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**Microbiome and pancreatic cancer: A comprehensive topic review of literature**

Ertz-Archambault N *et al.* Microbiome and pancreatic cancer

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**Abstract**

The relationship of an imbalanced microbiome to carcinogenesis has gained attention in several malignancies. Among the most controversial is dysbiosis related to pancreatic cancer. The purpose of this article is to review microbiome alterations associated with pancreatic cancer, its potential utility as an early screening biomarker, examine the influence of the microbiome in antitumor therapy, and the potential impact of microbiome manipulation to affect pancreatic cancer patient outcomes.

**Key words:** Pancreatic Cancer**;** Human microbiome**;** Biomarkers, cancer**;** Cancer screening tests**;** Treatment effectiveness

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**Core tip:** Recent literature reports influences of microbiome alterations contributing to carcinogenesis of pancreatic cancer. The poor prognostics of pancreatic cancer are related to late recognition and treatment resistance, thus warranting investigations for modifiable risk factors, early screening biomarkers, and microenvironment elements that affect outcomes. Learning the role of microbiome in carcinogenesis may lead to identifying reliable, non-invasive screening strategies, and additional modifiable risk factors. Microbiome studies in pancreatic cancer could offer therapeutic targets and an extraordinary opportunity to favorably transform cancer response to existing treatment protocols and improve survival by reduction of cancer-related cachexia by manipulating human gut microbiota.

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**INTRODUCTION**

A commensal microbiome, by definition maintains a symbiotic relationship in healthy individuals, offering protection from disease by nutritive, inflammatory-modulating activity, hormonal homeostasis, detoxification, and metabolic effects of bacterial metabolites[1-3]. Dysbiosis is the manifestation of a corrupt, imbalanced microbiome, which contributes to pathogenesis of several diseased states[2]. Recently, there are literature reports on influences of microbiome alteration contributing to carcinogenesis of multiple malignancies[1,2,4-6]. A classic pathogen in the literature is *Helicobacter pylori* (*H. pylori*), which has revealed inconsistent and paradoxical associations pending the body site studied[7,8]. *H. pylori* has been extensively scrutinized as a risk factor for development of pancreatic cancer and an association is controversial[9-11].Pancreatic cancer often denotes a poor clinical prognosis in part due to late recognition and treatment resistance, warranting investigations for modifiable risk factors, early screening biomarkers, and microenvironment elements that affect outcomes[18,19].

**MATERIALS AND METHODS**

Search methods: Pubmed, MEDLINE, and Web of Science for medical search terms: “pancreatic cancer” and “microbiome,” “carcinogenesis,” antibiotic,” “probiotic,” “microorganism,” “bacteria,” “colonization,” “cachexia,” or “infection.” The relevant articles reference lists were also searched manually for additional articles. The last search was performed in October 2016.

Selection criteria: Manuscripts and abstracts describing pre-clinical studies, animal models, epidemiological studies, case series, case-control, retrospective chart reviews, prospective studies, pilot, meta-analysis, and literature topic reviews were included. There were no randomized clinical trials identified from these search terms. Articles were limited to abstract and manuscript publications in the English written language.

**RESULTS**

Characterization of the healthy microbiome spectrum is ongoing. In 2012, the NIH Human Microbiome Project[3], demonstrated no microbial taxa were universally present across all humans in a single body site. The oral cavity contains an extensive reservoir of bacteria with more than 700 species observed, most of which have not been cultured in a laboratory[20,21]. Healthy oral habitats are dominated by Streptococcus, followed by Haemophilus in the buccal mucosa, Actinomyces in the supragingival plaque, and Prevotella in adjacent, low-oxygen subgingival region[3].

***Oral microbiome and pancreatic cancer***

Alterations in the ecological balance of the microbiome exist during diseased oral cavity states including gingivitis and periodontal disease compared to a healthy oral cavity[21-25]. Periodontal disease, manifested by an inflamed oral activity, pathogenic oral flora, and tooth loss are well-established independent risk factors associated with development of pancreatic cancer[12-14]. Therefore, the shifts in taxa dominance and diversity of bacterial communities that deviate from an established healthy microbiome may be reflective of disease states[2,3]. Pilot studies have proposed a role in oral pathogenic bacteria in periodontal disease as an early screening test and as a biomarker of pancreatic cancer[15-17]. Several dedicated studies have aimed to define microbiome changes in the oral cavity associated with pancreatic cancer, results are summarized in Table 1.

***Oral microbiome and pancreatic cancer summary***

Oral flora alterations exist in pancreatic cancer patients compared to healthy populations. Salivary RNA studies reveal *bacteroides* genus and *Granulicatella adiacens* are more common in pancreatic cancer patients than healthy subjects[15,17]. However, *Neisseria elongata*, *Streptococcus mitis*, *Corynebacterium* genus, and the *Aggregatibacter* genus are present in lower concentrations in pancreatic cancer than healthy subjects[15,17]. Combining salivary RNA biomarkers for *N. elongata* and *S. mitis* yielded an ROC-plot AUC value of 0.90 with 96.4% sensitivity and 82.1% specificity in distinguishing patients with pancreatic cancer from healthy subjects[17]. A cross-sectional study[16] identified of a significantly higher *Leptotrichia* and lower *Porphyromonas* colonization in pancreatic cancer patient saliva, translating to an *Leptotrichia:Porphyromonas* (L:P) ratio of biomarker significance. In this same study, a patient classified with an unknown digestive disease presented with an elevated L:P ratio that led to dedicated workup revealing a new diagnosis of pancreatic cancer[16]. Pilot successes deserve further exploration into utilizing salivary markers as potentially valuable non-invasive, economical screening strategies.

Interestingly, the highest concentration of plasma antibodies *to Porphyromonas gingivalis* (strain ATTC 53978), a pathogenic bacteria associated with periodontal disease, was linked with a 2-fold increased risk of pancreatic cancer[23]. The association was amplified over time, with the addition of 5 or 7 year lag[23]. Similar to case control studies of saliva samples revealing oral pathogens, *P. gingivalis* and *A*. *actinomycetemcomitans* are associated with increased risk for subsequent development of pancreatic cancer[62]. This finding is consistent with epidemiologic data that periodontal disease is an independent risk factor for pancreatic cancer development[14,25,43]. Alternatively, high antibody titers against non-pathogenic, commensal bacteria were associated with 45% decreased risk of pancreatic cancer compared to those with a lower antibody level profile[23]. Similarly *Fusobacterium* and *Lepotrichia* are protective and decreases risk, also in a dose dependent relationship[62]. *Lactobacillus* is a commensal oral cavity bacterium that diminishes gingival inflammation and cariogenic periodontal pathogenic bacteria[44]. Thus, with the clearly established role of periodontal disease and associated periodontal pathogens for pancreatic cancer risk profiles, any measures to prevent periodontal pathogens may serve protective role to prevent pancreatic cancer, but has not been studied on this topic specifically.

***H. pylori and pancreatic cancer***

There is literature that illustrates a paradoxical nature of microorganisms relative to by site and tumor studied. For example, eradication of *H. pylori* causes regression of MALT lymphoma and decreases risk of metachronous gastric carcinoma after endoscopic resection for early stage gastric cancer[1,26]. However, *H. pylori* gastric colonization decreases the risk of oesophageal adenocarcinoma that does not involve the gastric cardia[27]. H. pylori is a diverse bacteria with several virulent strain variations. Among the best studied are *Cytotoxin-associated gene A* (*Cag-A*) positive strains that express Cag-A virulence factor, which is linked to gastric inflammation, ulceration, and promoting malignant transformation in gastric cancer[28,29]. H. pylori and *Cag-A* dominate microbiome studies in pancreatic cancer. Study results are variable and complex, as is noted in Table 2.

***H. pylori and pancreatic cancer summary***

Results from *H. pylori* case studies in pancreatic cancer reveals complex mixed results pending virulence strain *cag-A* status. Consensus from recent meta-analysis is that there is a modestly significant increased risk associated with development of pancreatic cancer for *cag-A*-negative *H. pylori* strain[9-11,36], with positive correlated adjustment factors including non-O blood type[34,45] and active smoking status[31,33]. The general literature trend summarized in Table 2 is *cag-A*-positive strains results in decreased risk or non-significant association with pancreatic cancer. Notable global population differences exist as the majority of studies highlighted in this review are mainly relevant to Western European or North American ethnic groups. The results of one meta-analysis addressing global studies[38] and pancreatic cancer risk including two Eastern Asian population case-cohorts that suggest a decreased risk of pancreatic cancer risk for *H. pylori* seropositivity overall, including *Cag-A*-positive strains in Eastern Asian ethnic region[38].

***Tissue microbiome and pancreatic cancer***

We found three human pancreatic adenocarcinoma tissue studies dedicated to microbiome alterations or their effect on the tumor microenvironment (Table 3).

***Tissue microbiome and pancreatic cancer summary***

In one case control study, enteric strains of *Helicobacter* DNA were demonstrated to colonize the pancreas in 75% of adenocarcinoma patients but not in pancreatic controls with benign disease[40]. Among proposed mechanisms for dissemination may result from hepatobiliary translocation or hematogenous seeding[40,42]. However, DNA of different *Helicobacter* species is mutually exclusive by sampled site[40]. For example, *Helicobacter* identified in the pancreas compared with *Helicobacter* of gastroduodenal tissue of the same patient were different *Helicobacter* subspecies[40]. Thus, dissemination of *H. pylori* from the stomach to the pancreas is unlikely, instead a subspecies tissue tropism may exist[40].

Both direct microbe colonization and downstream proliferative metabolic affects may promote tumor-associated inflammation preserved by low-grade chronic inflammation[6,26,50] . Evidence of this effect in a pre-clinical study of human a pancreatic cell line showed *H. pylori* colonization of a human pancreatic cell line expressed increased factors for malignant potential including proliferative factors, NF-kappa-B, activator protein-1, proflammatory IL-8 activity, vascular endothelial growth factor secretion, and the growth factor promoter, serum response element[41]. The overall result is activation of molecular pathways for tumor growth and progression in the setting of *H. pylori* infection[41].

*Fusobacterium* is an anaerobic, oral bacterium that has been identified in pancreatic abscesses and carries unfavorable prognostic implications in some gastrointestinal cancers[42]. To explore a role for *Fusobacterium* in pancreatic cancer, surgical specimens of pancreatic adenocarcinoma were analyzed for presence of this bacterium. Only 8% of specimens in this cohort contained *Fusobacterium* colonization[42]. However, pancreatic ductal adenocarcinoma surgical specimens with presence of *Fusobacterium* colonization was identified as an independent predictive factor for shorter survival compared to *Fusobacterium* negative tumors[42]. The *fusobacterium* positive sample group also demonstrated 28% detection of paired normal tissue[42]. The presence of *Fusobacterium* in normal tissue margin suggests it may contribute to malignant potential, but this theory requires further exploration[42].

**DISCUSSION**

The oral microbiome has a protective role against pancreatic cancer in a healthy, commensal state, but may promote malignancy in a pathologic state[1,2,4-6,15-17,23]. Shifts in taxa dominance and diversity of oral bacterial communities, especially those reflective of periodontal disease are associated with increased pancreatic cancer risk[15-17,23]. This correlates clinically with periodontal disease status, a validated independent risk factor for development of pancreatic cancer[12-14]. Bacterial markers of periodontal disease23 and shifts in microbial taxa diversity[15-17] have promising potential to serve as non-invasive screening biomarkers of pancreatic cancer. The evidence is strong enough to warrant targeted risk reduction strategies in patient education and modifiable lifestyle counseling regarding maintenance of oral hygiene.

A directly carcinogenic role for *H. pylori* has been explored after discovering enteric strains of *Helicobacter* DNA demonstrated to colonize the pancreas in a majority of sampled pancreatic adenocarcinoma but not in patients with benign disease[40]. A preclinical study[41] examined direct H. pylori colonization and associated activation of molecular pathways for tumor growth and progression[41]. These downstream molecular effects highlight oncogenic potential with microbiome influence that promotes tumor-associated inflammation preserved by low-grade chronic inflammation[6,26,50]. Despite the existence of several proposed carcinogenic mechanisms of dysbiosis, inflammation is a central facilitator illustrated in pancreatic cancer murine models, human cell lines, and tumor translational expression profiles[6].

***Future directions***

There have been studies that indicate the microbiome and antibiotics modulate tumor response to chemotherapy[51,60]. Germ-free and antibiotic treated murine models highlight the protective effect of commensal bacteria by shaping the inflammatory network required for favorable response to anti-tumor therapy[51]. In murine models, platinum therapy eliminated most subcutaneous lymphoma tumors and prolonged survival in control mice[51]. However, antibiotic-treated and germ free mice failed to respond to platinum-treatment, in part by decreasing reactive oxygen species[51]. Similarly, CTLA-4 inhibitor treated murine models with sarcoma suggest that gut microbiota, specifically *bacteroides* subspecies, are required for the successful anti-tumor effects of CTLA-4 blockade[60]. Notably, antibiotic and germ free mice with sarcomas do not respond to CTLA-4 inhibitor at baseline, but recover antitumor activity with recolonization of gut commensals by human fecal microbiota transplantation of specific *bacteroides* subspecies[60]. Oral administration of *Bifidobacterium* in murine models with melanoma augments the immune response to tumor cells, in part by dendritic cell activation of the innate immune system[60]. This effect was not observed with administration of *lactobacillus* species, suggesting a complex, species specific modulation of the immune system *in vivo*[60]. The potential to utilize probiotics in humans to amplify antitumor response to existing chemotherapy and immunotherapy protocols requires further investigation.

Anti-tumor therapy and commensal flora collaborate in part, by loss of TNF- dependent early tumor necrosis response, down-regulation of inflammatory cytokines, phagocytosis, antigen presentation, and adaptive immune response gene expression controlling tissue development and cancer[51]. The loss of commensal organisms by antibiotics and the possibility of carcinogenic promoting effects of antibiotics have been explored. The risk related to pancreatic cancer seems limited to the penicillin class, especially with more than five courses, but this risk diminishes over time[52]. Macrolides, cephalosporins, tetracyclines, antivirals, and antifungals were not associated with increased risk of pancreatic cancer[52]. The impact of antibiotics on commensal framework may explain the need for repeated antibiotic exposures, leading to an enduring change in bacterial community diversity[52]. Murine models demonstrate *lactobacillus* was among quickest flora to recover in the gut after antibiotic therapy. However, the effect of antibiotics on the gut microbiome is enduring at four weeks after exposure; the population is deficient, and not reflective of its healthy, baseline, pre-antibiotic diversity[51].

Commensal bacteria offer protection from disease by inflammatory-modulating activity as above, but also by hormonal homeostasis, detoxification, and metabolic effects of bacterial metabolites. For example, murine models show *lactobacilli* are consistently reduced in cachectic mouse models[53]. A *lactobacilli* cocktail combination with prebiotic substrate that supports growth of microorganisms, changes the dysbiotic populations of cecal microbiota composition in murine models, clinically resulting in improved survival and reduction of cachexia[54]. These are highly important implications in pancreatic adenocarcinoma population since these patients carry the strongest burden of cancer cachexia among all malignancies, present in up to 80% of patients[55,56] resulting in reduced survival and progressive disease[56-58]. Weight stabilization alone significantly proven to improve survival in pancreatic adenocarcinoma patients with unresectable disease[59].

In conclusion, the initial motive to explore microbiome role in carcinogenesis may lead to identifying reliable non-invasive screening strategies and discern additional modifiable risk factors. With further investigation, potentially microbiome studies in pancreatic cancer could offer therapeutic targets. Perhaps the most extraordinary opportunity is to favorably transform cancer response to existing treatment protocols and improve survival by reduction of cancer-related cachexia by manipulating human gut microbiota.

**COMMENTS**

***Background***

Recently, there are literature reports on influences of microbiome alteration contributing to carcinogenesis of multiple malignancies. Among the most controversial is dysbiosis related to pancreatic cancer. Pancreatic cancer often denotes a poor clinical prognosis in part due to late recognition and treatment resistance, warranting investigations for modifiable risk factors, early screening biomarkers, and microenvironment elements that affect patient outcomes.

***Research frontiers***

Murine models demonstrate commensal microbiome taxa modulates a favorable tumor response to chemotherapy in multiple tumor types In addition, manipulation of cecal microbiome composition with lactobacillus in murine models, have resulted in improved survival and reduction of cachexiaa clinically significant burden in the majority of pancreatic cancer patients.

***Innovations and breakthroughs***

This review article serves to update literature on microbiome alterations associated with pancreatic cancer, its potential utility as an early screening biomarker, examine the influence of the microbiome in antitumor therapy, and the potential impact of microbiome manipulation to affect pancreatic cancer patient outcomes.

***Applications***

Exploring the microbiome role in carcinogenesis may lead to identifying reliable non-invasive screening strategies and discern additional modifiable risk factors. With further investigation, potentially microbiome studies in pancreatic cancer could offer therapeutic targets. Perhaps the most extraordinary opportunity is to favorably transform cancer response to existing treatment protocols and improve survival by reduction of cancer-related cachexia by manipulating human gut microbiota.

***Peer-review***

This review describes the relationships between microbiome and pancreatic cancer. The data in this report is of considerable importance in investigations for modigiable risk factors of pancreatic cancer.

**REFERENCES**

1 **Vogtmann E**, Goedert JJ. Epidemiologic studies of the human microbiome and cancer. *Br J Cancer* 2016; **14**: 237-242 [PMID: 26730578 DOI: 10.1038/bjc.2015.465]

2 **Sheflin AM**, Whitney AK, Weir TL. Cancer-promoting effects of microbial dysbiosis. *Curr Oncol Rep* 2014; **16**: 406 [PMID: 25123079]

3 **Human Microbiome Project Consortium**. Structure, function and diversity of the healthy human microbiome. *Nature* 2012; **486**: 207-214 [PMID: 22699609 DOI: 10.1038/nature11234]

4 **Sears CL**, Pardoll DM. Perspective: alpha-bugs, their microbial partners, and the link to colon cancer. *J Infect Dis* 2011; **203**: 306-311 [PMID: 21208921 DOI: 10.1093/jinfdis/jiq061]

5 **Zhu Q**, Gao R, Wu W, Qin H. The role of gut microbiota in the pathogenesis of colorectal cancer. *Tumour Biol* 2013; **34**: 1285-1300 [PMID: 23397545 DOI: 10.1007/s13277-013-0684-4]

6 **Zambirinis CP**, Pushalkar S, Saxena D, Miller G. Pancreatic cancer, inflammation, and microbiome. *Cancer J* 2014; **20**: 195-202 [PMID: 24855007 DOI: 10.1097/PPO.0000000000000045]

7 **Fukase K**, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; **372**: 392-397 [PMID: 18675689 DOI: 10.1016/S0140-6736(08)61159-9]

8 **Pakodi F**, Abdel-Salam OM, Debreceni A, Mózsik G. Helicobacter pylori. One bacterium and a broad spectrum of human disease! An overview. *J Physiol Paris* 2000; **94**: 139-152 [PMID: 10791696]

9 **Chen XZ**, Wang R, Chen HN, Hu JK. Cytotoxin-Associated Gene A-Negative Strains of Helicobacter pylori as a Potential Risk Factor of Pancreatic Cancer: A Meta-Analysis Based on Nested Case-Control Studies. *Pancreas* 2015; **44**: 1340-1344 [PMID: 26390415 DOI: 10.1097/MPA.0000000000000414]

10 **Schulte A**, Pandeya N, Fawcett J, Fritschi L, Risch HA, Webb PM, Whiteman DC, Neale RE. Association between Helicobacter pylori and pancreatic cancer risk: a meta-analysis. *Cancer Causes Control* 2015; **26**: 1027-1035 [PMID: 25951801 DOI: 10.1007/s10552-015-0595-3].]

11 **Trikudanathan G**, Philip A, Dasanu CA, Baker WL. Association between Helicobacter pylori infection and pancreatic cancer. A cumulative meta-analysis. *JOP* 2011; **12**: 26-31 [PMID: 21206097]

12 **Hujoel PP**, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. *Ann Epidemiol* 2003; **13**: 312-316 [PMID: 12821269]

13 **Stolzenberg-Solomon RZ**, Dodd KW, Blaser MJ, Virtamo J, Taylor PR, Albanes D. Tooth loss, pancreatic cancer, and Helicobacter pylori. *Am J Clin Nutr* 2003; **78**: 176-181 [PMID: 12816788]

14 **Michaud DS**, Joshipura K, Giovannucci E, Fuchs CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. *J Natl Cancer Inst* 2007; **99**: 171-175 [PMID: 17228001 DOI: 10.1093/jnci/djk021]

15 **Lin IH**, Wu J, Cohen SM, Chen C, Bryk D, Marr M, Melis M, Newman E, Pachter HL, Alekseyenko AV, Hayes RB, Ahn J. Pilot study of oral microbiome and risk of pancreatic cancer. *Cancer Res* 2013; **73** [DOI: 10.1158/1538-7445.AM2013-101]

16 **Torres PJ,** Fletcher EM, Gibbons SM, Bouvet M, Doran KS, Kelley ST. Characterization of the salivary microbiome in patients with pancreatic cancer. *Peer J* 2015; **3:** e1373 [PMID: 26587342 DOI: 10.7717/peerj.1373]

17 **Farrell JJ**, Zhang L, Zhou H, Chia D, Elashoff D, Akin D, Paster BJ, Joshipura K, Wong DT. Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer. *Gut* 2012; **61**: 582-588 [PMID: 21994333 DOI: 10.1136/gutjnl-2011-300784]

18 **Whatcott CJ**, Han H, Von Hoff DD. Orchestrating the Tumor Microenvironment to Improve Survival for Patients With Pancreatic Cancer: Normalization, Not Destruction. *Cancer J* 2015; **21**: 299-306 [PMID: 26222082 DOI: 10.1097/PPO.0000000000000140]

19 **Von Hoff DD**, Korn R, Mousses S. Pancreatic cancer--could it be that simple? A different context of vulnerability. *Cancer Cell* 2009; **16**: 7-8 [PMID: 19573807 DOI: 10.1016/j.ccr.2009.06.011]

20 **Meurman JH**. Oral microbiota and cancer. *J Oral Microbiol* 2010; **2**: [PMID: 21523227 DOI: 10.3402/jom.v2i0.5195]

21 **Aas JA**, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol* 2005; **43**: 5721-5732 [PMID: 16272510 DOI: 10.1128/JCM.43.11.5721-5732.2005]

22 **Michaud DS**, Izard J. Microbiota, oral microbiome, and pancreatic cancer. *Cancer J* 2014; **20**: 203-206 [PMID: 24855008 DOI: 10.1097/PPO.0000000000000046]

23 **Michaud DS**, Izard J, Wilhelm-Benartzi CS, You DH, Grote VA, Tjønneland A, Dahm CC, Overvad K, Jenab M, Fedirko V, Boutron-Ruault MC, Clavel-Chapelon F, Racine A, Kaaks R, Boeing H, Foerster J, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Sieri S, Palli D, Tumino R, Panico S, Siersema PD, Peeters PH, Lund E, Barricarte A, Huerta JM, Molina-Montes E, Dorronsoro M, Quirós JR, Duell EJ, Ye W, Sund M, Lindkvist B, Johansen D, Khaw KT, Wareham N, Travis RC, Vineis P, Bueno-de-Mesquita HB, Riboli E. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. *Gut* 2013; **62**: 1764-1770 [PMID: 22990306 DOI: 10.1136/gutjnl-2012-303006]

24 **Berezow AB**, Darveau RP. Microbial shift and periodontitis. *Periodontol 2000* 2011; **55**: 36-47 [PMID: 21134227 DOI: 10.1111/j.1600-0757.2010.00350.x]

25 **Ahn J**, Segers S, Hayes RB. Periodontal disease, Porphyromonas gingivalis serum antibody levels and orodigestive cancer mortality. *Carcinogenesis* 2012; **33**: 1055-1058 [PMID: 22367402 DOI: 10.1093/carcin/bgs112]

26 **Suerbaum S**, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]

27 **Anderson LA**, Murphy SJ, Johnston BT, Watson RG, Ferguson HR, Bamford KB, Ghazy A, McCarron P, McGuigan J, Reynolds JV, Comber H, Murray LJ. Relationship between Helicobacter pylori infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. *Gut* 2008; **57**: 734-739 [PMID: 18025067 DOI: 10.1136/gut.2007.132662]

28 **Kalaf EA**, Al-Khafaji ZM, Yassen NY, Al-Abbudi FA, Sadwen SN. Study of the cytoxin-associated gene a (CagA gene) in Helicobacter pylori using gastric biopsies of Iraqi patients. *Saudi J Gastroenterol* 2013; **19**: 69-74 [PMID: 23481132 DOI: 10.4103/1319-3767.108474]

29 **Chen S**, Duan G, Zhang R, Fan Q. Helicobacter pylori cytotoxin-associated gene A protein upregulates α-enolase expression via Src/MEK/ERK pathway: implication for progression of gastric cancer. *Int J Oncol* 2014; **45**: 764-770 [PMID: 24841372 DOI: 10.3892/ijo.2014.2444]

30 **Raderer M**, Wrba F, Kornek G, Maca T, Koller DY, Weinlaender G, Hejna M, Scheithauer W. Association between Helicobacter pylori infection and pancreatic cancer. *Oncology* 1998; **55**: 16-19 [PMID: 9428370]

31 **Stolzenberg-Solomon RZ**, Blaser MJ, Limburg PJ, Perez-Perez G, Taylor PR, Virtamo J, Albanes D. Helicobacter pylori seropositivity as a risk factor for pancreatic cancer. *J Natl Cancer Inst* 2001; **93**: 937-941 [PMID: 11416115]

32 **de Martel C**, Llosa AE, Friedman GD, Vogelman JH, Orentreich N, Stolzenberg-Solomon RZ, Parsonnet J. Helicobacter pylori infection and development of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 1188-1194 [PMID: 18483341 DOI: 10.1158/1055-9965.EPI-08-0185]

33 **Lindkvist B**, Johansen D, Borgström A, Manjer J. A prospective study of Helicobacter pylori in relation to the risk for pancreatic cancer. *BMC Cancer* 2008; **8**: 321 [PMID: 18986545 DOI: 10.1186/1471-2407-8-321]

34 **Risch HA**, Yu H, Lu L, Kidd MS. ABO blood group, Helicobacter pylori seropositivity, and risk of pancreatic cancer: a case-control study. *J Natl Cancer Inst* 2010; **102**: 502-505 [PMID: 20181960 DOI: 10.1093/jnci/djq007]

35 **Gawin A**, Wex T, Ławniczak M, Malfertheiner P, Starzyńska T. [Helicobacter pylori infection in pancreatic cancer]. *Pol Merkur Lekarski* 2012; **32**: 103-107 [PMID: 22590913]

36 **Xiao M**, Wang Y, Gao Y. Association between Helicobacter pylori infection and pancreatic cancer development: a meta-analysis. *PLoS One* 2013; **8**: e75559 [PMID: 24086571 DOI: 10.1371/journal.pone.0075559]

37 **Yu G**, Murphy G, Michel A, Weinstein SJ, Männistö S, Albanes D, Pawlita M, Stolzenberg-Solomon RZ. Seropositivity to Helicobacter pylori and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2013; **22**: 2416-2419 [PMID: 24089457 DOI: 10.1158/1055-9965.EPI-13-0680]

38 **Wang Y**, Zhang FC, Wang YJ. Helicobacter pylori and pancreatic cancer risk: a meta- analysis based on 2,049 cases and 2,861 controls. *Asian Pac J Cancer Prev* 2014; **15**: 4449-4454 [PMID: 24969867]

39 **Risch HA**, Lu L, Kidd MS, Wang J, Zhang W, Ni Q, Gao YT, Yu H. Helicobacter pylori seropositivities and risk of pancreatic carcinoma. *Cancer Epidemiol Biomarkers Prev* 2014; **23**: 172-178 [PMID: 24234587 DOI: 10.1158/1055-9965.EPI-13-0447]

40 **Nilsson HO**, Stenram U, Ihse I, Wadstrom T. Helicobacter species ribosomal DNA in the pancreas, stomach and duodenum of pancreatic cancer patients. *World J Gastroenterol* 2006; **12**: 3038-3043 [PMID: 16718784]

41 **Takayama S**, Takahashi H, Matsuo Y, Okada Y, Manabe T. Effects of Helicobacter pylori infection on human pancreatic cancer cell line. *Hepatogastroenterology* 2007; **54**: 2387-2391 [PMID: 18265671]

42 **Mitsuhashi K**, Nosho K, Sukawa Y, Matsunaga Y, Ito M, Kurihara H, Kanno S, Igarashi H, Naito T, Adachi Y, Tachibana M, Tanuma T, Maguchi H, Shinohara T, Hasegawa T, Imamura M, Kimura Y, Hirata K, Maruyama R, Suzuki H, Imai K, Yamamoto H, Shinomura Y. Association of Fusobacterium species in pancreatic cancer tissues with molecular features and prognosis. *Oncotarget* 2015; **6**: 7209-7220 [PMID: 25797243 DOI: 10.18632/oncotarget.3109]

43 **Meyer MS**, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. *Cancer Causes Control* 2008; **19**: 895-907 [PMID: 18478344 DOI: 10.1007/s10552-008-9163-4]

44 **Di Cerbo A**, Palmieri B, Aponte M, Morales-Medina JC, Iannitti T. Mechanisms and therapeutic effectiveness of lactobacilli. *J Clin Pathol* 2016; **69**: 187-203 [PMID: 26578541 DOI: 10.1136/jclinpath-2015-202976]

45 **Risch HA**. Pancreatic cancer: Helicobacter pylori colonization, N-nitrosamine exposures, and ABO blood group. *Mol Carcinog* 2012; **51**: 109-118 [PMID: 22162235 DOI: 10.1002/mc.20826]

46 **Risch HA**. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. *J Natl Cancer Inst* 2003; **95**: 948-960 [PMID: 12837831]

47 **Hecht SS**, Carmella SG, Murphy SE. Tobacco-specific nitrosamine-hemoglobin adducts. *Methods Enzymol* 1994; **231**: 657-667 [PMID: 8041285]

48 **Howatson AG**, Carter DC. Pancreatic carcinogenesis: effect of secretin in the hamster- nitrosamine model. *J Natl Cancer Inst* 1987; **78**: 101-105 [PMID: 3467121]

49 **Howatson AG**, Carter DC. Pancreatic carcinogenesis: effect of secretin in the hamster- nitrosamine model. *J Natl Cancer Inst* 1987; **78**: 101-105 [PMID: 3467121]

50 **Bongers G**, Pacer ME, Geraldino TH, Chen L, He Z, Hashimoto D, Furtado GC, Ochando J, Kelley KA, Clemente JC, Merad M, van Bakel H, Lira SA. Interplay of host microbiota, genetic perturbations, and inflammation promotes local development of intestinal neoplasms in mice. *J Exp Med* 2014; **211**: 457-472 [PMID: 24590763 DOI: 10.1084/jem.20131587]

51 **Iida N**, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, Molina DA, Salcedo R, Back T, Cramer S, Dai RM, Kiu H, Cardone M, Naik S, Patri AK, Wang E, Marincola FM, Frank KM, Belkaid Y, Trinchieri G, Goldszmid RS. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* 2013; **342**: 967-970 [PMID: 24264989 DOI: 10.1126/science.1240527]

52 **Boursi B**, Mamtani R, Haynes K, Yang YX. Recurrent antibiotic exposure may promote cancer formation--Another step in understanding the role of the human microbiota? *Eur J Cancer* 2015; **51**: 2655-2664 [PMID: 26338196 DOI: 10.1016/j.ejca.2015.08.015]

53 **Bindels LB**, Beck R, Schakman O, Martin JC, De Backer F, Sohet FM, Dewulf EM, Pachikian BD, Neyrinck AM, Thissen JP, Verrax J, Calderon PB, Pot B, Grangette C, Cani PD, Scott KP, Delzenne NM. Restoring specific lactobacilli levels decreases inflammation and muscle atrophy markers in an acute leukemia mouse model. *PLoS One* 2012; **7**: e37971 [PMID: 22761662 DOI: 10.1371/journal.pone.0037971]

54 **Bindels LB**, Neyrinck AM, Claus SP, Le Roy CI, Grangette C, Pot B, Martinez I, Walter J, Cani PD, Delzenne NM. Synbiotic approach restores intestinal homeostasis and prolongs survival in leukaemic mice with cachexia. *ISME J* 2016; **10**: 1456-1470 [PMID: 26613342 DOI: 10.1038/ismej.2015.209]

55 **Fearon KC**, Baracos VE. Cachexia in pancreatic cancer: new treatment options and measures of success. *HPB* (Oxford) 2010; **12**: 323-324 [PMID: 20590907 DOI: 10.1111/j.1477-2574.2010.00178.x]

56 **Ronga I**, Gallucci F, Riccardi F, Uomo G. Anorexia-cachexia syndrome in pancreatic cancer: recent advances and new pharmacological approach. *Adv Med Sci* 2014; **59**: 1-6 [PMID: 24797965 DOI: 10.1016/j.advms.2013.11.001]

57 **Mueller TC**, Burmeister MA, Bachmann J, Martignoni ME. Cachexia and pancreatic cancer: are there treatment options? *World J Gastroenterol* 2014; **20**: 9361-9373 [PMID: 25071331 DOI: 10.3748/wjg.v20.i28.9361]

58 **Bachmann J**, Büchler MW, Friess H, Martignoni ME. Cachexia in patients with chronic pancreatitis and pancreatic cancer: impact on survival and outcome. *Nutr Cancer* 2013; **65**: 827-833 [PMID: 23909726 DOI: 10.1080/01635581.2013.804580]

59 **Davidson W**, Ash S, Capra S, Bauer J. Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer. *Clin Nutr* 2004; **23**: 239-247 [PMID: 15030964 DOI: 10.1016/j.clnu.2003.07.001]

60 **Vétizou M**, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, Rusakiewicz S, Routy B, Roberti MP, Duong CP, Poirier-Colame V, Roux A, Becharef S, Formenti S, Golden E, Cording S, Eberl G, Schlitzer A, Ginhoux F, Mani S, Yamazaki T, Jacquelot N, Enot DP, Bérard M, Nigou J, Opolon P, Eggermont A, Woerther PL, Chachaty E, Chaput N, Robert C, Mateus C, Kroemer G, Raoult D, Boneca IG, Carbonnel F, Chamaillard M, Zitvogel L. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015; **350**: 1079-1084 [PMID: 26541610 DOI: 10.1126/science.aad1329]

61 **Sivan A**, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, Benyamin FW, Lei YM, Jabri B, Alegre ML, Chang EB, Gajewski TF. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015; **350**: 1084-1089 [PMID: 26541606 DOI: 10.1126/science.aac4255]

62 **Fan X**, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, Purdue MP, Abnet CC, Stolzenberg-Solomon R, Miller G, Ravel J, Hayes RB, Ahn J. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. *Gut* 2016; Epub ahead of print [PMID: 27742762 DOI: 10.1136/gutjnl-2016-312580]

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**Table 1 Oral microbiome and pancreatic cancer**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study Design** | **Case No.** | **Control** | **Detection** | **Bacteria association** | **Outcome** | **Author Conclusion** |
| **No.** | **Method** |
| Michaud *et al*[23], 2013, Western Europe | Prospective  | 405 | 416 | Plasma IgG |  |  High titer *p. gingivalis*  | Two fold increase in pancreatic cancer among individuals with high titer *p. gingivalis* |
| *Porphyromonas gingivalis* ATTC 53978 | (IgG > 200 ng/mL) |
|  | OR 2.14 |
|  | *P* = 0.05 |
| High titer, *commensal* bacteria  | OR = 0.55 | 45% lower risk of pancreatic cancer compared to individuals with lower antibody levels |
| 95%CI: 0.36-0.83 |
| Farrell *et al*[17], 2012, United States | Case-control | 28 | 28 | Salivary qPCR, Microarray | *Neisseria elongata* and *Streptococcus mitis* | *N. elongata* and *S. mitis* significantly decreased  | *N. elongate* and *S. mitis* combination ROC plot AUC 0.90 serves as 96% sensitive, 82% specific biomarker for pancreatic ca vs. healthy subjects |
| ROC-plot AUC 0.90;  |
| 95%CI: 0.78-0.96, *P* < 0.0001 |
| *Granulicatella adiacens* | *G. adiacens* |
| Significantly elevated compared to healthy control |
| Lin *et al*[15], 2013,  | Pilot | 13 | 12 | Salivary rRNA  | *bacteroides* genus | More common pancreatic cancer patient *vs* healthy subjects  | Oral flora alterations in microbiome in pancreatic cancer exist compared to healthy individuals |
| United States | *P* = 0.002 |
| 　 | *Corynebacterium* genus *Aggregatibacter* genus | Less common in pancreatic cancer *vs* healthy subjects *P* = 0.033 and 0.019 |
| Torres *et al*[16], 2015 | Cross-sectional | 8 | 22 | Salivary rRNA, PCR | Higher *Leptotrichia* and lower *Porphyromonas* colonization | *Lepotrichia:Porphyromonas* ratio elevated in pancreatic cancer versus healthy control *P* = 0.001 | L:P ratio may be reliable biomarker for pancreatic cancer diagnosis |
| United States |
| Author, Year | Study Design | Case No. | Control | Detection | Bacteria association | Outcome | Author Conclusion |
| No. | Method |
| Fan *et al*[62], 2016 | Nested Case control | 361 | 371 | Salivary rRNA gene sequencing | Oral pathogens | *P. gingivalis* | Presence of oral pathogensare related to subsequent increased risk of pancreatic cancer. On contrary, *Fusobacteria* and *Leptotrichia* are associatedwithdose or concentration dependent decrease risk of pancreatic cancer. |
| United States | *P. gingivalis,*  | AOR = 1.60 |
| 　 | *A. actinomycetemcomitans*. | (95%CI: 1.15 - 2.22) |
| 　 | 　 | 　 |
| 　 | 　 | *A. actinomycetes* |
| 　 | 　 | OR = 2.20 |
| 　 | 　 | (95%CI: 1.16 - 4.18) |
| 　 | *Fusobacteria* and *Leptotrichia* | *Fusobacteria* |
| 　 | decreased risk |
| 　 | OR per percent increase of relative |
| 　 | abundance |
| 　 | OR = 0.94 |
| 　 | (95%CI: 0.89 - 0.99) |
| 　 | 　 |
| 　 | *Lepotrichia* |
| 　 | OR = 0.87 |
| 　 | (95%CI: 0.79 - 0.95) |

**Table 2 *Helicobacter pylori* and pancreatic cancer**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study Design** | **Case No.** | **Control No.** | **Detection** | **Bacteria association** | **Outcome** | **Author conclusion** |
| **Method** |
| Raderer *et al*[30], 1998, Austria | Case-control | 92 | 27 | Plasma IgG ELISA | *H. pylori* | OR = 2.1 | *H. pylori* seropositivity prominent in pancreatic cancer patients compared with colorectal cancer combined with normal controls |
| 95%CI: 1.1 - 4.1 |
| *P* = 0.035 |
| Stolzenberg, *et al*[31] 2001, | Nested case-control, | 121 | 226 | Plasma IgG ELISA | *cytotoxin-associated gene-A (CagA)* virulence factor and *H. pylori* | *H. pylori*  | Male smokers seropositive for *H. pylori* were nearly twice as likely to develop pancreatic cancer compared to seronegative. Stronger influence adjusting for years of smoking. |
| Finland | OR = 1.87;  |
|  | 95%CI: 1.05 - 3.34 |
|  |  |
|  | CagA+ strains  |
|  | OR = 2.01; |
|  |  95%CI: 1.09 - 3.70 |
| Author, Year, Population | Study Design | Case No. | Control No. | Detection | Bacteria association | Outcome | Author Conclusion |
| Method |
| de Martel *et al*[32], 2008, United States | Nested Case-control | 104 | 262 | Plasma IgG | *cytotoxin-associated gene-A (CagA)* virulence factor and *H. pylori* | *H. pylori*  | *H. pylori* infection is not associated with development of pancreatic cancer. |
| ELISA | OR = 0.85;  |
|  | 95%CI: 0.49-1.48  |
|  |  |
|  | CagA+ |
|  | OR = 0.96;  |
|  | 95%CI: 0.48-1.92 |
| Lindkvist *et al*[33], 2008, Sweden | Nested Case-control | 87 | 263 | Plasma IgG | *H. pylori* | *H. pylori* overall  | Adjusted risk for development of pancreatic cancer highly increased in never-smokers seropositive for *H. pylori*. |
| ELISA | OR = 1.25  |
|  | 95%CI: 0.75–2.09 |
|  |  |
|  | *H. pylori* in Never smokers |
|  | AOR = 3.81  |
|  | 95%CI: 1.06–13.63 |
| Risch *et al*[34] 2010, | Case-control | 373 | 690 | Plasma IgG ELISA | *cytotoxin-associated gene-A (CagA)* virulence factorand *H. pylori* | *CagA negative H. pylori* non-O blood group | CagA-negative *H. pylori* seropositivity is a risk factor for pancreatic cancer among individuals with non–O blood type. |  |
| United States | OR = 2.78,  |
|  | 95%CI: 1.49 -5.20,  |
|  | *P* = 0.0014;  |
|  |  |
|  | *CagA negative H. pylori* O-blood group |
|  | OR = 1.28,  |
|  | 95%CI: 0.62 - 2.64, |
|  |  *P* = 0.51 |
| Trikudanathan *et al*[11], 2011 | Meta-analysis | 822 | 1513 | meta-analysis of 6 case control studies  | *H. pylori* | AOR = 1.38, | Significant positive association between the presence *of H. pylori* infection and pancreatic cancer. |
| 95%CI: 1.08-1.75 |
| Gawin *et al*[35], 2012, | Case-control | 139 | 177 | Plasma IGg, ELISA, western blot | cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori* | H. pylori | No association between seropositivity of H. pylori or CagA with development of pancreatic cancer.  |  |
| Poland | OR = 1.27; |  |
| 　 | 95% CI: 0.64- 2.61 |  |
| 　 | *P* = 0.514 |  |
| 　 | CagA+  |  |
| 　 | OR = 0.90; |  |
| 　 | 95%CI: 0.46 - 1.73, |  |
| 　 | *P* = 0.744 |  |
| Gao *et al*[36] 2013 | Meta-analysis | 1083 | 1950 | meta-analysis of 9 case-control studies | *cytotoxin-associated gene-A (CagA)* virulence factorand *H. pylori* | *H. pylori* Overall  | Borderline positive association H. pylori seropositivity overall. Adjusted risk for high quality studies revealed a significant, but modest association. CagA virulence seropositivity was not associated with pancreatic cancer. |  |
| OR = 1.47  |  |
| 95%CI: 1.22-1.77 |  |
| 　 |  |
| Adjusted for “High quality” studies |  |
| AOR = 1.28; |  |
| 95%CI: 1.01-1.63 |  |
| 　 |  |
| Adjusted for CagA positive |  |
| AOR = 1.47; |  |
| 95%CI: 0.79-2.57  |  |
| Yu *et al*[37], 2013, Finland[37] | Case-control | 353 | 353 | multiplex serology to 4 H. pylori antigens | *H. pylori* | OR = 0.85; | No association between seropositivity of *H. pylori* with development of pancreatic cancer.  |  |
|  | 95%CI: 0.49 -1.49  |  |
| Wang *et al*[38], 2014 | Meta-analysis | 2049 | 2861 | Meta-analysis of 9 case-control studies | *cytotoxin-associated gene-A (CagA)* virulence factorand *H. pylori* | *H. pylori* overall | Eastern Asian populations demonstrate significant decreased risk pancreatic cancer associated with *H. pylori* seropositivity. No association present in Western populations. |  |
|  | (2 non- English language) | OR = 1.06,  |  |
| 　 | 　 | 95%CI: 0.74-1.37 |  |
| 　 | 　 | 　 |  |
| 　 | 　 | Eastern Asian Population |  |
| 　 | 　 | *H. pylori* |  |
| 　 | 　 | OR = 0.62,  |  |
| 　 | 　 | 95%CI: 0.49-0.76 |  |
| 　 | 　 | 　 |  |
| 　 | 　 | *Cag-A positive* |  |
| 　 | 　 | OR = 0.66,  |  |
| 　 | 　 | 95%CI:0.52-0.80 |  |
| 　 | 　 | 　 |  |
| 　 | 　 | Western European population |  |
| 　 | 　 | *H. pylori* |  |
| 　 | 　 | OR = 1.14  |  |
| 　 | 　 | 95%CI: 0.89 -1.40 |  |
| 　 | 　 | *Cag-A* positive |  |
| 　 | 　 | OR = 0.84  |  |
| 　 | 　 | 95%CI:0.63, 1.04 |  |
| Risch *et al*[39], 2014, Shanghai | Case-control | 761 | 794 | Plasma IGg, ELISA | *cytotoxin-associated gene-A (CagA)* virulence factorand *H. pylori* | Cag-A positive *H. pylori* | Decreased pancreas-cancer risk was seen for CagA positive *H. pylori* compared to seronegativity for both H. pylori and CagA.  |  |
| AOR = 0.68;  | A modest increased risk for CagA-negative *H. pylori* seropositivity. |  |
| 95%CI: 0.54-0.84 | 　 |  |
| Cag-A negative *H. pylori* | 　 |  |
| AOR = 1.28;  | 　 |  |
| 95%CI: 0.76-2.13 | 　 |  |
| Chen *et al*[9], 2015 | Meta-analysis | 1446 | 2236 | meta-analysis of 5 case control studies  | *cytotoxin-associated gene-A (CagA)* virulence factorand *H. pylori* | Overall | CagA-negative, nonvirulent strains of *H. pylori* may be a risk factor for pancreatic cancer. No association with seropositivity for *H. pylori* infection overall, nor when adjusted for CagA or virulent strain infection. |  |
| OR = 0.99; |  |
| 95%CI: 0.65 - 1.50 |  |
| CagA+ |  |
| OR = 0.92; |  |
| 95%CI: 0.65 -1.3 |  |
| 　 |  |
| Virulent strain infection |  |
| OR = 0.97 |  |
| 95%CI: 0.50 - 1.89 |  |
| 　 |  |
| Nonvirulent infection |  |
| OR = 1.47 |  |
| 95%CI: 1.11-1.96 |  |
| Schulte *et al*[10], 2015 | Combination Case-control and meta-analysis | 580 | 626 | Plasma IGg, ELISA and meta-analysis of 10 case-control studies  | *cytotoxin-associated gene-A (CagA)* virulence factorand *H. pylori* | *H. pylori* overall | No overall association observed for *H. pylori* seropositivity and risk of pancreatic cancer, but evidence of non-significant CagA strain-specific associations. |  |
| OR = 1.00 |  |
| 95%CI: 0.74-1.35 |  |
| Cag-A negative |  |
| AOR = 1.23 |  |
| 95%CI: 0.83-1.82 |  |
| Cag-A positive |  |
| OR = 0.74, |  |
| 95%CI: 0.48-1.15 |  |

**Table 3 Tissue microbiome and pancreatic cancer**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study Design** | **Case Sample size** | **Detection Method and Sample** | **Bacteria association** | **Outcome** | **Author Conclusion** |
| Nilsson *et al*[40], 2006, Sweden | Case-control | 84  | DNA genus specific PCR, surgical specimen  | *H. pylori* |  *Helicobacter* DNA detected in pancreas of 75% patients with adenocarcinoma, but not detected in any control. | *Helicobacter* DNA, mostly *H. pylori* genus, commonly detected in pancreatic cancer. |
| Takayama n *et al*[41]. 2007, Japan | Abstract  | - | ELISA and western blot, Pre-clinical cell line | *H. pylori* | IL-8 and VEGF secretion and proliferation factors NF-kappa-B, AP-1, and serum response element of human pancreatic cells increased by *H. pylori* infection. | *H. pylori* infection of human pancreatic cells may increase malignant potential of pancreatic cells. |
| Mitsuhashi *et al*[42], 2015, Japan | Case-control | 283  | PCR, surgical specimen | *Fusobacterium* | Detected in 8.8% cases. Median cancer-survival (months) positive versus negative detection17.2 versus 32.5 forlog-rank *p* = 0.021 | significantly shorter survival observed in the *Fusobacterium* species-positive group |