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Abstract

Only 30% of patients diagnosed with pancreatic cancer survive one year post-diagnosis. Progress in understanding the causes of pancreatic cancer has been made, including solidifying the associations with obesity and diabetes, and a proportion of cases should be preventable through lifestyle modifications. Unfortunately, identifying reliable biomarkers of early pancreatic cancer has been extremely challenging, and no effective screening modality is currently available for this devastating form of cancer. Recent data suggest the microbiota may play a role in the disease process, but many questions remain. Future studies focusing on the human microbiome, both etiologically and as a marker of disease susceptibility, should shed light on how to better tackle prevention, early detection, and treatment of this highly fatal disease.

Keywords

periodontitis; inflammation; digestive tract; pancreas

Pancreatic cancer is an aggressively lethal cancer; 94% of pancreatic cancer patients succumb to their disease within 5 years from diagnosis. In the US, over 46,000 individuals will be newly diagnosed with pancreatic cancer and an estimated 20,170 men and 19,420 women will die of pancreatic cancer in 2014 (1). As with many other cancers, patients who are diagnosed with localized disease have higher survival (24% survival at 5 years), providing a strong rationale to focus research efforts on identifying early disease. To date, there is no screening test available for pancreatic cancer in the general population; screening for high-risk individuals exists, but is limited to academic medical centers as various strategies of differing effectiveness are still being evaluated (2). The obvious and urgent need for early biomarkers of detection has led many researchers to consider and sort through thousands of potential blood biomarkers; but to date, none have been validated for clinical use, and potentially promising biomarkers (3) are only rarely tested in pre-diagnostic blood samples (4). Given that protein expression in tumors is likely to vary over the course of disease evolution (5), it will be critical to identify markers that can identify pancreatic

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cancer at early stages of development. Only those early detection biomarkers will have translational value for screening. Understanding the etiology of a type of cancer can often lead to new opportunities in prevention, and identification of high-risk groups. This review will first summarize the evidence for the role of microbiota in pancreatic cancer etiology, followed by a summary of the literature on the potential use of the microbiome as a biomarker for early detection and screening for pancreatic cancer.

Pathogenic microbiota: evaluating evidence for a causal link

Epidemiological evidence

Understanding the etiology of cancer can lead to new opportunities for prevention and provide new insights into the biological mechanisms leading to carcinogenesis, which can in turn lead to new opportunities for early detection or treatment. The well-established risk factors for pancreatic cancer include tobacco smoke, chronic pancreatitis, obesity, and types II diabetes. All these risk factors share a commonality: they play a role in impacting the immune response. There is a large body of evidence implicating the role of the immune response in carcinogenesis (6), but the challenge remains to tie epidemiological evidence to the biology of each individual cancer. With advancing technology, we are now better positioned to ask the difficult questions; among these is examining the role that bacteria may play in disease pathology. In contrast to some viruses, like the well characterized human papilloma virus 16 (HPV16), bacteria do not integrate into the host DNA, but can contribute to carcinogenesis through other pathways. The role of bacteria in carcinogenesis is being elucidated through the extensive work undertaken to understand the relationship between *H. pylori* and gastric cancer, now classified as a causal agent by the International Agency of Cancer Research (7). We are only recently beginning to understand how this organism can lead to gastric cancer (8), and its ability to manipulate the host immune response (9, 10).

Epidemiological studies first started to describe a link between *H. pylori* and gastric cancer in the early 1990s, initially noting higher prevalence of antibodies to *H. pylori* in populations with high risks of gastric cancer (11). The literature on this association has grown exponentially in the past two decades and multiple prevention trials have been performed while others are underway to evaluate the impact and strategies for *H. pylori* eradication (12, 13). In contrast, research examining the possible association between *H. pylori* and pancreatic cancer is more recent and data on this association is comparatively sparse. The interest in *H. pylori* in pancreatic cancer etiology was largely initiated by observations that individuals with a history of gastric ulcer are at increased risk of pancreatic cancer (14).

To date, six epidemiological studies have examined the association between antibodies to *H. pylori* and risk of pancreatic cancer (15-20); however, results from these studies have been inconsistent. One of the original cohort studies to report a positive association for *H. pylori* using data from the ATBC cohort study (16) recently updated their analysis including a substantially larger number of cases (n=353) (20); the updated analysis found no overall or strain-specific associations with pancreatic cancer risk. An effect modification by ABO blood type (19) was reported in a large case-control study; an association between pancreatic cancer risk and CagA-negative *H. pylori* seropositivity was found among individuals with

non-O blood type but not among those with O blood type (OR = 2.78, 95% CI = 1.49 to 5.20, P = 0.0014; OR = 1.28, 95% CI = 0.62 to 2.64, P = 0.51, respectively). The authors hypothesize that the difference in risk could be due to differences in terminal binding antigens in gastrointestinal mucins for individuals with non-O blood type (A and B), which influences the binding potential of the *H. pylori*. The same study observed no association between CagA-positive *H. pylori* seropositivity and pancreatic cancer. In contrast, no effect modification by blood type was observed in the ATBC study (20).

Other supporting evidence for the role of microbiota in pancreatic cancer etiology has arisen from studies on periodontal disease and pancreatic cancer. The hypothesized link between periodontal disease and pancreatic cancer stems from the knowledge that periodontal disease gives rise to systemic inflammation and has been associated with a number of chronic diseases (21). Periodontal disease is an oral inflammatory disease associated with gum recession, soft tissue damage, and bone loss leading to tooth loss. A number of studies have also reported positive associations between tooth loss, periodontal disease and orodigestive cancers (22, 23). *Porphyromonas gingivalis* has been extensively studied as a periodontal pathogen due to its unique ability to evade the immune response (24), but many other have been linked to periodontal disease (25, 26).

The association between periodontal disease and pancreatic cancer has been examined in three studies to date, all of which utilized prospectively collected data from large cohort studies; all three studies reported statistically significant positive associations (27-29). The first study to report an association between periodontal disease and pancreatic cancer mortality was the NHANES I Epidemologic Follow-up Study, including 49 pancreatic cancer cases. Unfortunately, adjustment for smoking was not made in this initial study (which was exploratory), thus limiting interpretation of findings; nevertheless, a strong positive association was noted between periodontitis at baseline and subsequent risk of fatal pancreatic cancer (RR= 1.77, 95% CI = 0.85-1.85, compared to those with healthy periodontium) (27). In the second study, the analysis was conducted in the Health Professional Follow-Up Study (HPFS), a prospective cohort with data on self-reported baseline tooth loss and periodontal disease and 16 years of follow-up (28). During that period, 216 cases of pancreatic cancer were newly diagnosed. After adjusting for age, smoking, diabetes, body mass index, and a number of other dietary factors, men with periodontal disease (with tooth loss) had a 64% higher risk of pancreatic cancer compared to those reporting no periodontal disease (with tooth loss)(95% CI =1.19-2.26). Among never smokers, a 2-fold increase in pancreatic cancer risk was observed (RR = 2.09, 95% CI = 1.18-3.71), ruling out the possibility that the overall association was confounded by smoking. Furthermore, the association was stronger among dentists (representing over half of the professionals) (RR = 1.91, 95% CI = 1.31-2.78), who more accurately report history of periodontal disease (30). The third study, an analysis using NHANES III data, reported a 4-fold increase in risk of pancreatic cancer was observed among those with severe periodontitis (29). In the same study, elevated antibodies to *P. gingivalis* were associated with a 3-fold increase risk of orodigestive cancer mortality, but a separate examination of *P. gingivalis* with pancreatic cancer mortality could not be conducted due to insufficient case numbers (29).

While data was not available on history of periodontal disease, antibodies to various oral pathogens were related to the risk of pancreatic cancer in a large prospective cohort (the European Prospective Investigation into Cancer cohort - EPIC) (31). In this cohort, blood samples were stored on over 385,000 men and women at baseline (i.e., prior to disease) and participants were follow-up over up to 9 years in order to identify pancreatic cancer cases. A nested case-control study of 405 pancreatic cancer cases and 410 controls was conducted, matching cases and controls on age at blood collection, time of blood collection, fasting status, sex, and recruitment center and a greater than 2-fold increase in risk of pancreatic cancer was observed among participants with high levels of antibodies to a pathogenic strain of *P. gingivalis* at baseline (OR = 2.38, 95% CI =1.16-4.90, comparing >200 ng/ml vs. <200ng/ml)(31).

Mechanisms and biological plausibility for oral bacteria in causal pathway

The presence of bacteria in pancreatic tumor tissue would certainly provide support for a direct causal link between oral bacteria and pancreatic carcinogenesis. Unfortunately, existing data on this topic are limited. In healthy animals (e.g., feline models), bacteria can be found in the pancreas but the spread of bacteria and colonization do not lead to infection; invasion and infection only occur among animals with existing inflammation (pancreatitis) (32, 33). A few studies have looked in depth at the involvement of bacteria in acute pancreatitis in humans. These studies have reported a high number of bacteria present in the calcified pancreatic duct epithelium and in pancreatic abscess (33-37). Some of the bacteria isolated from pancreatic tissues are also known members of the oral microbiome (34, 35, 38, 39). Bacterial dissemination from the mouth to the pancreas may include the colon via bacterial translocation, general circulation, biliary duct, duodenum, and the lymphatic system (33, 40-43).

Oral bacteria are known to impact the immune response and their dissemination can lead to systemic changes in inflammatory cytokines. Animal model data provide strong support for the role of *P. gingivalis*, one of the bacterial pathogens linked to periodontal disease, in systemic inflammation and atherosclerosis (44). In both *in vitro* and *in vivo*, *P. gingivalis* shows an ability to evade the host immune activation (45-47). *P. gingivalis* infection of animal models shows an involvement of toll-like receptors (TLRs) including TLR4, involved in protective immunity (48); TLR signaling has been shown to play an important role in human pancreatic tumors, in particular TLR4 (49, 50), thereby providing a potential mechanistic link between microbial stimulation and pancreatic carcinogenesis. Additional microbial mediated pro-carcinogenetic effects include nitrosamine exposure and the increase of systemic inflammation (6, 51). Nitrosamine carcinogenic exposure is elevated in oral cavities of patients with gum disease (52, 53) as a result of increased levels of nitrate-reducing bacteria (53). The association between systemic inflammatory biomarkers and periodontal disease has been noted in a number of studies, including in the above mentioned HPFS cohort (54).

The human microbiome as indicators of cancer risk

In a recent study, the comparison of microbiota content in saliva from pancreatic cancer cases with those of healthy controls resulted in the identification of two bacteria (*Neisseria*

elongata and *Streptococcus mitis*) that, combined, could distinguish cases and controls with 96.4% sensitivity and 82.1% specificity (55). The discovery phase was based on 10 pancreatic cancer cases and 10 healthy controls to identify bacteria that were statistically different by case-control status (either increased or decreased levels in patient saliva using 16S rDNA based methodologies). The identified bacteria of interest were then validated using 28 pancreatic cancer cases, 28 healthy controls and 28 patients with chronic pancreatitis. While this study will need a separate replication in other samples, and validation using prediagnostic saliva samples, the suggestion that oral microbiota may provide an easy, non-invasive biomarker of disease is highly attractive.

Measuring markers in biological samples prior to diagnosis (i.e., nested case-control study design) provides more information on the potential use of biomarkers for early detection. In the large EPIC cohort, antibodies to 23 oral microbiota were measured in plasma of samples that had been stored prior to disease detection (in some cases up to 9 years prior to diagnosis). Levels of antibodies to commensal oral bacteria were generally lower in cases than controls and individuals with overall higher antibody levels had a significantly lower risk of subsequent pancreatic cancer (31). These findings suggest that antibody levels might provide a marker of disease susceptibility and may translate to a useful indicator of risk.

The impact of the immune response, including individual genetic susceptibility associated with immune response, are critical features to the process of inflammation and pancreatic carcinogenesis (6). The strong genetic link between the ABO locus and pancreatic cancer, identified by genome-wide association studies (GWAS) (56, 57), may be related to the role of ABO types in immune response. Several studies suggest that carriers of A or B alleles are at higher risk of hepatitis B viral (HBV) infection (58) or *H. pylori* infection (19). The ABO locus (9q34.2) was strongly associated with sICAM-1 concentrations, an inflammatory adhesion receptor that facilitates leukocyte adhesion and migration across the endothelium, in a recent GWAS analysis (59), suggesting that the histo-blood group antigens play a role in the inflammation processes. The composition of the oral microbiome is likely to reflect the individual immune response status, and may provide an integrated profile of susceptibility that reflects the genetic component of the immune response, as well as the environmental factors that influence it.

Conclusion

While the evidence is currently limited, when taken together, the epidemiological data on periodontal disease and periodontal pathogen *P. gingivalis* are sufficiently consistent to warrant larger and more comprehensive analyses to clarify the role of microbiota in the etiology of pancreatic cancer. Furthermore, research on the oral microbiome and pancreatic cancer may open new opportunities to develop biomarkers to identify high-risk individuals. With technological advances which allow for the efficient and accurate measure of the oral microbiome, we are now poised to address these exciting questions.

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