth loss, those who reported periodontal gum disease but no tooth loss had a 77% higher chance of being diagnosed with PC[25]. Their research revealed that PC diagnoses were twice as likely to occur in women without periodontal disease but with absent teeth. Furthermore, the risk was significantly increased among patients who had at least 5 extracted teeth[25]. The findings, according to researchers, might be related to the inflammation that some oral bacteria trigger[25]. In an older research paper, when periodontal disease and recent tooth loss were evaluated together, the risk of PC significantly rose, with a risk ratio of 2.71 compared to people who had neither periodontal disease nor recent tooth loss. These findings imply that recent tooth loss may be a sign of severe periodontal disease[26].

Compared to the link between tooth loss and PC, the relationship between periodontal disease and PC has showed more consistent evidence[16,24,27,28]. According to a meta-analysis, the summary relative risk for periodontitis and PC was 1.74, while the risk for edentulism was 1.54[18]. Nevertheless, data is inconsistent as other research reported no associations between tooth loss and PC[27,28].

So far, research indicates that, independently of other recognized risk factors, like smoking, periodontal disease may contribute to the development of PC[26,29]. A prospective research of 48375 male health professionals revealed that those who had a history of periodontal disease at baseline had a 64% higher risk of PC[26,27,30]. In people who had never smoked, there was a stronger correlation between periodontal disease and PC[26,27,30]. Smoking is also linked to a two-fold increase in the risk of PC[26].

In a research with a long follow-up (10 years) and a substantial population-based cohort (568273 participants), there was a strong positive association between periodontitis and cancer mortality, particularly PC mortality[31]. After adjusting for age, sex, and additional controls for smoking, education, race/ethnicity, and body mass index (BMI), orodigestive cancer mortality was higher in patients with periodontal disease. Furthermore, the severity of periodontal disease enhanced the risks for orodigestive cancer mortality[32]. With age, sex, smoking, education, race/ethnicity and BMI adjustments, the mortality for PC in periodontal patients increased by nearly four times[32].

Regarding the mortality of PC, periodontitis considerably raises the chance of dying from PC[1].

HUMAN MICROBIOME AND PC

Multiple diverse organisms, such as bacteria, viruses, fungus, and protozoa, compose the human microbiota, as the presence of certain microorganisms was reported even before birth, in the human placenta[14,33,34]. They are essential for maintaining human health and preventing illnesses. Bacteria's ability to cause cancer is linked to both individual species and dysbiotic ecosystems[11]. Some hepatitis viruses, particular oral, gastrointestinal, and pancreatic microorganisms may have an etiological role in PC development[14,33,35].

Microbial diversity in the colon and other internal organs is decreased as a result of human microbial system dysregulation and, in PC patients, the imbalance of the intestinal microbiota is common[14,33,35]. Regardless of the severity of PC, the bacterial DNA patterns in the pancreatic and duodenal tissue of the same participants were comparable, indicating that bacteria may be traveling from the gut to the pancreas[36]. Microbiome alterations in the gut, oral cavity and pancreatic tissues of PC patients occur when compared to healthy flora, demonstrating a link between PC and microecology (Table 1). Inflammation may also contribute to PC development, although the underlying pathway is not yet known[37].

According to scientific research, the human microbiota has a key contribution to the onset, progression, and prognosis of PC[14,33,35,38]. The NYU Langone study found that, in contrast to other research linking poor oral health to PC, oral microbiome dysbiosis actually occurred before the malignancy took hold[30].

The function of the microbiome in PC risk has drawn more focus over the last decade. Using 16S rRNA fluorescent probes and quantitative real-time polymerase chain reaction, it was discovered that PC patients had an intrapancreatic bacterial load that was 1000 times higher than that of normal pancreatic tissue. The mean relative proportions of certain taxa varied between the healthy cohort, pancreatic benign neoplasm, and PC[35]. A recent case-control study found that there were discrepancies in the overall bacterial communities between those with PC and controls. While the presence of *Enterobacteriaceae*, *Lachnospiraceae* G7, *Bacteroidaceae*, or *Staphylococcaceae* was linked to an increased risk

Table 1 Selected studies assessing various methods for detecting bacteria in different types of gastroenterological cancers

Ref.	Types of samples and methods used	Bacteria detected in patients with PC	Types of digestive cancers
Del Castillo et al[36], 2019	16S rRNA gene sequencing was performed on tissue samples (pancreatic duct, duodenum, pancreas), swabs (bile duct, jejunum, stomach), and stool samples	<i>Lactobacillus</i> , <i>Porphyromonas</i> , <i>Fusobacterium</i> , <i>Prevotella</i>	Pancreatic cancer
Torres et al [37], 2015	16S rRNA gene sequencing was performed on saliva samples	<i>Leptotrichia</i> , <i>Porphyromonas</i>	Pancreatic cancer
Vogtmann et al [39], 2020	16S rRNA gene sequencing was performed on saliva samples		Pancreatic adenocarcinoma
Fan et al[43], 2018	16S rRNA gene sequencing was performed on pre-diagnostic oral wash samples	<i>Porphyromonas gingivalis</i> , <i>Aggregatibacter actinomycetemcomitans</i>	Pancreatic adenocarcinoma
Farrell et al [47], 2012	16S rRNA gene sequencing was performed on saliva samples	<i>Streptococcus mitis</i> , <i>Granulicatella adiacens</i> , <i>Neisseria elongata</i>	Pancreatic cancer
Tan et al[48], 2022	16S rRNA gene sequencing was performed on oral wash samples, resected cancer tissue and matched normal adjacent tissues	<i>Porphyromonas gingivalis</i> , <i>Firmicutes</i> , <i>Proteobacteria</i> , <i>Neisseria</i> , <i>Haemophilus</i> , <i>Aggregatibacter</i> , <i>Pseudomonas</i> , <i>Sphingomonas</i> <i>Bacteroidota</i>	Pancreatic cancer
Mitsuhashi et al[52], 2015	Genomic DNA was extracted from pancreatic tissues specimens	<i>Fusobacterium</i>	Pancreatic ductal adenocarcinoma
Yamamura et al[53], 2017	Genomic DNA was obtained using a cotton swab in the oral cavity and from cancerous tissues	<i>Fusobacterium</i>	Esophageal, gastric, colorectal, liver and pancreatic cancer
Gaiser et al [58], 2019	Microbial DNA was isolated from cyst fluid and plasma	<i>Fusobacterium nucleatum</i> , <i>Granulicatella adiacens</i>	Pancreatic cystic neoplasms

PC: Pancreatic cancer.

of PC, increased relative levels of *Haemophilus* were linked to a lower risk[39]. Currently, *Neisseria elongata*, *P. gingivalis*, *Streptococcus mitis* and *Fusobacterium* are the key pathogens implicated in PC and it was postulated that *Fusobacterium* can significantly decrease a patient's survival time when it comes to the prognostic evaluation of PC[11,14].

By causing DNA damage, epigenetic alterations of phagocytosis-related genes, immunological response, chromatin organization, cellular proliferation, and higher DNA mutation rates, the microbiome can influence cancer's development. The microbiome can also potentially cause signaling pathway disruption, enhanced local inflammation, and impaired epithelial barrier function[11]. According to one study, the point mutations in the PC patient's p53 tumor suppressor gene may be caused by the peptidyl arginine deaminase enzymes that are specific to oral periopathogen *P. gingivalis* [40].

According to one study, periodontitis, PC and chronic pancreatitis may all share the excessive inflammatory response brought on by the mutations of certain genes, *Q705K* and *F359L*, which are amino acids in *NLRP2* and *NLRP3*. It has been shown that rs35829419 (*Q705K*, *NLRP3*) polymorphism is more common in people with PC, while rs17699678 (*F359L*, *NLRP2*) polymorphism is more common in people with chronic pancreatitis[41].

By triggering systemic inflammation or, alternatively, by increasing the synthesis of bacterial metabolites, such as nitrosamines, reactive oxygen species sulfides, butyrate or acetaldehydes, chronic periodontitis through periopathogens may facilitate pancreatic carcinogenesis[9-11,18]. According to various theories, nitrosamines, acetaldehyde and gastric acidity play a significant role in the development of PC[9,18,27,42], as they can cause DNA alkylation, mutations, damage or impaired repair, which can result in inflammation or tumorigenesis[11].

Although the underlying mechanism connecting periodontitis to gastrointestinal cancers is not fully understood, and it is still uncertain which stage of periodontitis may affect cancer risk, gastroenterological malignancies have a high biological plausibility in relation to oral infections and inflammation[1, 19]. Blood antibodies to certain oral pathogens and poor oral health status were linked to an elevated risk of PC[19,43]. A person's chance of developing PC was increased by 70% and 80%, respectively, whether they had oral mucosal lesions, or tongue lesions caused by *Candida*[1]. PC development was positively associated with tooth loss, although seropositivity to *Helicobacter pylori* was not significantly correlated with tooth loss[44]. Recent research could not establish a link between *Helicobacter pylori* and a higher risk of PC[45].

Future risk of PC has been linked to the oral microbiome, specifically increased levels of *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) and decreased relative abundance of *Leptotrichia* and *Fusobacteria*, suggesting that it may have an impact on the inflammatory condition by

expanding, altering, and regulating the commensal microbiome[11-13,29]. It's noteworthy that *Leptotrichia* species, which are opportunistic pathogenic bacteria, are also frequently discovered in immunosuppressed individuals[46]. Using direct bacterial DNA analysis from samples of people's saliva taken years before diagnosis, a cohort research found strong associations between two periopathogens, *P. gingivalis* and *A. actinomycetemcomitans*, and PC[1,10,43]. This connection is also confirmed by a research which found that pre-diagnostic blood samples from those diagnosed with PC had more antigens to *P. gingivalis* than samples from controls[13]; in contrast, phylum *Fusobacteria* appeared to be linked with a reduced chance of developing PC[10,33]. There are still unanswered doubts regarding the mechanism underlying this connection and whether there is a direct causal correlation[13].

Oral microbiome profiles in patients with PC and controls significantly differ, according to scientific research[47]. Combining immunological dysregulation, genomic damage, and microbial variations between PC cases, early PC cases, and healthy controls, these factors point to a mechanistic role for oral microbiome components in PC development[11].

Bacteria can have a significant impact on carcinogenesis' mechanisms[43,45]. The bacterial "driver-passenger model" best describes this method of collaboration, in which the "driver" pathogen, such as *A. actinomycetemcomitans*, causes DNA damage in the host cells. A more stable ecosystem results from the modifications this driving pathogen makes to the microenvironment around the host cell. These changes make it easier for other germs to proliferate and survive. Once the cancer cells have been located, the "passenger" bacteria, such as *F. nucleatum*, will operate as a connecting organism between the early colonization microorganisms (*A. actinomycetemcomitans*) and the late colonizing microbes (*P. gingivalis*). *P. gingivalis* has the ability to block cancer cell death and encourage tumor growth[43,45]. The three microorganisms could have a significant synergistic impact on the onset and progression of cancer. This means that a diversified microbial environment is both more stable and harmful than a single species of bacterium, which may be a key element in the development of cancer[45].

Porphyromonas gingivalis

A recent study revealed that numerous bacterial taxa which were often detected in the tumoral milieu were also discovered in the oral microbiome, raising the possibility of bacterial translocation from the mouth to the pancreas. Unexpectedly, *P. gingivalis*, one major periodontal pathogen, which usually colonizes the oral cavity, was found in the saliva samples, normal surrounding tissues and the malignant tissues of PC patients in the same report[42,48]. The oral-derived migration of *P. gingivalis* into the pancreas as well as its capacity to cause PC were further shown. The explanation is that *P. gingivalis* induces the aggregation of neutrophils and the release of neutrophil elastase, which eventually promotes pancreatic neoplasms[48].

There is growing evidence that PC and periodontal infections are closely related[12] as *Leptotrichia* and *Porphyromonas* were more prevalent in PC patients' saliva than in healthy controls' saliva[37].

A 1.6-fold higher risk of PC was found in one of the biggest prospective cohort analyses to date when *P. gingivalis* taxa were directly detected in saliva using 16S RNA genes[43]. Unlike past studies assessing bacterial DNA in cancer patients' saliva, this cohort study was distinctive in that saliva samples were taken up to 10 years before a cancer diagnosis[28,43].

Participants who had *P. gingivalis* in their oral microbiome were shown to have a 59% higher chance of developing PC than those who did not[32]. In a European cohort research, those with high levels of antibodies to *P. gingivalis* (> 200 ng/mL) had a twofold increased probability of developing PC[1,10,30,33].

Although the dose-response was not linear and tended to flatten at higher immunoglobulin G (IgG) levels, a cohort research demonstrated a threefold increase in orodigestive cancer mortality, including pancreatic tumors, with rising *P. gingivalis* IgG levels[28,30,32].

Periodontal disease, oral pathogenic microorganisms, and PC have all been linked in a direct manner *via* biological pathways that have been hypothesized. One theory proposes a novel apoptosis-resistant mechanism that promotes immunosuppression and oncogenesis, with *P. gingivalis* serving as the common link[1]. Inhibiting epithelial cells' ability to undergo apoptosis, which has an essential function in defending malignant cells, is one of *P. gingivalis*' major carcinogenic effects. Some signaling pathways that *P. gingivalis* activates are implicated in immune evasion, tumorigenesis, cell invasion of tumor cells, and induction of apoptosis[49].

The bacteria *P. gingivalis* was discovered to be enriched in the abundant intratumor microbiota composition in human PC tissue. *P. gingivalis* may create a tumor microenvironment that is pro-inflammatory and elevate neutrophil elastase levels, eventually promoting the development of PC[42,48]. It was discovered that *P. gingivalis* survives inside PC cells, a property that can be improved *in vitro* and is amplified by hypoxia, a key aspect of PC[50]. The capacity of the bacteria to survive intracellularly and to increase Akt signaling and cyclin D1 expression, two essential pathways associated with PC development, are connected to the enhancement of proliferation. *P. gingivalis* infection of tumor cells led to enhanced growth *in vivo*. The scientists concluded that *P. gingivalis* directly influences PC cells in a pro-tumorigenic manner[50]. PC cell proliferation was considerably increased by live *P. gingivalis*, but surprisingly, this effect was not mediated by Toll-like receptor 2, an innate immune receptor that is activated in response to *P. gingivalis* on immune and cancer cells and is necessary for the bacterium to

cause alveolar bone resorption[50].

Another link between *P. gingivalis* and tumors is the metabolism of possibly carcinogenic compounds produced by this bacteria[49]. Following the administration of lipopolysaccharide from *P. gingivalis*, increased expressions of certain genes (*Reg3A* and *G*) were reported, thus the authors suggested that it could play an important role in *P. gingivalis*-lipopolysaccharide-related PC in mice[51].

P. gingivalis was definitely able to influence the host immunological responses, according to RNA sequencing. After *P. gingivalis* infection, neutrophil chemokines (*Cxcl1*, *Cxcl2*, *Cxcr2*, *etc.*) were discovered to be strongly elevated, but genes linked to gram-negative bacterial defense and antitumor-origenic activities, such as lymphocyte chemotaxis and cell cytoskeleton, were significantly suppressed. In PC mouse models, *P. gingivalis* specifically bypasses the host immune system and severely reduces the host's ability to fight tumors[48].

High frequencies of mutations in the tumor suppressor gene *p53* were found in PC patients, leading researchers to draw the conclusion that alteration of the *p53* gene is a crucial event in the development of human pancreatic tumors[49]. Furthermore, *P. gingivalis* decreases *p53* levels while increasing the cell cycle's S-phase advancement[11].

Both *F. nucleatum* and *P. gingivalis* possess strong antiapoptotic properties as well as capabilities of immune evasion and disruption[11].

Fusobacterium nucleatum

Fusobacterium species were examined by Mitsuhashi *et al*[52] in 283 PC patients and their results found a detection rate of 8.8% in tumor tissue and 28% in normal adjacent tissues. When using multivariate Cox regression analysis, it was shown that the presence of these bacteria is associated with a greater mortality, in comparison with *Fusobacterium*-negative group[52]. Conversely, a recent study did not detect *F. nucleatum* DNA in PC tissues. They hypothesized that *F. nucleatum* would contribute to the development of gastroenterological tract cancer but not pancreatic or liver cancer[53], although Mitsuhashi *et al*[52] stated that the bacterium could be considered a prognostic marker of PC[52].

Moreover, greater abundance of *Fusobacteria* and its genus *Leptotrichia* was linked to a lower risk of PC, according to a cohort study that used direct bacterial DNA sequencing from samples of people's saliva obtained years before diagnosis[42,43]. In contrast, *F. nucleatum*-positive pancreatic ductal adenocarcinomas were linked to elevated cancer-specific mortality rates[11,46].

Fusobacterium species were more frequently discovered in pancreatic tail cancer than in head or body cancer, despite the lack of a significant association. Uncertainty surrounds the high incidence of *Fusobacterium* species in pancreatic tail tumors. The difference in vascular supply between the pancreas tail and head or body could represent one possibility for this observation[52].

Aggregatibacter actinomycetemcomitans

Moreover, although the connection was not as strong as for *P. gingivalis*, people who exhibited *A. actinomycetemcomitans* in their oral microbiome also had at least a 50% higher relative chance of developing PC[32]. When *A. actinomycetemcomitans* taxa were directly detected in saliva using 16S RNA genes, one of the biggest cohort analyses to date found a 2-fold increased risk of PC[43]. In contrast to past studies measuring bacterial DNA in cancer patients' saliva, the samples used in this cohort study were taken up to 10 years before the cancer diagnosis[28].

Through the insertion of DNA double-strand breaks *via* CDT activity, *A. actinomycetemcomitans* Y4 can cause genomic instability, a significant phase in the tumorigenesis[11].

Bacterial toxins, such as the cytolethal distending toxin released by *A. actinomycetemcomitans*, can disrupt the balance of the host's immune system, harm antigen-presenting cells, and prevent lymphocyte proliferation[11]. Moreover, their lipopolysaccharide may help accelerate carcinogenesis through NF- κ B signaling and TLR4 binding, both of which are elevated in the tumor microenvironment[11].

THERAPEUTIC APPROACHES

Previous research has demonstrated a connection between microbes and the development and spread of PC. The development of biomarkers that may control how responsive cancers are to therapeutic drugs may be regulated by the human microbial system, which is particularly advantageous for enhancing PC's clinical efficiency. Chemotherapy and immunotherapy can be paired with microbial systems, which may provide PC patients a significant amount of hope. But there is still a lot of disagreement in this area[14].

Early detection

It has been established that intestinal microbiota contributes to PC by producing tumor-specific immunity and systemic immunity, although the mechanism is yet unknown. In an effort to develop new therapeutic approaches, future research will concentrate on how microbiota influences the development and maintenance of immunological tolerance. In order to create more targeted techniques of response modulation, a thorough investigation of the PC-associated microflora can be performed to pinpoint

particular communities that contribute either positively or negatively to the onset and progression of PC [14]. The biggest chance of increasing survival rates would arise from early identification of PC. A particular oral microbiota analysis might be developed to enable the early diagnosis of cancer since mouth dysbiosis appears to be more pronounced in individuals with gastrointestinal tumors[29].

To determine if the presence of specific microbial species may be used as a biomarker for the early diagnosis of PC, the salivary bacterial profiles of 108 people were examined; 8 of them received a PC diagnosis, 22 were healthy controls and the other had other diseases. When compared to healthy participants or patients with other disorders, the ratio of *Leptotrichia* and *Porphyromonas* was considerably greater in the saliva of subjects with a future PC diagnosis[20,37]. *P. gingivalis* may serve as a biomarker for the emergence and progression of PC[49].

Similar shifts may be observed in individuals with preneoplastic lesions, such as intraductal papillary mucinous neoplasms, if alterations in the oral microbiota are connected to the probability of developing PC[20].

Saliva is a biofluid that is simple to acquire, making it perfect for the early identification of a variety of illnesses, including bacterial and viral infections, cardiovascular, renal, autoimmune disorders and, especially, malignancies[54-56]. Eight metabolites (leucine with isoleucine, tryptophan, valine, glutamic acid, phenylalanine, glutamine, and aspartic acid) were found in a research that thoroughly investigated salivary metabolites and identified metabolic patterns unique to several types of malignancies, including PCs. According to this, salivary metabolites could be considered cancer-specific markers[55].

Gut microbiome modulation

The identification of biomarkers for predicting future PC risk and prognosis is made possible by microbiota research, which offers the chance to fully explain the underlying processes. According to prior research, PC is linked to bacteria that may alter a tumor's susceptibility to therapeutic medicines. Through appropriate adjustment, the effectiveness of this deadly disease's therapy can be greatly improved. The development and application of novel antibiotics, prebiotics, probiotics or microbial transplantation in conjunction with chemotherapy and immunotherapy may hold considerable potential for PC patients[35,46,57].

Reducing the pancreatic inflammatory microbiome may be a viable treatment option for individuals with an early precursor of PC, like pancreatic cysts-intraductal papillary mucinous neoplasms-, because of the demonstrated co-occurrence and enrichment of oral bacterial species in their microbiome[58].

Pushalkar *et al*[59] showed that intestinal bacteria may invade the pancreas, and that in PC tissue, both in animal models and in people, there is an increased abundance of bacteria compared with control cases with a different microbiome community in PC samples compared to controls. Furthermore, compared to healthy animals, PC mouse models have a higher capacity for the gut microbiota to translocate to the pancreas[20,59]. In one investigation, the significance of the *P. gingivalis*-inflammatory system-pancreas axis in the progression of PC was clarified, and it was suggested that lowering *P. gingivalis* infections or inflammatory state would help with PC prevention and therapy[48].

Additionally, PC developed more slowly in germ-free mutated animals. Oral antibiotic therapy also showed a protective effect against tumor growth, while gut microbiome repopulation with PC mouse feces increased cancer progression[20].

It was discovered that microbe-free mice did not respond to immunotherapeutic medications, but mice that were administered *Bacteroides fragilis* responded positively. According to Sivan *et al*[60], *Bifidobacterium* increased the effectiveness of cancer immunotherapy in mice, which suggested that microbes, particularly gut bacteria, may be triggering the immune response by causing enterocytes to produce specific message molecules or send signals to immune cells, which enhances their capacity to fight tumors[35,60]. Due primarily to its poor response to chemotherapy, PC is often a fatal disease. Recent research suggests that the tumor microenvironment may be a significant factor in developing gemcitabine chemoresistance[57].

By analyzing patterns in the microbiome composition throughout PC development and establishing strategies to enhance the cancer-associated microbial system, we can increase the efficacy of therapy and eventually find an application for the microbial system. The development of immunogenomics and gut micro-genomics in the life sciences will result in a significant advancement in our understanding of how microbial systems and immunotherapy interact, and it may also have intriguing therapeutic implications for extending the lifetime of PC patients[14].

Periodontal treatment

Enhancing our knowledge of the connection between periodontal disease and other risk factors and how they affect cancer risk, as well as identifying potential bacteria that may be involved in carcinogenesis, may also open up new opportunities for early cancer detection (through the discovery of biomarkers), and provide information on whether active treatment for periodontal disease will lessen the burden of cancer[28,46]. It is uncertain to say at this point if the burden of cancer would decrease with the treatment of periodontitis[28].

Using the Taiwanese NHIRD, a research project investigated the link between periodontal disease and cancer, particularly PC, and the impact of periodontal disease therapy, which was defined as at least 10 procedures like scaling and periodontal flap surgery. Patients who received treatment had

significantly decreased incidence rate ratios for PC and adjusted hazard ratios. The modified model did not, however, take smoking into account[19,61].

CONCLUSION

These researches support the hypothesis that certain characteristics of the human microbiome play a significant role in shaping the immune response in a manner that facilitates tumor development. Given the growing epidemiological data linking periodontal disease to PC and the rapid unraveling of new molecular links between periopathogens and cancer development, the impact of bacterial infection on pancreatic carcinogenesis has to be given more consideration. More research in this field is expected to improve our knowledge of this aggressive malignancy and provide us with new chances for early identification and/or the development of treatments.

FOOTNOTES

Author contributions: Şurlin P, Şurlin VM, Gheonea DI contributed to conceiving the study; Nicolae FM, Ungureanu BS, Râmboiu S contributed to the investigation; Strâmbu VDE, Gheonea DI, Roman A contributed to the supervision; Nicolae FM, Gheorghe DN, Şurlin P wrote the original draft; Nicolae FM, Ungureanu BS, Radu PA, Şurlin P edited the original draft; All authors have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Fan JR

L-Editor: A

P-Editor: Fan JR

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