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Updated Risk Factors to Inform Early Pancreatic Cancer Screening and Identify High Risk Patients

Daniel R. Principe[1,2], **Ajay Rana**[2,3]

[1]Medical Scientist Training Program, University of Illinois College of Medicine, Chicago, IL

[2]Department of Surgery, Division of Surgical Oncology, University of Illinois at Chicago, Chicago, IL

[3]Jesse Brown VA Medical Center, Chicago, IL.

Abstract

Pancreatic adenocarcinoma (PDAC) is associated with poor clinical outcomes and incomplete responses to conventional therapy. Therefore, there is an unmet clinical need to better understand the predisposing factors for pancreatic cancer in hopes of providing early screening to high-risk patients. While select risk factors such as age, race, and family history, or predisposing syndromes are unavoidable, there are several new and established risk factors that allow for intervention, namely by counseling patients to make the appropriate lifestyle modifications. Here, we discuss the best-studied risk factors for PDAC such as tobacco use and chronic pancreatitis, as well as newly emerging risk factors including select nutritional deficits, bacterial infections, and psychosocial factors. As several of these risk factors appear additive or synergistic, by understanding their relationships and offering coordinated, multidisciplinary care to high-risk patients, it may be possible to reduce pancreatic cancer incidence and improve clinical outcomes through early detection.

1 - INTRODUCTION

Pancreatic cancer is projected to be the second leading cause of cancer related death in the United States by 2030 (1). Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic cancer histotype, and typically presents at late clinical stages (2). As a result, most PDAC patients have poor responses to conventional therapy and median survival remains a dismal 6–12 months (2). Given the limited therapeutic options for pancreatic cancer patients and lack of adequate screening modalities, it is imperative to better

Correspondence to: Daniel R. Principe, Medical Scientist Training Program, University of Illinois College of Medicine, Department of Surgery, Division of Surgical Oncology, The University of Illinois at Chicago, 840 South Wood Street, 601 CSB, Chicago, IL 60612, Tel: (312) 413-7271, principe@illinois.edu Or Ajay Rana, Department of Surgery, Division of Surgical Oncology, College of Medicine, The University of Illinois at Chicago, 840 S. Wood Street, Suite 601 Clinical Sciences Building, MC 958, Chicago, IL 60612, Tel: (312) 413-7271, arana@uic.edu.

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understand the clinically identifiable risk factors for PDAC in hopes of identifying high-risk patients in the primary care setting, and providing early imaging and appropriate counseling in order to reduce the likelihood of developing this largely incurable malignancy.

2.1 - UNAVOIDABLE RISK FACTORS

While many of the known risk factors for pancreatic cancer are actionable through direct patient counseling, there are several that do not provide the opportunity for intervention. Still, these risk factors are nonetheless informative as they may provide guidance regarding screening and differential diagnosis. While PDAC has a slight male predominance, this may be partially explained by lifestyle differences between men and women, and outcomes do not significantly differ between sexes (2). However, such lifestyle differences cannot fully explain the difference in disease incidence, particularly in light of recently identified sex differences in driving genes and biomarkers in a variety of cancer types (3). In fact, when evaluating the TCGA genomic databases of pancreatic cancer patients (N=185), we found that while male and female patients had no significant difference in clinical outcomes, the presence of any specific mutation, or copy number alteration, there were several highly significant differences in mRNA expression between the sexes (Figure 1A,B and Table 1). While the clinical relevance of these findings are not clear at this time, interestingly most genes comparatively overexpressed in women were found on the X chromosome, whereas men only had significantly increased expression of one gene located on chromosome 12 (Table 1).

In addition to these sex differences, ethnicity also appears to play a role in PDAC. Though African Americans have the highest rates of PDAC and worst outcomes compared to other ethnic groups (4), the reasons for this are poorly understood and may implicate a variety of social factors discussed later in this article (5). As such, the associations between gender/ethnicity with PDAC may be avoidable to a degree. However, it is also highly likely that these factors may be compounded by an increased genetic susceptibility in certain ethnic groups. Using the previously mentioned TCGA cohort, we found that for the 180 patients where ethnicity was documented, 162 were listed as white, with the remaining 18 reported as either African American or Asian (Figure 1C). Despite the poor representation of minority groups in this sample set, we again identified significant differences in the mRNA expression of three genes between whites and non-whites (Figure 1D and Table 1). These data suggest that there may be an underlying genetic or epigenetic component to the differences in PDAC incidence and outcomes among racial groups. However, while the exact reasons select social and ethnic groups have higher rates of PDAC than others warrant further study, it is clear that certain communities are disproportionately affected by the disease, and may benefit from a greater emphasis on chemoprevention or early screening.

Beyond sex and race, select non-O blood types have also been suggested to be associated with PDAC risk (6), though the clinical utility of these data are unclear. Age, however, is one of the most established risk factors for PDAC (2). Per the most recent SEER data, the median age at the time of diagnosis is 70 years, with most patients being diagnosed between 65 and 74 (2). Fewer than 10% of patients develop PDAC before the age of 50, and these are

typically associated with a higher rate of predisposing genetic syndromes (7,8), discussed in detail below.

2.2 - PREDISPOSING GENETIC SYNDROMES

As with many cancers, genetics appear to play a role in PDAC etiology. For example, patients with a first degree relative with a history of PDAC have a 1.5 to 3-fold increase in disease risk (9,10). To this end, though PDAC is seldom inherited, several predisposing genomic alterations have been described (11). For instance, autosomal recessive ataxiatelangiectasia is associated with an increased risk of several cancers, including PDAC (12). This syndrome is well characterized, involving an inherited mutation to the DNA response and repair gene *ATM*. This leads to increased genetic instability due to a loss of high-fidelity double-strand break homologous recombination and dysregulation of cell cycle checkpoints (13). Several other inherited defects in DNA repair also increase PDAC risk. These include hereditary breast and ovarian cancer syndrome, which is predominantly caused by deleterious mutations in homologous recombination genes *BRCA1* and/or *BRCA2* (14). Similarly, truncating mutations to the homologous recombination gene *PALB2* also seem to increase risk of PDAC (15). Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer) is caused by a deficit in DNA mismatch repair caused by mutations to several genes including *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. Though classically associated with colon cancer, Lynch syndrome also increases the risk for several other tumor types including PDAC (16).

Beyond defects in DNA repair, several other syndromes increase the lifetime risk of PDAC. Familial adenomatous polyposis (FAP) also modestly predisposes to PDAC due to the presumptive loss of function of the *APC* tumor suppressor gene. However, like Lynch syndrome, FAP is better known for its strong association with colon cancer (17). Similarly, Peutz–Jeghers syndrome (PJS) is characterized by an autosomal dominant mutation in *STK11* tumor suppressor gene, also known as LKB1. PJS is classically associated with benign hamartomatous polyps in the gastrointestinal tract, though these have low rates of malignant transformation (18). However, PJS also significantly increases the risk of developing several other cancers including PDAC (19,20). PDAC is also associated with familial atypical multiple mole melanoma, an autosomal dominant mutation in *CDKN2A*. As the name implies, this syndrome is strongly linked with multiple dysplastic nevi and high rates of melanoma due to impaired function in the tumor suppressors $p16^{INK4a}$ and $p14^{ARF}$, both negative regulators of the cell cycle (21,22). Finally, hereditary pancreatitis is caused by autosomal dominant mutations to *PRSS1*, resulting in hyper-activation of its trypsinogen gene product. While the pancreatitis phenotype has high penetrance, patients suffering from hereditary pancreatitis also have an approximately 50% increase in their lifetime risk of PDAC (23,24).

While the above syndromes increase PDAC risk, very few influence the clinical management of PDAC once diagnosed. Though there is emerging evidence substantiating the use of PARP inhibitors in *BRCA*-mutated PDAC (25), no other pancreatic cancer associated syndrome is clinically actionable at this time. Hence, patients with a known or family history of these genetic events may benefit from early screening (26,27), and the

precise contributions of these genomic alterations to the PDAC phenotype warrants further study.

2.3 - GENETIC SUSCEPTIBILITY LOCI

In addition to the above syndromes, genome wide association studies (GWAS) have identified several susceptibility alleles for PDAC (28). These common germline variants predominantly single nucleotide polymorphisms (SNPs), conferring a modest risk increase of PDAC to carriers (29–34). For instance, in a 2009 GWAS, researchers genotyped 558,542 SNPs in 1,896 individuals with pancreatic cancer and 1,939 controls. The authors combined their results with an additional 2,457 pancreatic cancer patients and 2,654 controls from 8 additional studies, and found a significant association between a locus on 9q34 and disease incidence. This locus was marked by the SNP rs505922, mapping to the first intron of the ABO blood group gene (29). In 2010, a similar GWAS evaluating in 3,851 pancreatic cancer patients and 3,934 controls identified eight new cancer susceptibility loci. Five of these SNPs mapped to the gene *NR5A2* on chromosome 1q32.1, including rs3790844. Two additional SNPs (rs9543325 and rs9564966) mapped to a non-genic region on chromosome 13q22.1. Finally, a single SNP (rs401681) mapped to the *CLPTM1L-TERT* locus on 5p15.33 (30).

A larger 2014 study examined 7,683 pancreatic cancer patients and 14,397 controls, and identified several new susceptibility loci. These include rs6971499 that maps to the *LINC-PINT* gene at 7q32.3, rs7190458 that maps to *BCAR1/CTRB1/CTRB2* at 16q23.1, rs9581943 that maps to *PDX1* at 13q12.2, and rs16986825 that maps to *ZNRF3* at 22q12.1 The authors also identified a SNP (rs2736098) that mapped to exon 2 of *TERT* at 5p15.33, and another (rs1561927) mapping to *PVT1* on 8q24.21 (31). In 2015, 3 new *TERT* variants were identified (rs2736100, rs4583925, and rs2735948) all of which had a significant association with pancreatic cancer risk (32). In 2018, these investigators conducted their largest GWAS to date, including 9,040 pancreatic cancer patients and 12,496 controls. In this study, they identified five new susceptibility loci for pancreatic cancer. These include rs78417682 at the *TNS3* locus on 7p12, rs13303010 at the *NOC2L* locus on 1p36.33, rs2941471 at the *HNF4G* locus on 8q21.11, rs4795218 at the *HNF1B* locus on 17q12, and rs1517037 at the *GRP* locus on 18q21.32 (34). As additional susceptibility loci are beginning to emerge, it is becoming clear that these and other genetic variants may have important roles in guiding decisions regarding both pancreatic cancer screening and treatment (35–39).

2.4 - ADDITIONAL GENOMIC ALTERATIONS

While pancreatic cancers typically have fewer mutations than most other tumor types (40), exome and copy number variation (CNV) studies have determined that PDAC tumors have a highly complicated mutational landscape, with variable alterations to several different cell processes (41,42). A 2015 study shed further light on the complex genetic landscape of pancreatic cancer by conducting whole-genome sequencing and CNV analysis on 100 PDAC patients. This work identified frequent chromosomal rearrangements leading to copy number alterations in several genes with known roles in pancreatic carcinogenesis including

TP53, *SMAD4*, *CDKN2A*, *ARID1A* and *ROBO2*, as well as novel genes such as *KDM6A* and *PREX2*. Further, the authors used variation in chromosomal structure to group these PDAC patients into 4 subtypes: stable, locally rearranged, scattered, and unstable (43).

While these findings are likely to be most useful in managing advanced PDAC, other studies have suggested that copy number alterations in select genes may have relevance in determining pancreatic cancer risk. This includes copy number amplification of *SKAP2*/*SCAP2*, which may have an association with the development of PDAC (44). Additionally, a single study identified 93 non-redundant copy number variations associated with familial pancreatic cancer (45). However, others suggest that copy number variation may not have a significant role in the etiology of sporadic pancreatic cancer (46). It is important to note that the majority of copy number variation studies have been performed on advanced cancer specimens, where a certain degree of genetic instability is expected. Therefore, it is unclear which of these findings, if any, will have a role in helping to predict for pancreatic cancer in healthy populations. However, recent findings suggest that mitochondrial DNA copy number variations in peripheral blood leukocytes are associated with PDAC (47). Additionally, others report that leukocyte DNA from PDAC patients harbor as many as 431 copy number variations that may associate with disease incidence (48). Hence, this is an important area of research that warrants continued exploration.

3.1 - CLINCIALLY ACTIONABLE RISK FACTORS

Though the above factors may only inform screening modalities, there are several lifestyle and social factors that are also associated with pancreatic cancer incidence, as well as other serious health conditions that are often comorbid with pancreatic cancer. While these risk factors may also inform early screening, many are potentially reversible through proper patient counseling and education, particularly in the primary care setting.

3.2 - SMOKING

Smoking is one of the best-studied and most important avoidable risk factors for PDAC (49,50). Nearly 25% of pancreatic cancer deaths are linked to tobacco use (51,52), and a California-based study suggests that smoking 1 pack per day increases the lifetime risk of developing pancreatic cancer by 5–6 times (53). The exact risk increase seems to vary, as this is based largely on the duration and intensity of exposure (52,54). A META analysis evaluating 82 studies published between 1950 and 2007 determined that there was a 75% increase in the risk of pancreatic cancer in smokers compared to non-smokers, which persists for at least 10 years after smoking cessation (55). Interestingly, this pertains primarily to cigarette and cigar smokers, with no correlation between disease incidence and pipe or smokeless tobacco use (49,50). Cigarette smoking is also a strong predictor of pancreatic cancer mortality (5), further underscoring the importance of proper patient education.

Though this clinical phenomenon is well established, the cellular mechanisms linking smoking and PDAC are poorly understood. Several studies have sought to address this, providing unprecedented insight into the potential means through which tobacco smoke

promotes pancreatic carcinogenesis. For instance, cigarette smoke contains a variety of aryl hydrocarbon receptor (AhR) ligands that have been implicated in smoke-induced induction of the cyclooxygenase (COX)/prostaglandin (PG) pathways, as well as activation of fibroblasts in the lung (56,57). Inflammation is a key driver of pancreatic cancer (58), which is closely linked to fibroblast activation and tumor-associated fibrosis (59). Accordingly, AhR agonists 2,3,7,8-tetrachlorodibenzo-p-dioxin or benzo[a]pyrene accelerated chronic pancreatitis *in vivo*, particularly through the upregulation of the inflammatory cytokine IL22 (60). Similarly, clinical data suggests that circulating IL22 is elevated in chronic pancreatitis, is associated with cigarette smoking, and therapeutic inhibition of IL22 reduces disease progression *in vivo*. As discussed later in this article, chronic pancreatitis is another key risk factor for pancreatic cancer (61), and IL22 appears to promote pancreatic tumorigenesis through a variety of mechanisms (62). However, the link between smoking and IL22 in PDAC is not clear, and warrants further study.

Additional evidence appears to implicate aberrations to the epigenome in smoking-associated pancreatic carcinogenesis. For instance, histone deacetylase 3 (HDAC3) is a key regulator of several normal and pathologic cell processes, with important roles in PDAC (63,64). Studies in murine models of early disease demonstrated that aerial exposure to cigarette smoke accelerated lesion development in an HDAC3-dependent manner, promoting stellate cell activation, IL6 biosynthesis, and epithelial to mesenchymal transition (65). These events were reversed using the HDAC inhibitor Saha, offering a potential therapeutic option for smoking-associated PDAC (65).

In vitro studies have also helped identify potential mechanisms to link smoking and PDAC, namely via aberrant AKT signaling (66). Incubating human pancreatic duct cells with either cigarette smoke extract or the smoking-associated compound 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone reduced apoptosis and enhanced AKT activation, Bcl-xL expression, and the early formation of autophagic vacuoles (66). Interestingly, prolonged exposure with these compounds further suppressed apoptosis and abolished autophagy (66). Given the established roles for AKT (67) and autophagy (68) in PDAC, this is another potential means through which smoking may promote or accelerate PDAC development.

3.3 DIET & OBESITY

Obesity is an epidemic in the United States, affecting 1 in 3 adults and 17% of adolescents (69). Beyond the well-studied link between obesity and several serious health conditions including hypertension, cardiovascular disease, and diabetes (70), obesity is associated with the incidence of several cancers including PDAC (71). Obesity has been suggested to increase the incidence of PDAC by roughly 50% (72). This has been corroborated through several META analyses, the first of which found only a weak association between PDAC and body mass index (BMI) (73). Subsequent META analyses have substantiated a more significant association between an obese BMI and PDAC incidence (74–76), particularly with respect to waist circumference and centralized fat distribution (74,77).

Additional studies have suggested that obesity is also associated with poor clinical outcomes or treatment related complications. In patients undergoing pancreaticoduodenectomy, those

with a BMI ≥30 have longer operative times, more intraoperative blood loss, and an increased risk of developing pancreatic fistulas (78). Though this study did not find an association between obesity and post-operative survival (78), a large single institution study determined that obese patients have improved long-term survival independent of known clinical or pathologic factors (79). Paradoxically, another similar study determined that patients with a BMI ≥35 are more likely to have node-positive pancreatic cancer and decreased survival after surgical resection (80), and potentially poorer responses to cytotoxic chemotherapy (81). Though these conflicting results suggest that the predictive value for BMI in surgically resectable PDAC treatment is unclear, larger studies including inoperable disease suggest that an obese BMI is associated with poor overall survival in PDAC independent of additional factors such as diabetes and hyperglycemia (82).

Similarly, diet may also have a causative role in PDAC (83). In a META analysis of 11 prospective studies, increased consumption of red and processed meats was strongly associated with disease incidence in men (84). Deficiencies in several individual nutrients have also been suggested to correspond to pancreatic cancer risk, though these data are often contradictory (85). For example, studies have suggested that increased dietary intake of vitamin C is inversely associated with PDAC risk (86,87). However, a subsequent study suggested that the inverse association that had been observed in case-control studies may have been affected by recall and selection biases, and that additional prospective studies are required before substantiating vitamin C as a predictor of PDAC risk (88). Similarly, while case-control studies have suggested that low dietary folate (vitamin B9) may correspond to increased risk, others have contradicted these findings or suggest that supplemental folate does not provide any significant risk reduction (89–92).

Others have suggested potential protective roles of lipid soluble vitamins A, D, and E; however, none has produced conclusive evidence linking dietary deficiency with pancreatic cancer risk (86,93–101). Likewise, associations with PDAC and dietary lipids or selenium intake have only proven significant in case-control studies, and while low intake of omega-3 polyunsaturated fatty acids or high intake of cholesterol may have a positive association with overall risk, the predictive value of these factors also remains unclear (86,102–108).

Hence, studies evaluating single nutritional deficiencies have produced unclear and often contradictory results. Therefore, none has proven to be a clinically relevant predictor of pancreatic cancer risk. Recently, there is an increasing emphasis placed on overall dietary patterns rather than one specific nutritional deficiency (85). For example, a META analysis of 16 case-control and cohort studies determined that typical Western diets rich in animal products, starches, or fats are associated with a significant risk increase, whereas there was an inverse association between pancreatic cancer risk and diets high in fruits, vegetables, and fiber (109). Additional studies have suggested that a Western diet high in saturated fat confers an increased disease risk, and healthy/prudent or Mediterranean diets have favorable effects on disease incidence (110). Hence, rather than attempting to risk stratify or counseling patients to correct specific dietary deficiencies, all patients should be encouraged to make more sensible food choices and more closely adhere to a healthy diet, and care providers should be prepared to provide adequately resources to help patients make this transition.

3.4 - DIABETES MELITUS

Diabetes is closely linked with diet/obesity, and is associated with an increased risk of pancreatic cancer. Further, up to 80% of pancreatic cancer patients will present with new-onset type 2 diabetes or hyperglycemia at the time of diagnosis (111,112). This is particularly noteworthy, particularly in light of recent molecular evidence suggesting that increased glucose concentrations trigger nucleotide imbalance through aberrant O-GlcNAcylation, inducing *de novo* KRAS mutations in pancreatic epithelial cells (113). However, there also is a growing body of evidence highlighting diabetes as an early paraneoplastic consequence of PDAC, leading to controversy over whether diabetes mellitus is an independent risk factor or early marker for pancreatic cancer (112). While new onset diabetes has been suggested as a potential screening tool for pancreatic cancer (111), additional studies have evaluated the relative risk for diabetic patients of developing pancreatic cancer, particularly with respect to the duration of their diabetes.

For instance, a META analysis evaluating 20 case-control and cohort studies between 1975 and 1994 determined that diabetic patients had a relative risk of 1.8–2.6 (114). When evaluating patients with a diabetes duration of at least 5 years, the relative risk was 2.0 (114). An updated META analysis examining 36 studies between 1966 and 2005 determined that patients with a <4 year history of diabetes had a 50% greater risk of pancreatic cancer compared to those with who had diabetes for ≤5 years (115). Though these results suggest a modest causal relationship between pancreatic cancer and diabetes, subsequent studies have identified a more significant link.

This includes a 2011 META analysis which, despite similar heterogeneity within the individual studies, found that diabetes was associated with increased pancreatic cancer risk independent of alcohol consumption, BMI, geographic location, sex, smoking status, and study design (116). Similar to other studies, this META analysis also found the highest risk of pancreatic cancer to be among patients with ≤1 year history of diabetes (116). A more recent analysis suggests the relative risk for pancreatic cancer is nearly 5-fold for patients with a diagnosis of diabetes within the last year, with a more modest 2-fold risk increase for patients diagnosed 1–4 years ago (117). This has been corroborated by additional studies, which in addition to finding an inverse association between PDAC risk and years with diabetes, found an increased risk for insulin users compared to non-users, which was restricted to insulin use of ≤3 years (118).

Combined, these studies strongly suggest that pancreatic-cancer associated diabetes is largely a paraneoplastic event. Further, it is well established that most pancreatic cancer patients will develop either glucose intolerance or diabetes prior to their cancer diagnosis (119–121). Additionally, longstanding diabetics tend to worsen in the months before their pancreatic cancer diagnosis (121–123), and diabetes tends to improve following surgical removal of pancreatic cancer (120–124). Accordingly, the Chari group has recently developed a novel model to determine risk of pancreatic cancer in individuals with new-onset diabetes, which they refer to as “enriching new-onset diabetes for pancreatic cancer” or END-PAC (125). By retrospectively evaluating data from 1,561 patients with new-onset diabetes, they created a model weighting the three factors most significant to predict for

PDAC. These include change in weight, change in blood glucose, and age at onset of diabetes (125). This approach was highly effective in risk-stratifying patients for PDAC in an independent, population-based cohort of 1096 diabetics (125). Therefore, new-onset diabetes may be the most informative risk factor for early pancreatic cancer screening, and pancreatic cancer should be suspected in any patient meeting END-PAC criteria.

However, despite the well documented clinical association between pancreatic cancer and diabetes, as expertly reviewed by Sah and colleagues (121), the molecular mechanisms that underlie these events are only recently becoming clear. For instance, clinical evidence suggests that pancreatic cancer associated diabetes is at least in part due to a decline in β-cell function and increased insulin resistance (126). Accordingly, supernatants from PDAC cell lines promote insulin resistance in cultured hepatocytes and myoblasts *in vitro*, and intraperitoneal administration of MiaPaCa2-conditioned media induces β-cell dysfunction *in vivo* (127–130). While the soluble, tumor-derived factors that case these changes are not well characterized, a study examining pancreatic tumor tissue from patients with or without diabetes identified the 14 amino acid peptide from S100A8 as being differentially expressed in those with diabetes. Further, S100A8 impaired glucose catabolism by myoblasts *in vitro*, suggesting that it may very well have a causative role in pancreatic cancer-associated diabetes (131).

Other studies have also identified differences in proteins expression among PDAC patients with and without diabetes. For example, islets in PDAC patients with diabetes typically overexpress the gap junction protein Connexin-26 (132). Another study examined peripheral blood samples from either healthy controls, or patients diagnosed with pancreatic cancer and/or diabetes. This group found that blood from pancreatic cancer patients with diabetes had increased mRNA and protein expression of several factors, namely vanin-1 (VNN1) and matrix metalloproteinase 9 (MMP9) (133). Adrenomedullin is also upregulated in PDAC, particularly in those who develop diabetes. Additionally, adrenomedullin is carried in pancreatic cancer-associated exosomes, and also appears to cause insulin resistance in β-cells (134). Another study has identified pancreatic polypeptide (PP) as a potentially useful predictor of pancreatic cancer-associated diabetes. Though their sample size is small, the authors identified a blunted PP response in pancreatic cancer-associated diabetes compared to type 2 diabetics without a pancreatic cancer diagnosis. While this PP response may discriminate between type 2 diabetes and pancreatic cancer-associated diabetes, this phenomenon also appears to be exclusive to PDAC patients with tumors located in the head of the gland (135). Hence, by combining these observations with the END-PAC model, it may be possible to risk stratify newly diagnosed diabetics and identify those who would most benefit from early pancreatic cancer screening.

3.5 - ALCOHOL & PANCREATITIS

Alcohol has long been suspect to confer an increased risk of pancreatic cancer. The carcinogenic properties of alcohol and its metabolites are well-documented (136). Accordingly, alcohol has been implicated in the development of a variety of solid tumors, and genetic variants of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are associated with increased overall cancer risk (137). Select studies have identified a

positive association between heavy alcohol consumption and PDAC, though this risk increase is not as strong as that caused by smoking (138–141). One case-control study suggested that alcohol consumption was not associated with pancreatic cancer risk overall, but that cigarette smoking modified the alcohol-cancer relationship, as heavy drinking is more frequently observed in smokers than non-smokers. In current smokers, light to moderate alcohol intake modestly increased pancreatic cancer risk, and heavy alcohol consumption significantly increased risk (142). Hence, it is difficult to establish alcohol as an independent risk factor for pancreatic cancer.

However, though the direct link between pancreatic cancer and alcohol remains unclear, the link between pancreatitis and pancreatic cancer has been known for decades. While gallstones are the most common cause of acute pancreatitis and the risk of future episodes can be eliminated through cholecystectomy, both alcohol and smoking also appear to be clinically significant risk factors (143). However, alcohol continues to be the most significant risk factor for chronic pancreatitis. While a diagnosis of acute pancreatitis appears to increase the long-term risk of pancreatic cancer (144), chronic pancreatitis is a much more significant risk factor (145), particularly in patients requiring surgery (146). Therefore, chronic pancreatitis is likely more informative when stratifying patients for early screening. In META analysis, chronic pancreatitis confers a nearly eight-fold increased risk of pancreatic cancer 5 years after diagnosis. However, this risk appeared to diminish with long-term follow up. The authors resultantly recommend close follow-up in the first years following a diagnosis of chronic pancreatitis (145), though aggressive surveillance of any patient with a history of pancreatitis and other known risk factors may be warranted.

4.1 - NEWLY EMERGING RISK FACTORS

Recent evidence has illuminated several added risk factors that may also have utility when identifying high-risk patients. Interestingly, these appear to involve a number of infectious processes as well as a variety of underappreciated psychosocial factors. While the individual predictive values for several of these factors is still unclear, these may warrant clinical consideration particularly when patients also have a known history of more established risk factors.

4.2 - INFECTION & THE MICROBIOME

Bacterial and viral species are of paramount importance to the etiology of several cancers (147). While the pancreas has long been considered a sterile organ, a recent study identified an abundance of select bacterial species in both human and murine pancreatic cancer specimens (148). The microbial signature of PDAC tumors also appears to have a prognostic value, as a signature rich for *Pseudoxanthomonas, Streptomyces, Saccharopolyspora, and Bacillus clausii* predicts long-term survival in PDAC patients (149) Further, ablation of intratumoral bacteria enhanced the efficacy of immunotherapy *in vivo*, which is particularly noteworthy as immunotherapy is beginning to show promise in PDAC (148,150–159). Interestingly, other roles for select bacterial species in PDAC are also emerging. For example, a recent study identified a potential role for intratumoral *Gammaproteobacteria* in the emergence of chemoresistance both *in vitro* and *in vivo* (160). However, a more causal

role for select bacterial species has been suggested, particularly in light of clinical observations linking specific infections with pancreatic cancer risk.

For instance, a 1998 study identified a positive association between serum IgG antibodies against *Helicobacter pylori* (*H. pylori*), with 65% of PDAC patients testing positive compared to 45% of healthy controls (161). Subsequent studies have expanded on this relationship, including a larger 2001 study that found 82% of PDAC patients to be seropositive for *H. pylori* compared to 73% in controls. Additionally, compared to seronegative subjects, those seropositive for gene-A-positive *H. plylori* strains had a statistically significantly increased risk of pancreatic cancer (162).

A 2007 study evaluating gastric and duodenal ulcers suggested a 20% excess risk increase for unoperated gastric ulcer patients (163). This study also states that gastric ulcers are primarily associated with corpus colonization of *H. pylori* and the formation of N-nitrosamines, whereas duodenal ulcers are associated with antral colonization, hyperacidity and uninhibited secretin release. Hence, they suggest that N-nitrosamines may have a role in PDAC pathobiology (163), though this remains untested. While additional studies have contradicted these findings, a 2011 META analysis including 2,335 patients across 6 studies found a significant risk increase for *H. pylori* seropositivity (164). Hence, while *H. pylori* can colonize the pancreas and these infections may have a role in PDAC (165), its independent predictive value for *H. pylori* seropositivity is not clear, though this may warrant consideration in combination with other risk factors.

Beyond *H. pylori*, several other gut microbiota species also appear to be involved in PDAC. The microbial species that colonize the pancreas appear to have significant overlap with those of the gastrointestinal tract (149). Accordingly, microbes from the gastrointestinal tract, particularly the small intestine, are able to access the pancreas through both the biliary tract and the bloodstream (148,166,167). Depletion of the gut microbiome significantly reduced tumor burden in murine models of PDAC, however, this was not observed in mice lacking functional T and B cells (168). Further, human-into-mice fecal microbiota transplantation has been shown to differentially modulate the tumor microbiome *in vivo*, with significant effects on tumor growth and local immune responses (149). Hence, further investigation into the contributions of the gut microbiome into PDAC may lead to new insights into cancer treatment, prevention, and screening (169).

Oral microbiota also appear to have important roles in PDAC etiology, and may have a place in PDAC screening given the ease at which saliva samples can be obtained in the primary care setting. Periodontal disease has also been linked to PDAC risk, particularly those caused by *Porphyromonas gingivalis* (*P. gingivalis*). For example, an early study found a positive association between tooth loss and PDAC risk (170), with similar observations in periodontal disease (171). Several subsequent studies have affirmed this relationship (172), including a European study examining the relationship between serum antibodies to 25 different oral bacteria and pancreatic cancer risk. This identified found a near two-fold risk increase in patients with a high *P. gingivalis* antibody titer (173). Though the mechanisms underlying this association warrant investigation, *P. gingivalis* antibody titers may be informative in the appropriate clinical context.

There is emerging evidence that the oral microbiome may also have a role in helping to select patients for pancreatic screening. A large nested case–control study examining 361 pancreatic cancer patients and 371 matched controls found that the presence of *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* were associated with higher risk of pancreatic cancer, whereas the presence of phylum *Fusobacteria* and its genus *Leptotrichia* were associated with a decreased disease risk (174). Additionally, *Neisseria elongata* (*N. elongata*) and *Streptococcus mitis* (*S. mitis*) were found to be significantly lower in the saliva of PDAC patients than that of healthy controls (175). As the authors conclude that these two bacterial species has strong predictive value for PDAC, the relative absence of *N. elongata* and *S. mitis* warrant consideration in risk stratifying patients for early imaging (175). Additional studies have identified several other bacterial species that seem to be differentially present in the saliva of healthy controls and PDAC patients. These include bacteria belonging to the genera *Corynebacterium* and *Aggregatibacter* that are frequently reduced in PDAC patients, and *Bacteroides* and *Granulicatella adiacens* that are more represented in the saliva of PDAC patients (167). Hence, while our understanding of this topic is evolving, it is clear that the microbiome is an important and long underappreciated aspect of PDAC pathobiology that may have clinical utility in disease detection, prevention, and therapy.

4.3 - FAMILY, EDUCATION, INCOME, AND ACCESS TO CARE

As discussed, while several studies have implicated race as a risk factor for pancreatic cancer, recent evidence has also identified a variety of additional social factors that may in part explain some of these associations. A study evaluating nearly diagnosed patients found that while only 13% eventually undergo pancreatic resection, this was largely influenced by residential instability and material deprivation (176). Specifically, patients living in rural areas or urban patients with lower incomes are less likely to undergo surgical intervention, however, socio-demographic marginalization was not a predictive factor of outcomes in patients who did undergo surgical resection (176). Hence, there may be significant barriers to care that not only dictate the treatment of pancreatic cancer, but may also limit the availability to intervene with the many actionable risk factors listed above.

Finally, mental health is emerging as a potential factor in PDAC risk. Though the importance of providing appropriate mental health support has been emphasized in patients already diagnosed with PDAC, others have suggested that psychosocial distress may even play a more causative role in PDAC etiology. For instance, a 2013 study of 16,522 cases and 82,107 controls found that the loss of a child was associated with a risk increase for PDAC, particularly within the first 5 years or if losing a child to suicide (177). Hence, extreme psychosocial stress may be implicated in PDAC risk, through this warrants additional investigation, as other factors such as maladaptive coping strategies e.g. alcohol and tobacco use may confound these observations.

5 - PERSPECTIVE & FUTURE DIRECTION

In recent years, due to advances in both early detection and therapy, survival has improved for nearly all solid malignancies. However, despite significant improvement in our

understanding of pancreatic cancer pathobiology, there remain extremely limited therapeutic options for patients with advanced disease. It is now more important than ever to both identify high-risk patients for who would benefit from early imaging, as well as counsel patients to avoid key risk factors in hopes of reducing disease incidence. As the preventable risk factors for PDAC are shared with any number of other conditions, all patients can and should be counseled to make these lifestyle modifications by their primary care physicians. However, screening poses a more significant challenge, particularly as there is a lack of consensus regarding which asymptomatic patients should be evaluated for PDAC. Unlike other cancers, there is no practical test that can be used to inform these decisions. Early detection for PDAC is based almost entirely on imaging studies, which simply cannot be offered to all patients and must be reserved for those showing one or more early warning signs for PDAC.

For example, as discussed a new diagnosis of diabetes is one of the most telling early signs of disease. However, it is important to note that very few cases of diabetes will be due to an underlying etiology of PDAC. Therefore, while it is easy to recommend that all newly diagnosed diabetics be screened for PDAC, this may not be practical or feasible given the expense, particularly in low resource settings. Therefore, it is imperative to better develop a multivariate “risk signature” in order to identify the patients that would most benefit from early imaging. As demonstrated, patients who both smoke and have a family history of PDAC have a staggering 12.8 fold risk increase (Table 2). Similarly, current smokers with a diagnosis of diabetes mellitus had a 9.3 fold risk increase (Table 2). These and the many other studies described in this review clearly show that certain risk factors can synergize with others to increase the likelihood of developing PDAC. However, there is a lack of consensus regarding the combinations that are the most informative. As a result, who is screened for PDAC is left solely to the discretion of care providers, and the patients sent for imaging will vary based on provider experience, expertise, and local resources. Through more careful and rigorous analyses of the interactions between the risk factors described above, it may be possible to reach consensus regarding which patients should be screened, thereby improving outcomes through earlier detection.

6 - SUMMARY

Given the significant clinical challenge of treating late stage PDAC, it is imperative that high-risk patients be identified as early as possible in order to provide early and aggressive screening, as well as allow for appropriate intervention to support the appropriate lifestyle modifications. While many of the factors described in this review appear to have independent predictive value for PDAC risk, pancreatic cancer etiology is highly complex and involves a variety of cell types and processes. Through understanding the interactions between these many risk factors, it may be possible to better identify those with the highest risk, and improve outcomes in what is generally considered an incurable disease.

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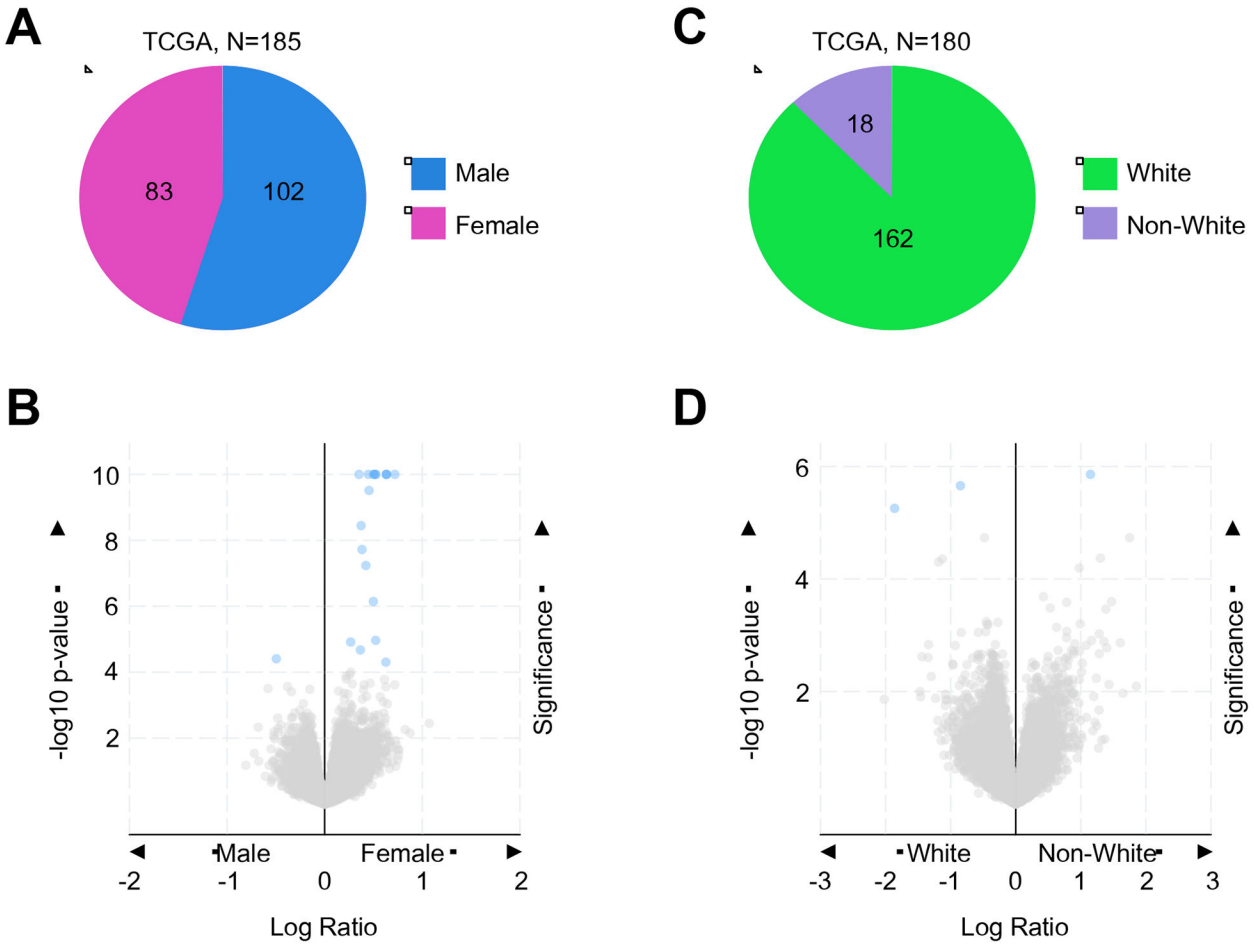

Figure 1. Differences in gene expression by sex and race in the TCGA cohort of pancreatic cancer patients

(A,B) Using the TCGA genomic databases of pancreatic cancer patients (N=185), we evaluated differences in gene expression between male (N=102) and female (N=83) patients. Differences in mRNA expression were visualized via volcano plot, and genes with significant (FDR adjusted p-value < 0.05) differences between groups colored blue. For a complete list of these genes see Table 1. **(C,D)** In the same patient cohort, we evaluated differences in gene expression based on race. Of the 180 patients for which ethnicity was documented, 162 were white, and the remaining 18 African American or Asian (non-white). Differences in mRNA expression were visualized via volcano plot, and genes with significant (FDR adjusted p-value < 0.05) differences between groups colored blue. For a complete list of these genes see Table 1.

Table 1.

Genes differentially expressed between males and females, or white and racial minority patients from the TCGA pancreatic cancer cohort

Gene	Cytoband	p-Value	q-Value	Higher Expression
EIF1AX	Xp22.12	$1.9*10^{-21}$	$2.68*10^{-17}$	Female
KDM5C	Xp11.22	$2.66*10^{-18}$	$1.88*10^{-14}$	Female
KDM6A	Xp11.3	$3.13*10^{-17}$	$1.47*10^{-13}$	Female
JPX	Xq13.2	$9.15*10^{-17}$	$3.23*10^{-13}$	Female
ZRSR2	Xp22.2	$1.49*10^{-13}$	$4.21*10^{-10}$	Female
PNPLA4	Xp22.31	$1.31*10^{-12}$	$3.09*10^{-9}$	Female
PUDP	Xp22.31	$3.7*10^{-12}$	$7.46*10^{-9}$	Female
SYAP1	Xp22.2	$1.44*10^{-11}$	$2.27*10^{-8}$	Female
ZFX	Xp22.11	$1.45*10^{-11}$	$2.27*10^{-8}$	Female
DDX3X	Xp11.4	$1.62*10^{-11}$	$2.29*10^{-8}$	Female
SMC1A	Xp11.22	$3.07*10^{-10}$	$3.94*10^{-7}$	Female
CA5BP1	Xp22.2	$3.59*10^{-09}$	$4.222*10^{-6}$	Female
FUNDC1	Xp11.3	$1.9*10^{-08}$	$2.064*10^{-5}$	Female
RPS4X	Xq13.1	$5.81*10^{-08}$	$5.86*10^{-5}$	Female
ARSD	Xp22.33	$7.17*10^{-07}$	$6.747*10^{-4}$	Female
STS	Xp22.31	$1.086*10^{-05}$	$9.58*10^{-3}$	Female
TRAPPC2	Xp22.2	$1.221*10^{-05}$	0.0101	Female
CA5B	Xp22.2	$2.114*10^{-05}$	0.0166	Female
GYG2	Xp22.33	$4.977*10^{-05}$	0.0351	Female
DDIT3	12q13.3 V	$3.913*10^{-05}$	0.0291	Male
TMC5	16p12.3	$1.381*10^{-06}$	0.0155	Non-White
LRRC37A2	17q21.31	$2.196*10^{-06}$	0.0155	White
USP32P1	17p11.2	$5.541*10^{-06}$	0.0261	White

q = FDR adjusted p-value

Table 2.

Abbreviated list of key clinical risk factors for PDAC

Risk Factor	OR	95% CI	Reference
Smoking			
Current Smoker (overall)	1.77	1.38–2.26	(54)
Current Smoker ≥30 cigarettes/day	1.75	1.27–2.42	-
Current Smoker ≥40 cigarettes/day	1.78	1.35–2.34	-
Current Smoker v. Never Smoker	2.20	1.70–2.80	(49)
Former Smoker v. Never Smoker	1.20	1.00–1.30	-
Alcohol			
1–3 drinks/week	0.78	0.58–1.05	(142)
4–20 drinks/week	0.86	0.63–1.17	-
≥21 drinks/week	1.35	0.81–2.27	-
Medical Histor			
Diabetes mellitus (≤2 years after diagnosis)	2.90	2.10–3.90	(118)
Diabetes mellitus (3–5 years after diagnosis)	1.90	1.30–2.60	-
Diabetes mellitus (6–10 years after diagnosis)	1.60	1.20–2.30	-
Diabetes mellitus (11–15 years after diagnosis)	1.30	0.90–2.00	-
Diabetes mellitus (>15 years after diagnosis)	1.40	1.00–2.00	-
Chronic pancreatitis	2.23	1.43–3.49	(178)
All pancreatitis	3.42	1.98–5.91	-
Gastric ulcer disease	1.20	1.00–1.40	(163)
H. pylori seropositive	1.38	1.08–.75	(164)
P. gingivalis antibody ≥200ng/ml	2.38	1.16–4.90	(173)
Family history of PDAC	1.76	1.19–2.61	(179)
Multivariate Risk Factors			
Non-smoker, ≥21 drinks/week	2.01	1.50–8.18	(142)
Current Smoker, ≥21 drinks/week	4.04	1.58–10.37	-
Current smoker, diabetes mellitus	9.30	2.00–44.1	(180)
Current smoker, family history of PDAC	12.8	1.60–108.9	-

OR = Odds Ration, CI = Confidence Interval