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Epidemiology and inherited predisposition for sporadic pancreatic adenocarcinoma

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I. Epidemiology for pancreatic adenocarcinoma

Descriptive Epidemiology

Although pancreatic cancer accounts for less than 3% of cancer incidence, it ranks 7th for cancer mortality globally [1] and 4th in the United States (US) [2]. Annually an estimated 338,000 and 46,420 people will be diagnosed with pancreatic cancer and 331,000 and 39,590 will die from the disease, worldwide and in the US, respectively [1, 2]. There is no effective screening test for the malignancy; therefore it is most often diagnosed at advanced stages with metastatic disease, which contributes to its high fatality with a mortality to incidence ratio of 0.98 [1]. Its five-year survival of 6.7%, which is poorer than other cancers [2]. Only 9% of pancreatic cancer cases are diagnosed with localized disease when surgical resection may be an option for a cure [3]. Those with localized disease have a 5 year survival of 25.8% [3]. More than 90% of pancreatic cancers are ductal adenocarcinomas, with neuroendocrine tumors constituting about 5% [4].

Internationally, rates of pancreatic cancer vary by 7-fold with higher rates in developed than developing countries [1]. In part the variation in incidence and mortality patterns worldwide may be explained by under ascertainment of the disease and imperfect mortality data [1]. Pancreatic cancer occurs slightly more often in men than women and in African Americans than Caucasians and other ethnicities in the US [2]. Its incidence and mortality rates increase with age. More than 88% of pancreatic cancer is diagnosed among people 55 years old or older with the median age at diagnosis 71 years old [3]. In the US, incidence and mortality rates for pancreatic cancer either decreased or remained relatively stable during the latter part of the 20th century but increased slightly since 2000 (Figure 1 and Figure 2) [5, 6].

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Given the changing demographics in the US, namely the aging population and minority distribution, one recent study has projected that the number of pancreatic cancer deaths will surpass that of breast and colorectal cancer by the year 2030 [7].

Risk Factors

Diabetes—Diabetes is associated with approximately a 2-fold risk for pancreatic cancer overall [8–10]. Excess risks tend to be particularly high (2.5 to 10-fold) for diabetes diagnosed within 5 years of pancreatic cancer diagnosis and become attenuated with long duration of diabetes [8–10]. A recent large pooled case control study showed that the association with pancreatic cancer remained significant among those having 20 years or more duration diabetes however the excess risk was diminished to 30% [10].

Biomarkers for diabetes and insulin resistance: Although diabetes as defined by fasting glucose, glucose intolerance [8] or hemoglobin A(1c) [11, 12], a marker for glucose control, have consistently been associated with pancreatic cancer in prospective epidemiologic studies, studies of other biomarkers hypothesized to mediate the diabetes-pancreatic cancer relationship have shown no association or inconsistent results (Table 1) [11–18]. Insulin is a mitogen and has growth promoting on pancreatic cancer cells and patients with type 2 diabetes exhibit hyperinsulinemia during the early stages of their disease [19]. Two studies that examined insulin and subsequent risk of pancreatic cancer showed significant elevated risks that were graded with significant trends across increasing categories of insulin. In both studies, the associations were stronger among cases occurring 10 years or more after their blood collection [12, 13]. These findings support that the positive associations observed among the later occurring cases are not the consequence of sub-clinical pancreatic cancer and that insulin resistance may play a role in pancreatic cancer etiology.

A recent nested case control study of four cohorts examined the association between 83 metabolites and pancreatic cancer [20]. The investigators observed significant positive associations between plasma branch chain amino acids (i.e. isoleucine, leucine, and valine) and subsequent risk of pancreatic cancer in both humans and in a mutant KRAS mouse model [20]. The associations were independent of body mass index (BMI) and biomarkers related to insulin resistance and diabetes. Circulating branch chain amino acids are elevated with obesity, glucose intolerance, and insulin resistance [21]. The strongest association for these metabolites in this nested case control study however was among subjects with samples collected between 2 to 5 years prior to pancreatic cancer diagnosis [20]. The investigators hypothesized that this association was explained by breakdown of tissue protein that occurs in early stage pancreatic cancer.

These studies support diabetes being an early manifestation of the malignancy, as well as, a risk factor involved in the etiology of pancreatic cancer.

Pancreatitis and Type 3c diabetes: Chronic pancreatitis is a known risk factor for pancreatic cancer with risks ranging from 2 to 3 fold [22, 23]. The risk is particularly strong for familial pancreatitis. A large pooled analysis of 10 case control studies estimated pancreatitis to account for approximately 1.34% of pancreatic cancer [22].

Type 3c diabetes (T3cDM) due to exocrine pancreatic disease has recently been recognized to play a role in pancreatic carcinogenesis [24, 25]. Type 3c diabetes is estimated to account for 5–10% of diabetes in Western populations [24]. Patients with T3cDM have pancreatic inflammation with 78% of patients having pancreatitis and 8% pancreatic cancer [24]. Although pancreatic cancer contributes to T3cDM [24], it is also plausible that the pancreatitis associated with T3cDM participates in the development of the malignancy.

Maturity Onset Diabetes of the Young: Maturity onset diabetes of the young (MODY) is estimated to account for ~1 to 5% of all diabetes [26]. Although MODY is typically diagnosis in young adults, it can be diagnosed at older ages [26]. MODY is caused by autosomal dominant gene mutations that alter islet beta-cell function [26].

Loci in genes linked to MODY have been associated with pancreatic cancer in studies utilizing genome-wide genotyping data (see section below) [27–29]. In particular, common variants in three genes HNF1A, HNF1B and PDX1 were associated with pancreatic cancer in individuals of European descent [27–29]. These genes are also important components for transcriptional networks governing embryonic pancreatic development and differentiation, in addition to maintaining pancreatic homeostasis in adults [28, 30, 31].

Antidiabetic drugs: A number of studies have examined the association between antidiabetic drugs and pancreatic cancer [10, 32, 33]. Metformin works by suppressing glucose production in the liver, so there been a particular interest in whether metformin has antitumor effects by decreasing circulating insulin concentrations [32]. In contrast to metformin, sulfonylureas lower blood glucose levels by increasing the release of insulin from the pancreas. A very large well conducted case-control study that used drug prescription and other data derived from the UK-General Practice Research Database showed that compared to those with no prior respective drug treatment, no associations were observed for metformin use while significant positive associations were observed overall long duration of sulfonylureas and insulin use as quantified by the number of recorded prescriptions [32]. The same pattern of association was observed when this analysis was restricted to participants with a history of diabetes [32]. A recent meta-analysis of clinical trials and observational studies similarly showed no association between metformin use and pancreatic cancer [33]. In contrast, a very large pooled case control study showed a significant inverse association with long duration (15 years or more) of oral antidiabetic drug use and positive association for less than 10 years duration of insulin treatment compared to their respective non-treatment groups [10]. A limitation of these studies is that the referent group for the observations studies includes participants receiving treatment of the other antidiabetic drugs, which could potentially influence the individual drug risk estimates [33].

Modifiable risk factors

Tobacco use: Current cigarette smoking is the most consistent potentially modifiable factor associated with pancreatic cancer with a close to a 2-fold elevated risk observed in most studies [34–36] and has been estimated to account for up to 24% of pancreatic cancer. Compared to never smokers, the risk starts to decrease 10 years after smoking cessation,

with the risk approaching that of never smokers 15 or more years after smoking cessation [34, 35]. Cigar and pipe smoking and smokeless tobacco are also associated with increased risk for pancreatic cancer [35] in some but not all studies [36].

Overweight and obesity: Obesity is known to contribute to insulin resistance and type 2 diabetes. Most prospective studies show positive associations between middle aged and older adult BMI and pancreatic cancer, with risk stronger among non-smokers [37, 38]. Cigarette smoke contains a multitude of carcinogens so it is possible the obesity does not play a substantial role in the etiology of pancreatic cancer in smokers. A meta-analysis of 23 prospective cohort studies, totaling 9500 cases showed that per 5 unit increase in BMI was associated with a significant 10% increase risk for pancreatic cancer [38]. There was some evidence for a non-linear relationship between BMI and pancreatic cancer with the most pronounced increased risk being among participants with a BMI > 35 kg/m² [38]. Waist circumference and waist-to-hip ratio are measures of abdominal adiposity that have consistently been associated with type 2 diabetes and are also associated with pancreatic cancer [38].

Adiposity at younger ages and across a lifetime in the same individuals and risk of pancreatic cancer has not been examined extensively. Ten studies, five case-control [39–43] and five prospective [37, 44–47], examined BMI during adolescence or early adulthood and risk of pancreatic cancer with six showing statistically significant positive associations with excess risks ranging from 20% to 2-fold [37, 39, 41, 43, 46, 47]. Three studies showed significant positive associations between adiposity in early, middle or older age in the same individuals and subsequent pancreatic cancer [37, 41, 43, 46, 47]. One very large prospective study of AARP members indicated longer duration of overweight was significantly associated with pancreatic cancer such that for every 10 years of having a BMI > 25 kg/m², pancreatic cancer risk increased 6% overall and 18% among those diagnosed with diabetes [47]. The association was not as strong among participants without diabetes [47]. This pattern of association with long duration of adiposity and diabetes supports the notion that diabetes may be on the causal pathway between obesity and pancreatic cancer. The proportion of pancreatic cancer explained by ever being overweight or obese at any age was substantial in the AARP population, 14% overall and 21% never smokers [47].

Although weight change has inconsistently been associated with pancreatic cancer [48], one pooled study of 14 cohorts showed that compared to subjects that maintained their BMI during from early adulthood to older age, those who gained more than 10 kg/m² had a significantly elevated risk of pancreatic cancer [37]. The NIH-AARP study showed an association for BMI gain more than 10 kg/m² after age 50 years was associated with pancreatic cancer but not gain earlier in life [47]. A weight gain of 10 kg/m² corresponds to a rise from normal weight to obese.

Maintaining a normal BMI and avoiding adiposity at any age may prevent pancreatic cancer.

Dietary exposures: Pancreatic cancer's low incidence and rapid fatality have made it difficult for epidemiologists to examine dietary risk factors. Pancreatic cancer cases often have gastrointestinal problems, weight loss, or diabetes prior to being diagnosed due to sub-

clinical cancer which can influence dietary intake and related biomarkers. Retrospective ascertainment of diet for this cancer site in particular may have biases including control selection, recall, and proxy reporting that can result in inaccurate risk estimates. Prospective studies are less likely subject to these methodological problems. Dietary exposures are also subject to measurement error. Recent large prospective studies, including pooled efforts that harmonize data, have provided adequately powered analyses to detect small magnitudes of risk that are typical of nutritional exposures.

Among dietary exposures, coffee consumption is consistently not associated with pancreatic cancer [49]. There is suggestive evidence for heavy alcohol use (> 3 drinks per day), and high red meat, total and saturated fat, and fructose intake playing a role in pancreatic cancer [49]. Some but not all studies have shown protective associations between healthier lifestyle and dietary patterns and pancreatic cancer [50–53].

Heavy alcohol use is the most common cause of both acute and chronic pancreatitis and high levels of alcohol use could plausibly contribute to pancreatic cancer development via pancreatitis. Recent large studies have observed 35 to 80% increased risk between heavy alcohol use and pancreatic cancer [54–57]. Individual who are heavy drinkers often tend to also smoke cigarettes and there is a concern about residual confounding by smoking. One large prospective study with more than 6500 cases that occurred over 24 years showed a significant increased pancreatic cancer risk for participants who consumed more than 3 drinks per day compared to non-drinkers with the association remaining significant in never smokers [55].

Several nested case-control studies that examined the association between vitamin D status and subsequent pancreatic cancer have shown varying results [58–61]. 25-hydroxyvitamin D (25(OH)D) is the best measure of vitamin D exposure as it represent that from both the diet and that synthesized endogenously from solar UVB light exposure. A large pooled analysis of eight cohorts showed a statistically significant 2-fold increase risk among participants with circulating 25(OH)D concentrations > 100 nmol/L compared to those with concentrations of 50 to 75 nmol/L and no association for concentrations < 50 nmol/L [60]. A subsequent pooled study using comparable clinically relevant 25(OH)D cut-points and referent category, observed a statistically significant 40% increased risk for participants with concentrations 37.5 to < 50 nmol/L but did not observe associations for participants with concentrations below 37.5 nmol/L or 75 nmol/L and above [61].

Other nutrition related exposures such as glycemic load and index, total carbohydrate, sucrose, fiber, folate, vitamin C, vitamin E, sweetened beverage, soft drink, and cholesterol intake, and folate and multivitamin supplement use, and physical activity are not consistently associated with pancreatic cancer [49].

II. Inherited predisposition for sporadic pancreatic adenocarcinoma

Common low risk pancreatic cancer susceptibility loci

The first pancreatic cancer Genome Wide Association studies (GWAS) were performed by the Pancreatic Cancer Cohort Consortium and the Pancreatic Cancer Case Control

Consortium (PanC4) with the aim of identifying common susceptibility markers for this deadly disease. Three phases of the GWAS have been reported, PanScan I in 2009, PanScan II in 2010 and PanScan III in 2014 [62–64]. The first two phases consisted of twelve case-control studies nested within prospective cohort studies and eight case-control studies. The total number of subjects included 3,851 patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) and 3,934 control subjects of European ancestry [62, 63]. Combined analysis identified four genome wide significant pancreatic cancer risk loci at chromosomes 9q34.2 (in the *ABO* blood group gene), 1q32.1 (*NR5A2*), 5p15.33 (*CLPTM1L–TERT* gene region) and 13q22.1 (non-genic). The third phase of PanScan (PanScan III) added 1,582 newly genotyped pancreatic cancer cases and 5,203 control subjects; five new cohort studies, two new case-series and one case-control study were included. Replication was mainly performed in samples from the PANDoRA consortium [65] resulting in a grand total of 7,683 cases and 14,397 control subjects [64]. Figure 3 depicts our current knowledge of the landscape of common and rare pancreatic risk variants identified through the GWAS approach as well as through linkage analysis of familial cancer syndromes and sequencing approaches.

The protective allele of the most significant SNP on 9q34.2 in the *ABO* gene (rs505922, $OR=1.20$, $P=5.4\times10^{-8}$) is in complete linkage disequilibrium (LD) with the O allele of the *ABO* locus ($r^2=1$). The *ABO* gene encodes a glycosyltransferase (Histo-blood group ABO system transferase) that catalyzes the transfer of carbohydrates to the H antigen, thereby forming the A, B and O blood group proteins as described initially by Karl Landsteiner in 1900. A set of small studies published over 50 years ago reported an association between ABO blood type and gastrointestinal cancers [66, 67]. The discovery of the ABO risk locus reawakened interest in the connection between blood groups and pancreatic cancer. Using PanScan GWAS data, individual ABO alleles were inferred and their association with pancreatic cancer risk determined showing that individuals with inferred A ($OR=1.38$), AB ($OR=1.47$) and B ($OR=1.53$) blood groups had an increased risk of pancreatic cancer as compared to the O group [68]. The fact that the A1 alleles conferred an increased risk of pancreatic cancer ($OR=1.38$, 95% CI 1.20–1.58), whereas A2 alleles did not furthermore indicated that increased glycosyltransferase activity of the former, either towards the H antigen or other proteins, might explain the risk [69] [70]. Since the PanScan GWAS report linking ABO blood groups and risk of pancreatic cancer was published in 2009, numerous studies have investigated the association of blood groups with cancer risk; the most consistently significant findings are for gastric and pancreatic cancer [71–74].

The most significant SNP on chr1q32.1 (rs3790844, $OR=0.77$, $P=2.5\times10^{-10}$) maps to the first intron of the *NR5A2* gene. This gene encodes nuclear receptor subfamily 5 group A member 2 (*NR5A2*, also referred to as liver receptor homolog-1 or LRH-1), a transcription factor that plays an important roles in early development, cholesterol synthesis, bile acid homeostasis, steroidogenesis and in regulating stemness [75–77]. *NR5A2* is furthermore an important regulator of exocrine pancreatic function in the adult pancreas, where it cooperates with pancreas-specific transcription factor 1 (PTF1) to directly bind and activate a series of acinar specific genes [78]. *NR5A2* is required for early embryonic development and mice that lack both copies of *Nr5a2* die at embryonic day 7 [79]. Heterozygous *NR5A2*

mice are viable but exhibit increased rates of pancreatic acinar to ductal metaplasia (ADM) and impaired recovery after chemically induced acute pancreatitis [80]. Furthermore, *NR5A2* haploinsufficiency cooperates with pancreatitis in a pancreatic cancer mouse model driven by oncogenic *KRAS*, increasing the number of preneoplastic PanIN (Pancreatic Intraepithelial Neoplasia) lesions and driving their progression toward PDAC [80]. Likewise, in mouse models, the induction of pancreatitis leads to a transient down regulation of multiple acinar and endocrine genes (including *NR5A2*, *HNFI1A* and *PDX1*) and increased acinar cell proliferation [81]. Thus, reduced expression of *NR5A2* and other acinar genes may contribute to increased proliferation and faster progression of PanINs in mouse pancreatic cancer models. Although the mechanism by which variants on chr1q32.1 mediate risk of pancreatic cancer is not clear, this may be related to effects on regulation of *NR5A2* gene expression and consequent effects on cell growth, especially in the presence of inflammatory conditions of the pancreas.

Two independent pancreatic cancer risk loci have been identified in the *TERT-CLPTMIL* gene region on chr5p15.33. This multi-cancer locus has been associated with lung, bladder, prostate, breast, melanoma, glioma, ovarian, melanoma, testicular, basal cell skin cancer and chronic lymphocytic leukemia, intriguingly, with the same alleles showing increased risk for some cancers but decreased risk of other cancer types [82–94]. *TERT* encodes the catalytic subunit of telomerase, well known for its essential role in maintaining telomere ends and increased telomerase activity often seen in human cancers [95–97]. Telomerase also has telomere-independent functions including in the regulation of gene expression, cell survival, epithelial to mesenchymal transition (EMT) and mitochondrial function [98]. The cleft lip and palate associated transmembrane 1 like protein (CLPTMIL), appears to be a survival factor in lung cancer where it protects cells from apoptosis after treatment with DNA damaging agents [99, 100]. It has also been shown to induce cell growth and rates of aneuploidy in pancreatic cell lines and it is overexpressed in pancreatic tumors [101]. The first pancreatic cancer signal (from PanScan II) was tagged by an intronic SNP (rs401681, OR=1.19, $P=3.7\times10^{-7}$) in *CLPTMIL* [63]. A second independent signal was identified in PanScan III, marked by a synonymous SNP in the second exon of *TERT* (rs2736098, OR=0.80, $P=9.8\times10^{-14}$) [64]. Both SNPs were also identified in a subset based meta-analysis of multiple cancer types in which pancreatic cancer contributed to risk in six independent loci [102] indicating that approaches leveling other cancer phenotypes can be useful to identify additional pancreatic cancer susceptibility variants in multi-cancer risk loci. The synonymous SNP in *TERT*, and several correlated variants, have been associated with telomere length in white blood cells and with *TERT* promoter activity *in vitro* [88, 103, 104].

On chr13q22.1, the top ranked GWAS SNP (rs9543325, OR=1.26, $P=3.27\times10^{-11}$), lies in a 600 kb non-genic region [63] suggesting that the functional variant could impact gene expression at great distance through intra- or inter-chromosomal interactions. The chr13q22.1 risk locus is flanked by two genes encoding transcription factors of the Kruppel-like family: *KLF5* and *KLF12*; both encode proteins that regulate cell growth and transformation [105–107]. Furthermore, *KLF5* is upregulated in pancreatic cancer [108].

Additional genes, either nearby or at a greater distance could be functionally relevant to the mechanism by which the chr13q22.1 GWAS locus confers risk of PDAC.

A second independent signal was identified on chr13 in PanScan III, on 13q12.2 (rs9581943, OR=1.15 $P=2.4\times 10^{-9}$). The top ranked SNP is located in the promoter of the *PDX1* (pancreatic and duodenal homeobox 1 protein 1) gene and is also intronic to *PDX1-AS1* (*PDX1* antisense RNA 1), a noncoding RNA with unknown function. *PDX1* plays a critical role in early pancreatic development, as well as the differentiation of exocrine pancreas, and regulates beta-cell function in the mature pancreas [109, 110]. Mutations in this gene have been linked to agenesis of the pancreas [109] and maturity onset diabetes of the young (MODY) [111]. Furthermore, *PDX1* has been implicated in glucose-dependent regulation of insulin gene transcription [112],

The signal on 7q32.3 (rs6971499, OR=0.79, $P=3.0\times 10^{-12}$) lies in an intron of the *LINC-PINT*, gene, a p53-induced long intergenic noncoding RNA. This SNP is also located between two additional plausible candidate genes, *MKLN1*, encoding Muskeln 1, a mediator of cellular responses to the extracellular matrix, and, *KLF14*, which encodes a member of the Kruppel-like family of transcription factors, which have been implicated as tumor suppressors [113, 114]. *KLF14* has also been identified as a regulator of several metabolic phenotypes, including type 2 diabetes [115].

A synonymous SNP residing in the last exon of *BCAR1* (also known as p130Cas) was noted on 16q23.1 (rs7190458, OR=1.46, $P=1.1\times 10^{-10}$). *BCAR1* functions as an adaptor protein that coordinates cell cycle control, cytoskeleton organization, and cell migration and whose aberrant expression has been linked to transformation and progression of multiple cancer types, and [116, 117]. Two chymotrypsinogen genes, *CTRB1* and *CTRB2* are also located close to this SNP (5kb and 23kb, respectively) and as important members of a family of serine proteases that are secreted by the pancreas into the gastrointestinal tract are plausible target genes for susceptibility variants at this locus [118].

The most significant SNP at 22q12.1, (rs16986825, OR=1.18 $P=1.2\times 10^{-8}$), is intronic in the zinc and ring finger 3 (*ZNRF3*) gene, which encodes a transmembrane E3 ubiquitin protein ligase that negatively regulates the Wnt signaling pathway [119]. Although located 162 kb centromeric to the most notable SNP in this locus, *CHEK2* encodes a cell-cycle checkpoint kinase that cooperates with p53, BRCA1 and ATM in response to DNA damage and may therefore represent a candidate gene worthy further follow-up [120, 121]. Finally, a near-GWAS significant risk locus was identified in the well-known multi-cancer risk locus on 8q24.21 (rs1561927, OR=0.87, $P=1.3\times 10^{-7}$). The closest genes are located 400–800 kb centromeric to this SNP: *MIR1208*, *PVT1*, and *MYC*. Chromosome 8q24.21 is known to contain multiple cancer susceptibility loci that span over 2Mb [122, 123] but most are located far away from this SNP, with low LD and are therefore not likely to represent the same signal. The highest LD is with a SNP that is 24 kb upstream and reported to be associated with ovarian cancer risk (rs10088218, $r^2=0.37$ in 1000G CEU data) [124].

Common pancreatic cancer risk loci in non-European populations

In addition to PanScan, in which the majority of subjects were of European ancestry, GWAS have now been performed in case-control studies from China and Japan. A Japanese GWAS of 991 advanced pancreatic ductal adenocarcinoma cases and 5,209 control subjects reported three GWAS significant loci on chromosomes 6p25.3/*FOXQ1* (rs9502893: OR=1.29, $P=3.30 \times 10^{-7}$), 7q36.2/*DPP6* (rs6464375: OR_{Recessive}=3.73, $P=4.4 \times 10^{-7}$), and 12p11.21/*BICD1* (rs708224: OR=1.32, $P=3.3 \times 10^{-7}$) [125]. Furthermore, a two phased GWAS with a combined set of 3,584 pancreatic cancer cases and 4,868 control subjects from China (ChinaPC) identified five risk loci on chr5p13.1/*DAB2* (rs2255280: OR= 0.81, $P=4.18 \times 10^{-10}$), chr10q26.11/*PRLHR* (rs12413624: OR=1.23, $P=5.12 \times 10^{-11}$), chr21q21.3/*BACH1* (rs372883: OR=0.79 $P=2.24 \times 10^{-13}$), chr21q22.3/*TFF1* (rs1547374: OR=0.79, $P=3.71 \times 10^{-13}$), and chr22q13.32/*FAM19A5* (rs5768709: OR=1.25, $P=1.41 \times 10^{-10}$) [126]. Both the Chinese and Japanese GWAS scans replicated the chr13q22.1 locus initially discovered in PanScan, and noted the risk locus on chr1q32.1, albeit with less significance. Chromosome chr5p15.33 was only noted in the Chinese scan (rs401681, $P=7.35 \times 10^{-5}$) and 9q34.2 (rs505922) only in the Japanese scan.

Assessment of the Chinese and Japanese pancreatic cancer risk loci in the European PANcreatic Disease ReseArch (PANDORA) case-control consortium and in PanScan III did not replicate any of the pancreatic cancer susceptibility loci identified in Asians [64, 127].

Pathway analyses of pancreatic cancer GWAS datasets

Pathway based analyses of GWAS data have been used to mine PanScan I and II data to identify genes, or groups of genes, enriched with variants whose individual effects may be too small to be detected in the GWAS [62, 63]. These approaches have highlighted pancreatic development genes such as *HNF1A*, *HNF4G*, *HNF1B* and *PDX1* [27, 28] that encode important components of the transcriptional networks that govern embryonic development of the pancreas, and maintain homeostasis in adults [30, 31]. In addition, mutations in *HNF1A*, *PDX1*, and *HNF1B* are responsible for maturity onset diabetes of the young (MODY) [128–130] and common variants in *HNF1A* and *HNF1B* have been associated with risk of type II diabetes [131–133]. Interestingly, with the added numbers of cases and controls in the third phase of PanScan as compared to the first two phases, the significance of two of these genes (*PDX1* and *HNF1A*) improved markedly, indicating that pathway analysis can be a useful approach to tease out additional genes that influence risk of disease. These results furthermore suggest possible functional inter-relationships between inherited variation in genes important for pancreatic development, diabetes and cancer risk.

Functional understanding of common pancreatic cancer risk loci

As germline variants discovered in GWAS are usually non protein coding, and in most cases not the functional variants themselves. Much work is needed after GWAS to uncover the biological mechanism of the risk. Fine-mapping efforts followed by genomic and functional analysis of multiple highly correlated tag SNPs are the next steps after a GWAS identifies a risk locus for a specific disease or trait. These efforts involve genomic and functional approaches such as investigating gene expression levels, splicing, promoter or enhancer strength, DNA methylation, protein to DNA binding, and chromosome conformation, in

order to link risk genotypes to differences in specific molecular phenotypes to establish the underlying mechanism at each locus.

Future gene mapping approaches

GWAS has already yielded valuable insights into the etiology of pancreatic cancer. Although functional explanation of these loci is in its early stages, the results implicate genes that mediate diverse functions ranging from pancreatic development (*NR5A2*, *PDX1*), exocrine glandular function (*CTRB1/2*), endocrine function (*PDX1*, *HNF1A*) and blood groups/glycosylation (*ABO*). As compared to more common cancers, the GWAS approach is still at a relatively early stage for pancreatic cancer, and more findings can be expected as sample sets increase and additional populations are analyzed. For breast [134] and prostate cancer [135], GWAS have already led to the identification of 67 and 100 risk loci, respectively. Altogether, these loci explain approximately 33% of the familial risk of prostate cancer and 28% for breast cancer in European populations. For pancreatic cancer, 18 risk loci have been identified to date through GWAS (in European and Asian populations) albeit with limited replication between European and Asian populations. Imputation and meta-analyses of existing and new GWAS datasets are bound to uncover even more loci. Efforts in pancreatic cancer GWAS studies outside of main effects are likely to expand by investigations of susceptibility variants for survival, pharmacologic responses as well as gene-gene and gene-environmental interactions [136–138]. However, as for other diseases, susceptibility loci identified through GWAS may not explain the majority of inherited risk for pancreatic cancer. With the emergence of next-generation sequencing, these efforts will grow in use for gene mapping. The recent identification of mutations in the *ATM* and *PALB2* genes in pancreatic cancer kindreds with unknown etiology nicely demonstrated this use of next-generation sequencing [139, 140]. Exome (ES) and whole genome (WGS) sequencing studies are likely to also be undertaken in sporadic cases, and in cases with specific phenotypes such as an early age of onset, and epidemiologic risk factors (e.g. BMI, smoking, pancreatitis). As population based sequencing studies have already shown, the number of uncommon and rare polymorphic variants in the human genome is very high [141], and may explain a substantial portion of germline risk for disease. High throughput sequencing approaches will furthermore enable the assessment of variants not captured on GWAS platforms, such as indels and copy number variants.

Summary

Given the changing demographics of western populations, the numbers of pancreatic cancer cases are projected to increase during the next decade [7]. Diabetes, recent cigarette smoking and excess body weight are the most consistent risk factors for pancreatic cancer [49]. The diabetes associated with pancreatic cancer may have more heterogeneity than previously appreciated. In addition to Type 2 diabetes, Type 3c diabetes related to exocrine pancreatic disease and common loci in genes related to *MODY* may contribute to the association between diabetes and pancreatic cancer [24, 25, 27–29]. Chronic pancreatitis is also associated with pancreatic cancer but accounts for a small proportion of the disease [22, 23]. Coffee consumption is not associated with pancreatic cancer while there is suggestive evidence for heavy alcohol use (> 3 drinks per day), and high red meat, total fat and

saturated fat, and fructose intake as risk factors [49]. Other nutrition related factors and antidiabetic drugs are not consistently associated with pancreatic cancer [10, 32, 33, 49].

A small proportion of the familial aggregation of pancreatic cancer can be explained by hereditary cancer syndromes and inherited forms of pancreatitis, caused by rare high-risk inherited mutations [139, 142–149]. However, the genetic basis for the majority of familial aggregation of pancreatic cancer has yet to be explained. The search for common and rare germline variants that influence risk of pancreatic cancer through genome-wide association studies (GWAS) and high throughput sequencing based studies is underway, and holds the promise of increasing our knowledge of variants and genes that play a role in inherited susceptibility of this devastating disease.

Although research gaps remain, the research reported in this review has advanced our understanding of pancreatic cancer. Understanding the etiology of pancreatic cancer and identifying modifiable factors may reduce the burden of this highly fatal disease. In addition, the need for translational research to improve prognostic and therapeutic modalities is urgent.

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Key Points

Given the changing demographics of western populations, the numbers of pancreatic cancer cases are projected to increase during the next decade. Diabetes, recent cigarette smoking, and excess body weight are the cancer's most consistent risk factors. The search for common and rare germline variants that influence risk of pancreatic cancer through genome-wide association studies and high throughput sequencing based studies is underway, and holds the promise of increasing our knowledge of variants and genes that play a role in inherited susceptibility of this devastating disease. Although research gaps remain, research reported in this review has advanced our understanding of pancreatic cancer.

Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 13 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.1.0, April 2014, National Cancer Institute.

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Figure 1.

Incidence rates for pancreatic cancer in the United States overall and by sex and race, 1992 to 2011

Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics. <http://seer.cancer.gov/faststats>

Figure 2.

Mortality rates for pancreatic cancer in the United States overall and by sex and race, 1992 to 2011

Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics. <http://seer.cancer.gov/faststats>

Figure 3.

The current landscape of inherited pancreatic cancer risk variants. Allele frequencies ranging from rare to common are shown on x-axis, and effect sizes ranging from low to high on the y-axis. The clusters represent genes with germline mutations identified through linkage, candidate gene and sequencing approaches (top left and middle) and chromosomal band locations of common susceptibility loci identified through GWAS (lower right). Genes that are mutated as part of multi cancer syndromes are listed in black, genes that influence hereditary pancreatitis are listed in green. Risk loci that are discussed in this chapter are shown in the lower right hand part of the figure and colored according to PanScan GWAS phase they were identified: PanScan I (blue), PanScan II (red) and PanScan III (purple). GWAS loci from non-European populations were not included in the figure. Figure layout was adapted from Manolio T. *et.al*, *Nature* 2009

Table 1

Prediagnostic diabetes or inflammation-related biomarkers measured in peripheral blood and pancreatic cancer risk

Biomarker	Number of studies	Association for higher compared to lower concentration^I
HbA(1c) [11, 12]	2	↑↑
Insulin [12, 13] or proinsulin [12]	2	↑↑ overall, stronger among cases occurring > 10 years after blood collection
C-peptide [11, 150]	2	↑↑ but not significant
Adiponectin (high) [18, 151, 152]	3	↓↓ null
IGF-1, IGFBP-3 [14, 153–155]	4	null
IGFBP-1 (low) [156]	1	↑
IGF-2 [14]	1	null
sRAGE [16, 17]	2	↓ null
CML-AGE [16, 17]	2	null
C-reactive protein [15, 157, 158]	4	null or ↓ in male smokers
IL6, sTNF-R1, sTNF-R2 [157, 158]	2	null, (↑sTNF-R1 but not significant in women only)
TGF-B [159]	1	↑ among cases occurring > 10 years after blood collection

^I each arrow or null represents one study