



## **Influence of Periodontal Diseases in the Development of Pancreatic Adenocarcinoma**

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**Abstract**

*Pancreatic cancer is a malignant transformation of pancreatic cells. The etiology is still very poorly known. Despite advances in medical imaging and therapeutics, the prognosis for this cancer remains serious. In terms of incidence, pancreatic cancer is a relatively rare disease. In terms of frequency, it is the 10th most common cancer while it ranks 4th in the causes of cancer deaths. These figures can be explained by the absence of preventive measures and a delayed diagnosis. While some risk factors have been identified (Smoking, obesity), some pathological conditions (chronic inflammation, diabetes, pancreatitis) are known to promote the risk of developing pancreatic cancer. Evidence suggests that periodontal disease may play a role in pancreatic carcinogenesis. Oral bacteria can spread throughout the body (heart, lung, liver, stomach, pancreas, uterus, brain). Periodontal infections can affect the appearance of a tumoral pathology by two sides. They induce chronic systemic inflammation and appear to disrupt cellular regulation mechanisms, acting as a direct etiological agent of the pancreatic tumor. If the studies converge towards a direct etiology, the alteration of the oral microbiota by pathogenic bacteria could constitute a diagnostic way and a very easy means of prevention to be put in place. This test will constitute a considerable advance in public health.*

**Keywords:** *Periodontal Disease, Pancreatic Cancer*

**Introduction**

Pancreatic cancers are tumors that affect men as well as women and whose survival prognosis is very poor[1]. This year, 50,000 people will be diagnosed in the United States and it is estimated that less than 5,000 of them will still be alive in 5 years [2]. According to the World Health Organization, pancreatic cancer will become the second leading cause of cancer deaths in the world in 2030[3]. This cancer does not show any distinctive clinical signs, which makes the diagnosis of the pathology delayed. Premature diagnosis could improve cancer management and reduce mortality [4]. Periodontal disease is an irreversible destruction of the deep periodontium due to periodontal disease bacteria in a susceptible host [5]. Periodontal diseases are mixed infections intermediate between a specific bacterial infection and a nonspecific opportunistic infection. Bacterial aggression increases the production of PGE<sub>2</sub>, IL-1 and TNF $\alpha$  by periodontal cells [6]. These products can activate osteoclasts

and induce the resorption of periodontal bone. Already known to have involvement in cardiovascular [7] disease and diabetes, pregnancy and lung disease[8], recent studies have shown that periodontal disease is associated with an increased risk of pancreatic cancer[9]. The purpose of this study is to review current knowledge of the link between pancreatic adenocarcinoma and periodontal disease by exploring research perspectives in this area. The presence of two periodontal bacteria in the mouth may be linked to a greater risk of later developing pancreatic cancer. If this hypothesis is confirmed, it could be a significant diagnostic tool that would significantly change the management of patients with periodontal disease.

## Material and Methods

The systematic review was performed according as much as possible to PRISMA10 guidelines. The focus question of the research was to establish a link between periodontal disease and pancreatic cancer. An electronic search of the literature was performed using PubMed, MedLine and Google Scholar as databases. The initial electronic search was not limited to pancreatic cancer but sought to establish a link between oral bacterial flora and tumor pathology. The electronic search was followed by a manual search of the reference lists of all potentially eligible studies that could complete the information collected. Additional information in periodontics, pancreatology, epidemiology and oncology were needed to carry out this work. The numerical research was conducted using the keywords "Periodontal diseases", "Pancreatic cancer", "Periodontal diseases and pancreatic cancer" and "Cancer and Oral health". Cohort studies, comparative studies, prospective studies, retrospective studies and animal studies were included. Reviews of literature and studies involving periodontal disease in the development of cancers other than that of the pancreas have been excluded.

## Results

To evaluate the potential influence of periodontal disease on the development of pancreatic cancer, we assessed the relative risk and Odds-ratios of the various studies included in the literature review. The most intuitive parameter for quantifying the strength of the association between a disease and a risk factor is the relative risk (RR) of finding the quotient between the sick subjects with a risk factor divided by the percentage of sick subjects without risk factors. Relative risk can be supplemented by the odd-ratio. This is the ratio of the [Patient / Non-Patient] ratio of patients with gum disease to the ratio [Patient / Non-Patient] of patients who doesn't have periodontal disease. The odd ratio is important in this study because periodontal pathology presents risk factors common to cardiovascular

diseases and the development of certain cancers (tobacco, chronic inflammation). We need to find the weight of periodontal disease in the genesis of pancreatic cancer. The Odd-ratio can be used in case-control studies where a healthy subject is compared with a subject suffering from a pathology which is not the case of the risk relative. For rare diseases, such as pancreatic cancer, the odd-ratio, although difficult to interpret, is substantially identical to a relative risk. In our case, the Odd-ratio has many interests. The Swidsinki et al.[11] study revealed the interaction between the oral flora and the pancreas. Biopsies were performed on many patients (251) and on various digestive organs including the pancreas (9). Finally, it was revealed that oral bacteria were found in the nine biopsied pancreatic ducts. The study by Hujoel et al.[9] shows an increased risk of developing pancreatic cancer by 20% in a patient with periodontitis compared to a patient with gingivitis. The study by Michaud et al.[12] from 2013 found that individuals with high blood levels of antibodies against *P. Gingivalis* (> 200 ng / mL) had a two-fold increased risk of pancreatic cancer (OR = 2.14). The Wen et al.[13] study compares the risk of cancer in patients with periodontal disease (gingivitis and periodontitis). The risk of cancer is higher in patients with periodontitis than in patients with gingivitis. The suspected bacteria (*Porphyromonas Gingivalis* and *Aggregatibacter Actinomycetemcomitans*) are generally not found in gingivitis, which explains why the association between periodontal diseases (without discrimination between gingivitis and periodontitis) and cancer is not as significant (RR = 1.35) as the other studies. The Canadian Cancer Society, in the study of Alekseyenki A, et al.[14] revealed a significant increase in the risk of pancreatic cancer with *Porphyromonas gingivalis* (OR = 2.2) and *Aggregatibacter actinomycetemcomitans* (OR = 1.6). These conclusions are based on the analysis of saliva samples before the diagnosis. Genomic sequencing of 16S ribosomal RNA was performed to highlight the presence of a specific bacterium in the saliva of patients before they developed pancreatic cancer. In the study by Ahn et al.[15], Salivary specimens were obtained from healthy patients and patients with periodontal disease (12,000 people). The study showed that patients with *Porphyromonas Gingivalis* were 59% more likely to develop pancreatic cancer compared to those who did not. Patients were followed for several decades, which confirmed that periodontal disease is a risk factor for malignant pancreatic disease (OR = 2.6). The study by Chang J. and Al. [16] analyzed 139,000 patients with periodontitis and 75,000 healthy subjects.

It revealed that periodontal disease is positively associated with the risk of developing pancreatic cancer (OR = 1.7). The aim of the 2016 study by Michaud et al.[17] was to study a large panel of men who said they had never smoked in order to exclude the risk of smoking in the development of pancreatic cancer. Of these patients, some had periodontal disease (139,000) and some didn't (75,000). An increase in cancers in men who initially had periodontal disease (RR = 1.63) and severe periodontal

disease (RR 2.57) has been observed. However, the periodontal health of the patients was not initially evaluated by a dentist which limits the use of the results of this study. The study by Rickard Ljung et al.[18] is a study in which 29,218 cases of pancreatic cancer and 99,992 control patients were observed. It has been found that a pathology of the oral cavity was more often found in patients with pancreatic cancer than in control patients (RR = 1.74). However, the impact of these oral diseases is nuanced by the presence of other risk factors in cancer patients (alcohol, pancreatitis, diabetes). The study by Joshipura K et al.[19] studied periodontal health in more than 50,000 health professionals. In all these patients, 216 developed pancreatic cancer and a history of periodontitis has been shown to increase the risk of developing pancreatic cancer by 64%. There is a positive association between periodontal disease and pancreatic cancer. Since the link between periodontal disease and pancreatic cancer is established statistically, research is beginning to examine the pathophysiological mechanisms that involve bacteria in the genesis of pancreatic adenocarcinoma. The study by Zambirinis et al.[20] highlighted the ability of *A. actinomycetemcomitans* to activate the Toll Like Receptor whose TLR-9s are known to be involved in tumorigenesis. The study by Manosha et al.[21] has showed some mechanisms that periodontal bacteria use to inhibit the P53 gene and BCL-2, the guarantor of the human cellular-cycle.

Authors of the study	Types of studies	Issues studied	Methods	Results and conclusions
Swidsinki et Al. (2005)	Experimental analytical study	Study the presence of oral bacteria in the pancreatic ductal system	Biopsies and samples were taken to assess the presence of periodontal bacteria in the pancreatic ductal system.	Bacteria from the oral flora are found in the main pancreatic duct and in the accessory pancreatic ducts.
Hujpel et Al. (2008)	Prospective statistical study	Study the relationship between periodontal disease and pancreatic cancer	11,000 patients with gingivopathies (periodontitis or gingivitis) were followed until some of them developed pancreatic adenocarcinoma. A search for an association between gingival health status and the development of cancer was conducted.	This study suggests that there may be a correlation between gingival diseases and the occurrence of pancreatic cancer.
Michauld et Al. (2013)	Prospective statistical study	Study the influence of circulating antibodies against oral flora bacteria in the genesis of pancreatic adenocarcinoma	A serum assay of circulating anti-GP antibodies was performed on 405 patients with pancreatic cancer.	A serum antibody level higher than 200ng/mL directed against <i>Porphyromonas gingivalis</i> has been found in patients with pancreatic adenocarcinoma.

Wen et Al. (2014)	Prospective statistical study	Study the differential influence of gingivitis and periodontitis on the development of pancreatic cancer	1,000,000 individuals with known gingival and periodontal health status were followed for 20 years. A detailed analysis of patients who developed pancreatic adenocarcinoma was performed to search for a correlation between gingival health status and the development of pancreatic cancer.	The risk of developing pancreatic cancer is higher in patients with periodontitis than in healthy or gingivitis patients (RR = 1.35).
Alekseyenki et Al. (2016)	Prospective statistical study	Demonstrate the relationship between oral flora bacteria and pancreatic tumorigenesis	Genomic sequencing of saliva from 361 patients with pancreatic cancer was performed and compared to the genomic sequencing analysis of 361 healthy patients.	We observe a significant increase in the risk of developing pancreatic cancer in the presence of Porphyromonas gingivalis (OR = 2.2) and in the presence of Aggregatibacter actinomycetemcomitans (OR = 1.6).
Ahn et Al. (2016)	Prospective statistical study	Study the relationship between periodontal disease and pancreatic cancer	12,000 salivary samples were collected and analyzed, and the analysis of the samples was conducted to investigate the increased risk of developing pancreatic cancer in relation to the presence of certain bacteria.	The presence of Porphyromonas gingivalis appears to significantly increase the risk of developing pancreatic cancer (OR = 2.6).
Chang et Al. (2017)	Prospective statistical study	Study the relationship between periodontal disease and pancreatic cancer	75,000 patients with healthy gingival status and 139,000 patients with periodontal disease were followed up until the appearance of pancreatic cancer to see if the prevalence of pancreatic cancer was influenced by periodontal health status.	The presence of periodontal disease is positively associated with the risk of developing pancreatic cancer (OR = 1.7).
Michaud et Al. (2017)	Prospective statistical study	Analysis of the periodontal health status of patients with pancreatic cancer	Study of the influence of periodontal health on the development of pancreatic cancer in exclusively non-smoking patients.	Mild to moderate periodontal disease (RR = 1.63) and severe periodontal disease (RR = 2.57) appear to be associated with the development of pancreatic cancer.
Rickard et Al. (2018)	Prospective statistical study	Study the relationship between periodontal disease and pancreatic cancer	Observation of the periodontal health status in patients who already have pancreatic adenocarcinoma" se traduit en anglais par "Observation of the periodontal health status in patients who already have pancreatic adenocarcinoma.	Periodontal disease is observed in a majority of patients and appears to be associated with pancreatic cancer (OR = 1.74).

Joshipura et Al. (2019)	Prospective statistical study	Study the relationship between gingival health status and pancreatic cancer in healthcare professionals	The gingival and periodontal health status of over 50,000 healthcare professionals was studied, analyzed, and correlated in those who developed pancreatic cancer.	Among all the patients who were followed up and developed pancreatic cancer, 64% had periodontal disease or had stabilized periodontitis in the past.
Manosha et Al. (2019)	Experimental analytical study	Demonstrate the relationship between oral flora bacteria and pancreatic tumorigenesis	Clinical study on the influence of periodontal bacteria on cell cycle regulatory genes.	Porphyromonas gingivalis inhibits the proteins P53 and BCL2, which induces inhibition of cellular apoptosis and ultimately the proliferation of certain tumor cells.
Zambirinis et Al. (2019)	Experimental analytical study	Demonstrate the relationship between oral flora bacteria and pancreatic tumorigenesis	Clinical study on the influence of periodontal bacteria on the activation of TLRs responsible for chronic inflammation of pancreatic tissue.	Porphyromonas gingivalis activates the TLR-9 receptor, which is known to have an influence on chronic inflammation of the pancreatic parenchyma.

## Discussion

Pancreatic cancer is a disease often diagnosed at a late stage which complicates its management. The prognosis of the cancer is mediocre to the point that pancreatic cancer will be the second leading cause of cancer deaths in the world [22].

Early diagnosis and improved management are a major public health issue. Recent studies have shown a correlation between the presence of certain periodontal bacteria and the risk of developing pancreatic cancer [23]. The underlying biomolecular mechanisms need to be determined. Moreover, the presence of certain bacteria in the ecosystem of the oral cavity can enable the appearance of a malignant pathology [24] and constitute a diagnostic test in the future. Periodontal bacteria can colonize the pancreatic environment by hematogenous means or through swallowing [25].

For this reason, scientists have sequenced saliva-extracted DNA from samples of people who have developed pancreatic cancer. In the same time, they have sequenced the genome of saliva taken from healthy people [26]. This study has highlighted that the presence of a periodontal bacterium, Porphyromonas Gingivalis, in saliva greatly increases the risk of developing pancreatic cancer. All of these studies show that there is a link between some form of oral flora but it is not possible to determine if Porphyromonas Gingivalis is an etiological agent. Many studies [27] have shown an association between periodontal disease and pancreatic cancer, but to determine the involvement of bacteria in pathogenesis, it is necessary to prove the presence of certain periodontal bacteria before the occurrence

of the disease. This experiment was conducted by the Boston School of Medicine[28], where Pr. Michaud's teams were able to confirm that the presence of certain bacteria in the mouth predisposed to the appearance of pancreatic cancer. It remains to be determined if bacteria are direct etiologic agents or whether chronic inflammation induced by periodontal disease promotes the development of cancer. Periodontal disease is an infection that can translate immunodepression that we can only see in the oral cavity[30].

This immunodepression including the secretion of a leukotoxin by bacteria involved in the active stage of bone destruction of periodontal disease. The immune frustration that accompanies periodontal disease could actually be an element that would provide information on a particular inflammatory phenotype predisposing to the development of chronic low-level inflammation which is directly involved in the development of cancers[31]. Current dental medicine tends to consider the dental organ as a single entity without direct communication with the rest of the body. It's now clear that there is a link between periodontal disease and systemic diseases[32].

Recent studies have shown link between the alteration of an oral bacterial flora and the development of pancreatic cancer. Studies have shown that Porphyromonas Gingivalis can interfere with the cellular cycle, in particular by inhibiting the synthesis of the cell-protective protein P53[33], suggesting that this bacterium is an etiological agent of the disease. More than the virulence of bacteria, the decrease in the presence of certain protective bacteria in the mouth seems to favor the appearance of systemic disease. Qualitative and quantitative alteration of the oral microbiome appears to be the key element in the impact of periodontal disease on the rest of the body. Studies have shown that oral bacteria can activate inflammatory receptors already known as the causative agent of tumor degeneration. More recently, studies have shown that under the influence of certain endocrine disruptors, oral bacteria can create carcinogenic substances[34].

These pro-oncogenic products can constitute an important research road. These can explain the link between periodontal disease and increased risk of tumor pathology. However, in vivo functional studies based on inoculation of parodontogenic bacteria in the pancreatic environment would directly establish a causal link between periodontal bacteria and pancreatic tumor pathogenesis. The identification of such a link would considerably transform the management of patients with periodontal diseases by the dentist and considerably reduce the morbidity and mortality of pancreatic neoplasms. Current research needs to be nuanced by the small number of studies conducted.

## Conclusion

In conclusion, we can say that there is some evidence that strongly suggests an association between periodontal diseases and pancreatic cancer<sup>35</sup>. Nevertheless, the direct link is not yet clearly established and constitutes an approach of research for the future. The link between periodontal disease and other pancreatic diseases (diabetes) is already established<sup>36</sup>. Similar studies explore the involvement of periodontal bacteria in Alzheimer's disease<sup>37</sup>. These studies seem to implicate *Porphyromonas Gingivalis* in Alzheimer's disease too. Other studies on Alzheimer's disease link the onset of this disease to excessive carbohydrate consumption and consider Alzheimer's disease as type III diabetes<sup>38</sup>. All research could converge towards a common oral etiology. The purpose of current research will be to perform screening tests by simple buccal sampling. These multidisciplinary studies should involve hygienist, periodontologist, dentist, oncologist, researcher and medical specialist and require a deepening of knowledge on pancreatic neoplasms and periodontal disease from all these health professionals. If these statements are confirmed, the practice of oral medicine and oncological management of patients would be considerably modified. Clinical studies are underway to design tests to detect biomarkers of Alzheimer's disease in the saliva of patients several years before the first symptoms appear. Pending further studies and a sufficient clinical follow-up in the involvement of periodontal bacteria in pancreatic tumor pathogenesis, the dentist's role in oral prevention and therapeutic education has never been greater. A collaboration between dentist and gastroenterologist in the identification of patients at risk seems essential.

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