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THE IMPACT OF BACTERIAL DYSBIOSIS ON THE DEVELOPMENT OF PANCREATIC CANCER AND ITS TREATMENT IN HUMANS?

Agata Mikołajczyk[1], Amelia Wardak[1], Stanisław Głuszek[1], Wioletta Adamus-Białek[1*]

[1]Institute of Medical Sciences, Jan Kochanowski University of Kielce, Av. IX Wieków Kielc 19a, 25-317 Kielce, Poland

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Abstract: Pancreatic cancer is one of the deadliest types of cancer and is still difficult to treat, despite recent medical advances. Many studies show correlations between the human oral and intestinal microbiota and pancreatic cancer. The mechanism of action of microorganisms on the pancreatic microenvironment is still not fully understood. The aspect of immune response related to treatment and the microorganisms present has also been addressed. This review presents current evidence on the human microbiota, mainly focusing on its bacterial contribution and influence, and identifies the areas that may benefit most from earlier diagnosis and the potential for less invasive treatment of pancreatic cancer. A review of all the latest literature (n=86) in peer-reviewed English-language journals with an Impact Factor from PubMed (NCBI) and Google Scholar was conducted; most studies concerned the analysis of bacteria in the human microbiota or in a mouse model.

Keywords: microbiome, pancreas, tumor

1. Introduction

Pancreatic cancer (PC) is characterised by a high mortality rate and low survival rates. It is classified as the third most common cancer as a cause of cancer deaths, right after lung cancer and colon cancer. The estimated number of deaths in 2024 from pancreatic cancer in the United States for both sexes is 66.440 thousand, of which 51.750 thousand will be fatal cases, accounting for 77.89% of pancreatic cancer mortality (Siegel *et al.* 2023; Siegel *et al.* 2024). A study by Santucci *et al.* (2024) forecasts a continued decline in cancer mortality across the EU, with age-standardized rates expected to fall by 6.5% for men and 4.3% for women relative to 2018 levels. On the contrary, pancreatic cancer shows an unfavorable prediction in studies in the EU, and mortality from this cancer is increasing in both sexes. Mortality rates for both sexes (+1.6% in men and +4.0% in women) (Santucci *et al.* 2024).

Pancreatic cancer is non-specific and difficult to diagnose in its early stages. The anatomical location of the pancreas is an additional complication in the diagnosis of pancreatic cancer (Maitra *et al.* 2024). The cancer can develop in the exocrine cells of the pancreas, which are responsible for producing digestive juices, or in the endocrine cells of the pancreas, which produce hormones. However, pancreatic cancer starts to develop in the exocrine cells in approximately 95% of cases and belongs to the histological subtype of ductal adenocarcinoma, which is associated with a poor prognosis and a lack of effective therapies (Grant *et al.* 2016; PDQ Adult Treatment Editorial Board 2024). Pancreatic exocrine insufficiency, resulting from obstruction of the pancreatic duct, fibrosis, or tissue loss, contributes to malnutrition and weight loss in patients (Vujasinovic *et al.* 2017; de la Iglesia *et al.* 2020; Sabater *et al.* 2016).

* Corresponding author: Wioletta Adamus-Białek, Jan Kochanowski University of Kielce, Institute of Medical Sciences, Av. IX Wieków Kielc 19a, 25-317 Kielce, Poland, e-mail: wioletta.adamus-bialek@ujk.edu.pl

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The etiological factors of PC include non-modifiable germline genetic factors as well as modifiable factors such as smoking, obesity, and diabetes (Stanciu *et al.* 2022; Gentiluomo *et al.* 2022). Approximately 5-10% of pancreatic cancer patients have a familial background, while the genetic contribution in the remaining cases is unknown, suggesting a role for the environment in the etiology of the disease (Goggins *et al.* 2020). Molecularly, epigenetic alterations and somatic mutations, especially activating mutations in the *KRAS* gene, play a central role in the pathogenesis of PC. *KRAS* mutations, though rarely inherited, are commonly acquired and act as a critical driver of tumor initiation and progression (Baylin and Jones 2016; Chen *et al.* 2021; Alonso-Curbelo *et al.* 2021).

The study and development of epigenetic mechanisms of metastasis in pancreatic duodenal carcinoma has the potential to facilitate effective therapeutic intervention(Wang *et al.* 2021; Chen *et al.* 2021).

Recently, the role of the microbiome in the context of pancreatic cancer has also received much attention. A correlation has been observed between the commensal microbiome (classified as an environmental factor) and certain gastrointestinal cancers, including those affecting patients with pancreatic cancer. However, the available data remain inconclusive (Sexton et al., 2022). Further study of the epigenetic mechanisms underlying metastasis in pancreatic duodenal carcinoma could facilitate the development of effective therapeutic interventions. The natural ecosystem of microorganisms is also susceptible to various environmental factors, which may contribute to the disruption of the organism's overall homeostasis. It has been shown that alterations of the microbiota in the pancreas-gut axis can cause chronic pancreatic inflammation, which is one of the risk factors for pancreatic cancer. It has been proven that fungal intestinal microbiota is also associated with carcinogenesis. Fungal dysbiosis with yeasts of the genus *Malassezia* has been implicated in the development of cancer at an early stage (Speth *et al.* 2022). The previous studies have shown the influence of fecal and oral microbiomes not only on pancreatic carcinogenesis but also on immune modulation in pancreatitis (Thomas and Jobin 2020). Microbiota can be a powerful source of biomarkers for identifying individuals with pancreatic ductal adenocarcinoma and their prognosis (Pourali *et al.* 2024).

This review specifically highlights research on the bacterial microbiome, which represents the most extensively studied microbial group in the context of pancreatic cancer. In this article, we present a general overview of what is known about the impact of the bacterial oral and gut microbiome on the incidence of pancreatic cancer and discuss the effectiveness of therapy by modulating the microbiome. A literature search was performed using databases such as PubMed and Google Scholar, with search terms including "Pancreatic Cancer," "Resistance," "Therapy" and "Microbiota". The analysis included 89 articles, which were primarily based on meta-analyses, as well as prospective, retrospective, clinical, metagenomic, and expectorant studies. The study population comprised individuals diagnosed with pancreatic cancer or pancreatic ductal adenocarcinoma, as well as a control group of healthy individuals. We also included pancreatitis as one of the most important etiological factors of pancreatic cancer.

2. The association between the oral microbiome and pancreatic cancer

To date, 619 bacterial taxa representing 13 phyla have been identified in the human oral microbiome (Dewhirst *et al.* 2010). It is a highly diverse and dynamically changing group of microorganisms that varies even in terms of where the sample is taken from, for example oral mucous membrane, tooth pockets, teeth, and tongue. Examples include saliva, tongue plaque, and mouthwash (Nearing *et al.* 2020). Saliva contains a broad spectrum of bacterial species, and the sampling method is convenient and relatively cost-effective. Studies show that using diagnostic models to characterize the oral microbiota, microbial biomarkers can provide a diagnostic tool for pancreatic cancer. The studies with 16S rRNA sequencing revealed there are significant differences in quantitative and qualitative species composition between the microorganisms found in the saliva of healthy individuals and those with pancreatic cancer or a pre-cancerous condition (Fan *et al.* 2018; Wei *et al.* 2020). A malignant condition such as pancreatic ductal adenocarcinoma, is a consequence of chronic inflammation and is driven by ongoing inflammation associated with immunosuppressive CD4+ T lymphocytes. It can be concluded that chronic inflammation of the pancreas induces carcinogenesis (Guerra *et al.* 2007).

In the study presented by Chen *et al.* (2023), a group of patients with pancreatic cancer and chronic pancreatitis was compared to healthy controls. Fecal and saliva samples analyzed by the 16S rRNA sequencing method and real-time qPCR revealed that oral pathogenic genera significantly predominated in pancreatic cancer, especially *Granulicatella*, *Peptostreptococcus*, *Alloprevotella*, *Veillonella, Bacteroidetes*, *Firmicutes,* and *Proteobacteria*, accounting on average for more than 80% of all observed species. In patients with chronic pancreatitis, the average relative abundance of the two phyla of *Firmicutes* and *Verrucomicrobia* was significantly higher than that in healthy controls. A marked

enrichment of pathogenic bacterial genera, including *Granulicatella, Peptostreptococcus, Alloprevotella, Veillonella, Solobacterium,* and *Streptococcus*, was detected in the oral microbiota of patients diagnosed with pancreatitis. These results were similar to those described by Farell *et al.* (2012). Other studies, using the same technology of sequencing, demonstrated that the relative abundance of *Porphyromonas*, *Haemophilus,* and *Paraprevotella* genera was significantly higher in the healthy tongue plaque microbiome, while in patients with chronic pancreatitis, *Leptotrichia*, *Fusobacterium*, *Actinomyces*, *Rothia*, *Solobacterium*, *Oribacterium*, *Campylobacter*, *Atopobium,* and *Parvimonas* families occurred significantly more often. The most notable differences between the microbiota of the tongue lining of patients with chronic pancreatitis and healthy controls were low levels of *Haemophilus* and *Porphyromonas* and high levels of *Leptotrichia* and *Fusobacterium* (Mitsuhashi *et al.* 2015; Lu *et al.* 2019).

Further extensive research included: 361 cases of pancreatic adenocarcinoma and 371 matched controls selected from two large prospective cohort studies: The American Cancer Society Cancer Prevention Study II (CPS-II) and the National Cancer Institute Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. The pre-diagnostic oral wash samples collected from participants were also analyzed by 16S rRNA gene sequencing. It showed that carrying *Tannerella forsythia* and *Prevotella intermedia* in the mouth, in contrast to *Porphyromonas gingivalis,* was not associated with pancreatic cancer risk. This association was evident for both those with low bacterial abundance (below the median relative abundance) and those with high bacterial abundance (above the median relative abundance) (Fan *et al.* 2018). Another large European prospective cohort study – The European Prospective Investigation into Cancer and Nutrition (EPIC) – analyzed 405 patients with pancreatic cancer compared to 416 controls. Using Luminex-based immunoassays, it was noted that individuals with high levels (>200 ng/ml) of antibodies to the periodontal pathogen *Porphorymonas gingivalis* had twice the risk of pancreatic cancer compared to those with lower levels of these antibodies (≤200 ng/ml). It was found that people with consistently high levels of antibodies to common oral bacteria had a 45% lower risk of pancreatic cancer compared to those with lower levels of antibodies. The antibody levels were measured in blood samples taken up to 10 years before the cancer was diagnosed, which is likely to minimize changes in the immune response after the development of pancreatic cancer (Michaud *et al.* 2013). The association between an elevated level of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* and an increased risk of pancreatic cancer was also shown. A long-term study involving 59,000 African American women, with a follow-up period of 21 years, found that participants with poor dental health had a higher likelihood of developing pancreatic cancer. Periodontitis has been associated with at least a 50% increased risk of pancreatic cancer and can be considered a potential risk factor for this malignancy (Pietzner *et al.* 2021; Ungureanu *et al.* 2023). Kaci *et al.* (2014) also found that the most prominent feature of the oral microbiome for pancreatic ductal adenocarcinoma was a significant reduction in *Streptococcus salivarius*, a bacterium known for its anti-inflammatory properties. It has been demonstrated that metabolically active *Streptococcus salivarius* JIM8772 exerts significant anti-inflammatory effects in murine models of both moderate and severe colitis. Based on these findings, it can be hypothesized that high levels of *Streptococcus salivarius* colonization in the mouth and intestine may be associated with a reduced risk of pancreatic cancer, possibly due to its anti-inflammatory and immunomodulatory effects (Kaci *et al.* 2014). In another study, it was shown that Ganoderma *atrum* polysaccharide (PSG) and White Hyacinth Bean polysaccharide (WHBP) were used to investigate their effects on the microbiota of the oral cavity, gut, pancreas, and lungs in rats with type 2 diabetes. The results showed that oral microbiota was significantly similar to pancreatic microbiota, more than the gut microbiota. This suggests a potential role for saliva as an early biomarker of pancreatic changes. Treatment with PSG and WHBP not only improved pancreatic condition but also helped stabilize the oral microbiota, indicating a strong correlation between these two environments (Wu *et al.* 2022).

3. The association between gut microbiome and pancreatic cancer

It is well known that the human gut microbiota plays an important role in the functioning of the body, both by influencing metabolism and regulating the immune system. Disturbances in the bacterial balance can have negative effects on various organs, including the pancreas (Adolph *et al.* 2019; Zhou *et al.* 2020). Altered gut microbiota is influenced by factors related to inflammatory, metabolic, and malignant diseases (Montenegro *et al.* 2022; Maev *et al.* 2023). A study involving 1.795 volunteers who provided stool samples found that changes in gut microbiota composition were primarily associated with pancreatic stromal cell function. Ductal cell function appeared to play a less significant role (Frost *et al.* 2019). To detect bacteria in human pancreatic ductal adenocarcinoma (PDAC) samples, Geller *et al.* (2017) used real-time quantita-

tive polymerase chain reaction targeting the bacterial 16S rRNA gene and confirmed bacterial presence with non-PCR methods: ribosomal RNA fluorescence in situ hybridization (FISH) and immunohistochemistry using an anti-LPS antibody. Research has shown that the most frequently identified species in pancreatic ductal adenocarcinoma (approx. 52% of all reads) belong to the class *Gammaproteobacteria*, with the majority represented by the *Enterobacteriaceae* and *Pseudomonadaceae* families in the *Proteobacteria* cluster. *Proteobacteria* are abundant in the duodenum, into which the pancreatic duct opens. This suggests that retrograde migration of bacteria from the duodenum into the pancreas may be the source of bacteria associated with pancreatic ductal adenocarcinoma (Geller *et al.* 2017). In a study comparing the gut microbiota between pancreatic cancer patients and healthy controls, it was found that the composition of the gut microbiota was similar in both groups, among the bacterial phyla, *Firmicutes* and *Bacteroidetes* were dominant. However, it showed again that patients with pancreatic ductal adenocarcinoma had a significantly higher presence of *Proteobacteria*, *Synergistetes,* and *Euryarchaeota* phyla compared to the control group (Pushalkar *et al.* 2018).

The above study mentioned Chen *et al.* (2023) described an interesting study of the gut microbiome in a group of cancer patients compared to healthy participants. They found that *Prevotella* spp. was present at significantly higher levels in cancer patients. In the study, its percentage of the pancreatic microbiota was 17.64% (relative average) compared to the control group, in which *Prevotella* spp. accounted for only 6.4% of the tested microbiota (relative average). Andréasson *et al.* (2024) analyzed stool samples from rheumatoid arthritis (RA) patients (n=50) before and after treatment using a 16S rRNA-based GA-map Dysbiosis Test and qPCR for *Prevotella copri,* assessing microbiota changes in relation to disease activity (DAS28-CRP). They have shown that *Prevotella copri* was involved in the development of RA in mice through the Th17/IL-17 pathway. Similarly, isolated *P. copri* strains (n=13) from RA patients and healthy controls were whole-genome sequenced. To assess their arthritis-inducing potential, two mouse models were used: collagen-induced arthritis under specific-pathogen-free conditions and SKG mice monocolonized with *P. copri*. *In vitro* stimulation of bone marrow–derived dendritic cells (BMDCs) showed that *P. copri* induced stronger IL-17 and Th17-related cytokine responses (IL-6, IL-23), suggesting a higher pro-inflammatory potential (Nii *et al.* 2023). The same pathway can also accelerate the development of pancreatic precancerous conditions (PanIN), suggesting that *Prevotella copri* may play a role in promoting pancreatic cancer through Th17 activation.

Additionally, multicenter study revealed distinctive gut microbiota profiles for PDAC patients, including significant increases in *Streptococcus* spp. and *Veillonella* spp. and a reduction in *Faecalibacterium prausnitzii*. The study was based on shotgun metagenomic analysis of fecal and salivary samples collected from 47 treatment-naïve PDAC patients and 235 non-PDAC controls across Japan, Spain, and Germany (Nagata *et al.* 2022). Studies have also shown that a cancerous pancreas contains a significantly more diverse microbiome compared to a healthy pancreas. An increased number of specific types of bacteria have been observed in pancreatic ductal adenocarcinoma compared to their presence in the gut, and it has been shown that these bacteria can migrate through the pancreatic duct (Dickson 2018; Del Castillo *et al.* 2019). Studies investigating the presence of bacteria in pancreatic juice and bile from patients with pancreatic ductal adenocarcinoma, using PCR targeting the 16S rRNA gene, consistently identified *Enterococcus* spp. and *Enterobacter* spp. as predominant in bile samples, suggesting a potential route of pancreatic infection. This method was applied in two separate studies: one analyzing 36 samples (Maekawa *et al.* 2018) and another analyzing 101 samples (Stein-Thoeringer *et al.* 2025), both confirming the frequent presence of bacterial DNA. Additionally, pancreatic cancer patients showed significantly elevated serum antibody levels against *Enterococcus faecalis* envelope polysaccharide compared to healthy individuals.

Analysis of the gut microbial profile showed that 15 taxonomic groups were significantly enriched in pancreatic cancer patients, mainly including the genera *Prevotella*, *Veillonella*, *Klebsiella*, *Selenomonas*, *Hallella*, *Enterobacter,* and *Cronobacter*. On the contrary, 25 taxonomic groups, primarily *Gemmiger*, *Bifidobacterium*, *Coprococcus*, *Clostridium* cluster IV, *Blautia*, *Flavonifractor*, *Anaerostipes*, *Butyricicoccus,* and *Dorea* were significantly reduced in fecal samples from pancreatic cancer patients compared to healthy individuals. The results were obtained using linear discriminant analysis. These studies also highlight differences in microbial composition depending on the stage of pancreatic cancer. The genera *Lactobacillus*, *Haemophilus,* and *Streptococcus* were significantly more abundant in patients with stage II disease compared to those with stage I (Ren *et al.* 2017). Also, patients with a stomach infection due to pathophysiological colonization of *Helicobacter pylori*, may be at higher risk for increased pancreatic cancer (Maisonneuve and Lowenfels, 2015). Seropositivity of antibodies to *H. pylori* and its virulence protein for CagA-positive strains of *H. pylori* was determined using commercial IgG immunoassays.

The results of these studies suggest that colonization by Cag A-negative strains of *H. pylori* may affect the risk of pancreatic cancer. It is associated with changes in stomach acidity, Cag A-negative strain, and hyperchlorhydria modulate pancreatic carcinogens and increase the morbidity of pancreatic cancer (Risch *et al.* 2014). Gastric acidity stimulates bicarbonate and fluid secretion from pancreatic ductal cells. This mechanism allows *H. pylori* to reside in the stomach and interfere with the function of the pancreatic ductal epithelium. Thus, it can be suggested that the differential modification of chronic gastric acidity by CagA-negative strains of *H. pylori* may affect the risk of pancreatic cancer. However, further studies analyzing this relationship are needed to draw firm conclusions (Risch 2012; Hirabayashi *et al.* 2019), because the seropositivity of *H. pylor*i strains varies depending on the continent where the study was conducted, so the seropositivity test may show different results depending on the origin of the study group (Wang *et al.* 2014; Huang *et al.* 2017). There is a lot of evidence that *H. pylori* is significantly correlated with the occurrence of pancreatic cancer. Based on the results of a study of the Asian population, a correlation between *H. pylori* infection and the incidence of pancreatic cancer was proven (Hsu *et al.* 2014; Xu *et al.* 2022).

Literature data clearly indicate that differences in the composition of the gut microbiota may reflect or be associated with the presence of pancreatic cancer (Daley, 2022). This may become an important diagnostic marker. However, it should be remembered that patients with pancreatic cancer are often a heterogeneous group of patients with other comorbidities. Therefore, samples from cancer patients differ significantly in the microorganism's composition. Nevertheless, higher proportions of bacterial genera belonging to the phyla *Bacteroidetes* and *Firmicutes* have been observed in pancreatic cancer patients compared to healthy individuals (Half *et al.* 2015). The pancreas, which secretes substances outside the intestine, plays an important role in shaping the composition and stability of microorganisms found in the intestines of healthy people who do not suffer from any pancreatic diseases. Pancreatic lipase, trypsin, and glycoprotein 2 play an important role in shaping the composition and stability of microorganisms found in the intestines of healthy individuals. These enzymes also protect the intestines by inducing bacterial lysis and acting as antimicrobial agents (Nishiyama *et al.* 2018; Edogawa *et al.* 2020; Shin and Seeley, 2019). Figure 1 shows the types of microorganisms whose decreased or elevated levels in the mouth and intestines can increase the incidence of pancreatic cancer (Fig. 1).

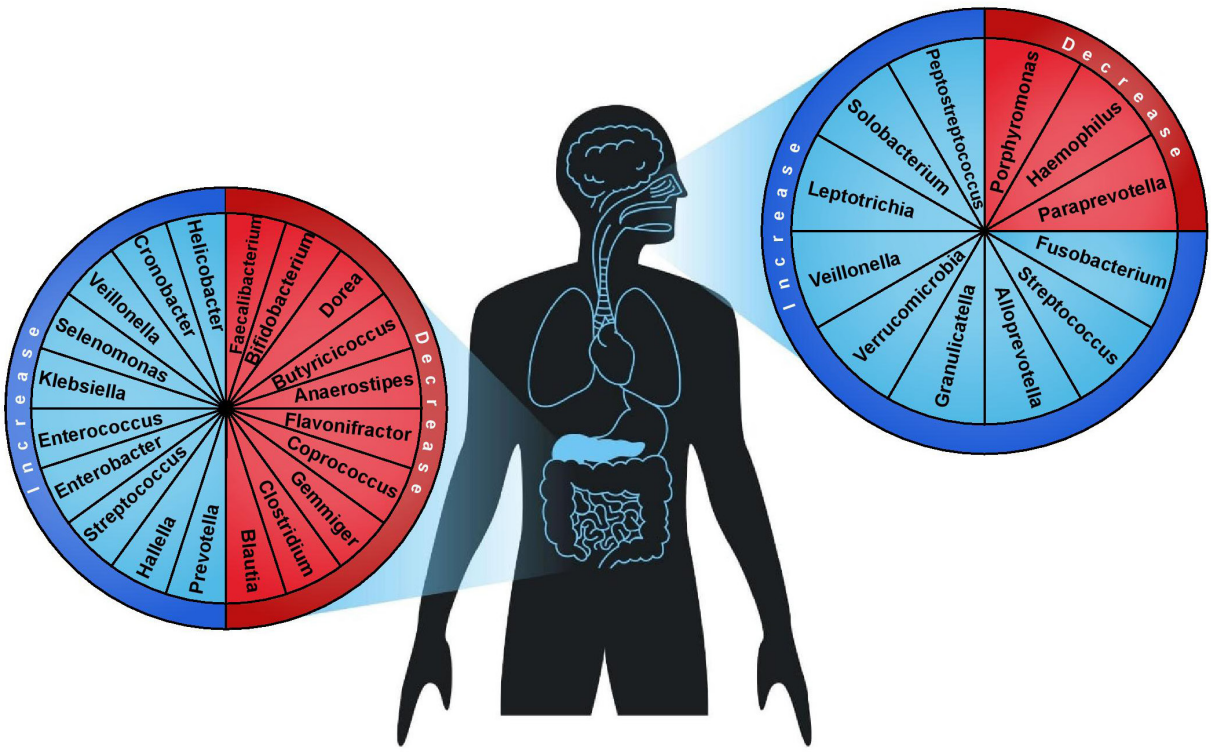

Figure 1. Occurrence of taxonomic groups of bacteria in the oral and intestinal microbiome of patients with pancreatic cancer compared to the population of healthy people. Red fields in the pie chart - a decrease in the number of bacteria, blue fields in the pie chart - an increase in the number of bacteria. Original graphic.

4. Known mechanisms of the association between microbiota and pancreatic cancer

Microbial dysbiosis as well as epithelial barrier dysfunction may affect tumor transformation through bacterial translocation (Plottel and Blaser, 2011). In most malignancies, the intestinal microbiome is in direct contact with or near the diseased organ. On the contrary, the anatomical location of the pancreas does not indicate that the gut microbiome can influence disease development (Meng *et al.* 2018). Changes in the microbiota may result from the movement of bacteria from the duodenal intestine to the pancreas through the opening of the pancreatic duct in the duodenal papilla, but this movement may not be a normal physiological process. However, studies suggest that there is a specific gut and pancreatic microbiome associated with pancreatic cancer that may accelerate the development of the disease by weakening the body's immune response (Pushalkar *et al.* 2018). Performing bacterial ablation leads to immunogenic reprogramming of the PDAC tumor microenvironment. It decreased the number of bone marrow-derived suppressor cells, and increased the differentiation of M1 macrophages, promoted the differentiation of CD4 Th1 T cells, and the activation of CD8 T cells. In addition, bacterial ablation enhanced the efficacy of checkpoint-targeted immunotherapy by upregulating PD-1 expression. Mechanically, the PDAC microbiome generated a tolerogenic immune program through differential activation of selected Toll-like receptors in monocyte cells (Seifert *et al.* 2016; Pushalkar *et al.* 2018). A continuous decrease in the number of short-chain fatty acid-producing bacteria, such as *Faecalibacterium prausnitzii, Eubacterium rectale,* and *Ruminococcus bicirculans,* was observed in the intestines of patients with pancreatic adenocarcinoma. This decline partially coincided with the characteristic changes in the gut microbiome found in various diseases. Short-chain fatty acids regulate intestinal immune function through G-protein-coupled receptors on the cell surface. Their absence leads to inflammation, which may promote the development of PDAC (Parada Venegas *et al.* 2019; Ubachs *et al.* 2021). In turn, oral pathogens such as *Porphyromonas gingivalis* cause mutations in the pro-tumorigenic genes *TP53* and *KRAS* by secreting peptidylarginine deaminase. On the other hand, *Fusobacterium nucleatum* promotes tumor formation and metastasis in several ways: it binds to host cells via FadA adhesion proteins, enabling their internalization and activation of NF-κB and IL-6 pathways, leading to pro-inflammatory cascades (Kostic *et al.* 2013; Gnanasekaran *et al.* 2020). Fecal microbiota transplantation is also beginning to play an increasingly important role. An experiment was performed in which fecal microbiota was transplanted from donors who were pancreatic cancer patients with either short- or long- term survival. As a result, scientists were able to influence tumor growth and immune infiltration of the tumor. This shows that the composition of the pancreatic microbiota of PDAC patients, communicating with the gut microbiota, influences the host immune response (Riquelme *et al.* 2019; Yang *et al.* 2022).

5. The impact of dysbiosis on the effectiveness of pancreatic cancer treatment

An increasing number of studies indicate that the intestinal microbiota may play a dual role in pancreatic cancer by contributing to its pathogenesis and modulating the efficacy and toxicity of anticancer therapies. These effects are mediated through alterations in drug pharmacokinetics, changes in the host metabolic milieu, and modulation of the tumor microenvironment composition. As a result, intestinal microbiota can affect the effectiveness of treatment, and its modulation can lead to different therapeutic effects. Microbes can be responsible for the resistance of cancer cells to various chemotherapeutic agents, for example, gemcitabine, 5-fluorouracil, or oxaliplatin. These drugs are used in pancreatic cancer treatment regimens, among others. While most of the studies on gut microbiota, and the efficacy of chemotherapy are based on colorectal cancers, it can be speculated that the same mechanisms occur in pancreatic cancer patients due to the use of a similar treatment regimen and the presence of similar microorganisms also in the pancreatic cancer microenvironment such as *Fusobacterium nucleatum* and bacteria belonging to *Gammaproteobacteria* class (Nejman *et al.* 2020; Sevcikova *et al.* 2022). The presence of these bacteria contributes to resistance to oxaliplatin and/or 5-fluorouracil therapies by activating autophagy in tumor cells (Yu *et al.* 2017) or increasing BIRC3 expression, which inhibits tumor cell apoptosis (Zhang *et al.* 2019).

Tests on human pancreatic ductal adenocarcinoma samples taken during surgery revealed the presence of an average of one bacterium per 146 human cells. These bacteria are part of the pancreatic tumor microenvironment. The most detected species belong to the class *Gammaproteobacteria*, mainly to the *Enterobacteriaceae* and *Pseudomonadaceae* families, which express CDDL. Gemcitabine is particularly important in the treatment of pancreatic cancer, and the presence of these bacteria may contribute to resistance to the drug (Geller *et al.* 2017). It can be eliminated after effective antibiotic therapy and contribute to clinical success (Ramanathan *et al.* 2016; Imai *et al.* 2019; Fulop *et al.*

2023). However, when the microenvironment of the pancreas is examined, fungi are found in addition to bacteria. Fungal ablation enhanced the effect of gemcitabine-based chemotherapy. It is also worth noting that fluconazole treatment had a protective effect. Moreover, consistent with the absence of increased fungal infiltration in pancreatitis, antifungal drugs did not alleviate mild pancreatitis. Thus, it can be concluded that fungal removal may have therapeutic effects only for pancreatic cancer patients (Aykut *et al.* 2019). There is a high degree of inter-individual variability, and an excess of different microbiota taxa and host-microbiota interactions are highly dynamic and complex. These include not only direct interactions between the microbiota and the tumor, but also indirect interactions through the immune system. All these mechanisms are not yet fully understood.

An increasingly successful therapeutic option is immune checkpoint therapy (O'Reilly *et al.* 2019). Drugs such as durvalumab and tremelimumab are the human monoclonal antibodies (mAbs) against programmed death 1 (anti-PD-L1) IgG class 1 and human anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) IgG class 2, respectively. In a study of PDAC patients, the two therapies were combined in the hope of an additive or synergistic effect of the drugs, but this did not have the desired effect. The use of anti-CTLA-4 blockade alone as part of the combination therapy shows a positive anti-tumor effect in patients participating in the clinical trial (Le *et al.* 2013). The modulation of the immune response by microbiota is significant and thus can have a huge impact on the efficacy of immunotherapy. The intestinal microbiome ablation performed showed protection against pre-invasive and invasive pancreatic ductal adenocarcinoma, while transfer of bacteria from pancreatic ductal adenocarcinoma hosts, but not from the control group, nullifies this anti-tumor protection. Bacterial ablation leads to immunogenic reprogramming of the PDAC tumor microenvironment, including reduction of bone marrow-derived suppressor cells and increased differentiation of M1 macrophages, which in turn promotes differentiation of CD4+ Th1 T cells and activation of CD8+ T cells. In addition, bacterial ablation enhances the efficacy of checkpoint-targeted immunotherapy by upregulating PD-1 expression (Pushalkar *et al.* 2018).

A complex from the NOD-like receptor family, the inflammasome containing pyrin domain 3 (NLRP3), is responsible for the initiation of innate inflammatory responses. During the study, NLRP3 levels were shown to be significantly increased in patients with pancreatic cancer in general, and it was demonstrated that selective ligation of NLRP3 could sustain this pro-tumorigenic pancreatic inflammation (Daley *et al.* 2017). Inhibition of dipeptidyl peptidase (DPP) may increase the efficacy of immunotherapy in pancreatic cancer. In mouse models, after oral administration and intraperitoneal injections of BXCL701, which is an oral small-molecule dipeptidyl peptidase inhibitor, increased NK and T cell immune infiltration and decreased tumor growth were observed. BXCL701 increases the movement of CXCR3+ NK and CD8+ T cells into tumors, which mediates tumor regression (Fitzgerald *et al.* 2021). Positively transforms the PDAC immune microenvironment, enhancing antitumor activity and improving the effectiveness of therapy. It should be noted here that the gut microbiota reduces the activity of tumor-infiltrating NK cells, which in effect promotes the development of pancreatic ductal adenocarcinoma. To improve patient survival, one possible solution may be to modulate microbiomes with antibiotic therapy, which may not be enough if patients have immune deficiencies. Reducing the number of NK cells with antibodies has been shown to lead to advanced cancers, even in the absence of microbiota (Shi *et al.* 2023; Yu *et al.* 2022).

With the development and plethora of immune therapies, the question arises as to how individual diversity, immunocompetence or lack thereof, and the individual microbiota of a pancreatic cancer patient affect the effectiveness of treatment.

6. Conclusion

The association between microbiome and pancreatic cancer is a rapidly evolving field that holds immense potential for early detection, risk assessment, and therapeutic intervention. It was proved that both the oral and gut microbiomes play significant roles in the pathogenesis of pancreatic cancer, with emerging evidence suggesting that microbial dysbiosis, imbalanced or altered microbial communities, may contribute to tumorigenesis through inflammatory pathways, immune modulation, and bacterial translocation to the pancreas. Specifically, bacteria like *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Prevotella* spp. have been implicated in promoting carcinogenesis via pro-inflammatory pathways, immune system manipulation, and direct interaction with cancerous cells.

Additionally, the composition of the microbiome in both the oral cavity and gut has been found to significantly differ in pancreatic cancer patients compared to healthy individuals. These differences in microbial composition could serve as diagnostic biomarkers or therapeutic targets in the future. More importantly, the role of microbiomes in modulating the efficacy of pancreatic cancer treatments, such as chemotherapy and immunotherapy, highlights the critical need for per-

sonalized therapeutic strategies that account for individual microbiome variations.

Furthermore, microbial interactions with the immune system, particularly through immune checkpoint inhibition and microbial ablation strategies, suggest that modulating the microbiome could enhance the effectiveness of current treatment options and offer a novel approach to improving patient outcomes. Although there is still much to learn about the complex associations between microbiota and pancreatic cancer, the growing body of research offers promising avenues for both early detection and innovative treatments that leverage microbiome modulation.

As we move forward, understanding the intricate role of the microbiome in pancreatic cancer will likely open doors to more effective, personalized therapies and could ultimately transform the way we approach both the diagnosis and treatment of this devastating disease. However, larger-scale studies and clinical trials are necessary to fully understand the underlying mechanisms and to validate microbiome-based diagnostic and therapeutic interventions.

Table 1. is a collection of studies analyzed in the article. It shows how the associations between the microbiome and the risk of pancreatic cancer were studied and what the conclusions of the studies were (Table 1).

Tab. 1 Summary of key research articles on the associations between the microbiome and pancreatic cancer.

Legend: CP - Chronic Pancreatitis, PC - Pancreatic Cancer, PDAC – Pancreatic Ductal Adenocarcinoma, NK – Natural Killer Cells, Th – T helper cells, PHC – Pancreatic Head Carcinoma, IM – Intestinal Microbiota, EPI – Exocrine Pancreatic Insufficiency, SI – surgical intervention, CPS – Chronic Pancreatitis Syndrome, IBS – Irritable Bowel Syndrome, PA – Pancreatic Adenocarcinoma, LTS – Long-Term Survival, PFS – progression-free survival, OS – overall survival, GI – gastrointestinal

References	Type of research	Materials and methods	Conclusions
Fan et al. 2016	Case- control study	Adenocarcinomaa of pancreas patients (n=361), 16S rRNA sequencing of mouth-wash samples	Carriage of oral pathogens, *P. gingivalis* and *A. actinomycetemcomitans* were associated with higher risk of pancreatic cancer
Wei et al. 2020	Prospective study	Pancreatic cancer patients (n=41), healthy individuals (n=69); 16S rRNA sequencing of saliva	Carriage of *Streptococcus* spp. and *Leptotrichia* spp. (z-score) was associated with a higher risk of PDAC
Chen et al. 2023	Multisite analysis	pancreatic cancer patients (n=40), chronic pancreatitis patients (n-15), healthy controls (n=39); 16S rRNA sequencing of saliva	The chronic pancreatitis group exhibited the lowest microbial diversity, while no significant difference was found between the pancreatic cancer and healthy controls groups
Lu et al. 2019	Clinical study / analysis	patients with pancreatic head carcinoma (n=30), healthy individuals (n=25); 16S rRNA sequencing of the tongue coating samples	The microbiota dysbiosis of the tongue coat in PHC patients and provide insight into the association between the human microbiome and pancreatic cancer
Pietzner et al. 2021	Study population / analysis	16S rRNA sequencing of fecal samples (n=2226)	The effect of exocrine pancreatic function on intestinal microbiota composition alters the availability of microbial-derived metabolites in the blood and thus directly contributes to the host metabolic changes associated with exocrine pancreatic dysfunction
Zhou et al. 2020	Correlation analysis	healthy controls (n=69), chronic pancreatitis (n=71); 16S rRNA sequencing of fecal samples	Patients with chronic pancreatitis have gut microbiota dysbiosis that is partly affected by pancreatic exocrine function
Maev et al.. 2023	Comparative analysis	patients (n=85) including pancreatitis without extrinsic pancreatic insufficiency (EPI, n=16), with chronic pancreatitis and mild EPI (n=11), with severe pancreatitis and EPI (n=17); 16S rRNA sequencing of fecal samples	The IM of all groups showed the dominance of phyla *Firmicutes* with the lowest representation in the severe EPI group, both with SI and CP, and the growth of the phyla of *Actinobacteria*, *Verrucomicrobiota* and *Fusobacteria*
Nii et al., 2023	Experimental study	Bacterial strains (n=13) isolated from the feces of patients and healthy controls; *in vitro* stimulation of bone marrow-derived dendritic cells, genome sequencing of *Prevotella copri*	Stimulation experiments have shown up-regulation of IL-17 and Th17-related cytokines (IL-6, IL-23) of *Prevotella copri*, which contributes to causing rheumatoid arthritis, the same pathway may contribute to pancreatic cancer through Th17 activation

Maekawa et al. 2018	Metagenomic analysis	16S rRNA sequencing of pancreatic juice from pancreatic cancer patients (n=20) and duodenal cancer patients (n=16)	*E. faecalis* was frequently detected in pancreatic tissue from patients with CP and PC, and antibody titers against *E. faecalis* capsular polysaccharide were elevated in *E. faecalis*-positive patients compared to healthy donors
Stein-Thoeringer et al. 2024	Prospective study	non-cancer participants (n=38), pancreatic cancers patients (n= 63); 16S rRNA sequencing of samples collected from various sites of the GI tract and surgical sites, microbial culturing	The presence of *Enterococcus* spp. in bile ducts of PDAC patients undergoing pancreatic surgery represents a significant risk factor for perioperative infections and, thereby, elevated postoperative and long-term mortality
Ren et al. 2017	Prospective study	pancreatic cancer patients (n=85), healthy controls (n=57); 16S rRNA sequencing of fecal samples	The gut microbial profile was unique in PC, providing a microbial marker for non-invasive PC diagnosis
Risch et al. 2014	Case-control study	pancreatic cancer patients (n=761), random controls (n=794); venipuncture specimens, antibody seropositivity for *H. pylori* and its virulence protein CagA was assessed using commercial enzyme-linked immunosorbent IgG assays.	*H. pylori* colonization may have diverse effects on cancer risk, depending on the organism strain type as well as on the cancer site.
Wang et al. 2014	Meta-analysis	cases of *H. pylori* infection on pancreatic cancer (n=2049), control group (n= 2861); databases analysis	Hp+ and CagA+ infections are associated with a decreased risk of pancreatic cancer in Eastern populations but have no significant associations in Western countries.
Xu et al. 2022	Meta-analysis	case-control studies (n=8), nested case-control studies (n=5), cohort studies (n=4); databases analysis	*H. pylori* infection can increase the incidence of pancreatic cancer in general. CagA/VacA-positive *H. pylori* infection is not associated with the incidence of pancreatic cancer
Half et al. 2019	Comparative study	pancreatic adenocarcinoma patients (n=30), pre-cancerous lesions patients (n=6), healthy individuals (n=13), non-alcoholic fatty liver disease patients (n=16); 16S rRNA sequencing of fecal samples	Find a distinct PC-associated gut microbiome signature in an Israeli cohort, manifesting primarily as an under-representation in several bacterial families prevalent in the healthy gut
Edogawa et al. 2020	Prospective study	patients with IBS (n=39), healthy volunteers (n=25), 16S rRNA sequencing of fecal samples	A subset of patients with IBS, especially in PI-IBS, has substantially high fecal PA, greater symptoms, impaired barrier and reduced microbial diversity.
Ubachs et al. 2021	Clinical study	Pancreatic cancer patients (n=107), household partners (n=76); 16S rRNA sequencing of fecal samples	There were no significant differences in the composition of the bacteriobiota, although cachexia prevalence was highest in pancreatic cancer (66.7%). Faecal calprotectin levels were positively correlated with the abundance of *Peptococcus*, *Enterobacteriaceae*, and *Veillonella*.
Riquelme et al. 2019	Clinical study	surgically resected PDAC tumor samples (n=68; 36 of LTS and 32 of STS); 16S rRNA sequencing of surgically resected PDAC tumors, PCR flow cytometry	The tumor microbiome unique to LTS may contribute towards shaping a favorable tumor microenvironment.
Yu et al. 2022	Cohort study	Mice model; NK cell depletion, bacterial manipulation	The gut microbiota mediates PDAC progression through NK cell modulation and that gut microbiota-derived supernatant can modulate anti-tumor NK cell activity

ORCID
Wioletta Adamus-Białek https://orcid.org/0000-0001-6129-0492
Stanisław Głuszek https://orcid.org/0000-0001-7752-0459

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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