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Genetic Susceptibility to Pancreatic Cancer

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Abstract

Pancreatic cancer is the fourth leading cause of cancer death in both men and women in the United States. However, it has the poorest prognosis of any major tumor type, with a 5-yr survival rate of approximately 5%. Cigarette smoking, increased body mass index, heavy alcohol consumption, and a diagnosis of diabetes mellitus have all been demonstrated to increase risk of pancreatic cancer. A family history of pancreatic cancer has also been associated with increased risk suggesting inherited genetic factors also play an important role, with approximately 5–10% of pancreatic cancer patients reporting family history of pancreatic cancer. While the genetic basis for the majority of the familial clustering of pancreatic cancer remains unclear, several important pancreatic cancer genes have been identified. These consist of high penetrance genes including *BRCA2* or *PALB2*, to more common genetic variation associated with a modest increase risk of pancreatic cancer such as genetic variation at the *ABO* blood group locus. Recent advances in genotyping and genetic sequencing have accelerated the rate at which novel pancreatic cancer susceptibility genes have been identified with several genes identified within the past few years. This review addresses our current understanding of the familial aggregation of pancreatic cancer, established pancreatic cancer susceptibility genes and how this knowledge informs risk assessment and screening for high-risk families.

Keywords

pancreatic cancer; genetics; familial cancer

INTRODUCTION

There will be an estimated 43,140 new cases of pancreatic cancer diagnosed in the United States in 2010 and 36,800 deaths [1]. In the United States, the age-adjusted incidence of pancreatic cancer is 13.5 per 100,000 for white males and 10.5 per 100,000 for white females. Risk is higher in blacks 17.1 per 100,000 and 14.8 per 100,000 in males and females, respectively [2]. Approximately, 80% of pancreatic cancer has metastasized at diagnosis and 5-yr survival rate is <5% [1]. Cigarette smoking, increased body mass index, heavy alcohol consumption, and a diagnosis of diabetes mellitus have been associated with increased pancreatic cancer risk [3–9]. Active cigarette smoking has been shown to be associated with a 1.74-fold increased risk (95% CI = 1.61–1.87) [4]. However, risk

decreases in former smokers 1.2-fold (95% CI = 1.11–1.29) and no evidence of increased risk is observed 20 yr after smoking cessation [4]. Type 2 diabetes has also been associated with an increased risk of pancreatic cancer, overall odds ratio (OR) = 1.8 (95% CI = 1.5–2.1) compared with non-diabetics. Risk is highest in new onset diabetics (duration <2 yr before diagnosis) OR = 2.9 (95% CI = 2.1–3.9) and decreases with duration of diabetes OR = 1.4 (95% CI = 1.0–2.0) for diagnosis more than 15 yr before pancreatic cancer diagnosis [10]. Approximately 1% of new onset diabetics develop pancreatic cancer within 3 yr of their diabetes diagnosis [11]. Risk of pancreatic cancer increases with increasing body mass index OR = 1.55 (95% CI = 1.16–2.07) for individuals with BMI >35 compared to individuals with BMI of 18.9–24.9 [7]. Heavy alcohol consumption (≥6 drinks per day) has also been associated with increased pancreatic cancer risk OR = 1.46 (95% CI = 1.16–1.83) compared with individuals who drank <1 drink per day [12].

Inherited genetic factors also play an important role in pancreatic cancer risk. Pancreatic cancer, like all cancers is a fundamentally genetic disease caused by both inherited and acquired genetic mutations. Inherited genetic variation plays an important role in both the familial and non-familial (sporadic) occurrences of pancreatic cancer. It is estimated that 5–10% of pancreatic cancer patients have a family history of pancreatic cancer [13,14]. While the genetic mutations responsible for the majority of the clustering of pancreatic cancer in families have yet to be identified, several pancreatic cancer genes have been established, including both high-penetrance genes such as *BRCA2* [15], *STK11* [16], *p16/CDKN2* [17], and *PALB2* [18] and low-penetrance genes such as the *ABO* blood group locus [19]. The goal of this review is to provide an understanding of the importance of the clustering of pancreatic cancer, as well as other cancers, in families and genes that have been associated with an increased risk of pancreatic cancer.

FAMILIAL AGGREGATION OF PANCREATIC CANCER

The first studies to suggest that pancreatic cancer has an inherited genetic component were case reports of families in which there were multiple cases of pancreatic cancer [20]. Observational epidemiological studies including, case-control and cohort studies have demonstrated that individuals with a family history of pancreatic cancer are at an increased risk of developing pancreatic cancer themselves. Overall, case-control studies have estimated the odds of having a family history of pancreatic cancer are 1.9- to 13-fold higher in pancreatic cancer patients compared with healthy controls [21,22]. One of the larger studies of 484 pancreatic cancer cases and 2,099 controls, ascertained through population-based registries in three regions of the USA (Atlanta, Detroit, and New Jersey), found pancreatic cancer patients reported a first-degree relative with pancreatic cancer more often than controls OR = 3.2 (95% CI = 1.8–5.6), and the risk was higher OR = 3.6 (95% CI = 1.5–8.7) among those with an affected sibling compared to those with an affected parent OR = 2.6 (95% CI 1.2–5.4) [23]. A recent pooled analysis of data from 5 cohort and one case-control study estimated the odds of pancreatic cancer to be 1.76 higher (95% CI = 1.19–2.61) among individuals with at least one first-degree relative with pancreatic cancer compared to those without a family history of pancreatic cancer [21]. Risk was even higher in individuals with two or more first-degree relatives with pancreatic cancer, OR 4.26 (95% CI = 0.48–37.79) [21]. Prospective studies from the National Familial Pancreatic Tumor Registry (NFPTR, www.NFPTR.org) have demonstrated that incidence of pancreatic cancer is greater in children, parents and siblings of patients with familial pancreatic cancer (defined as a pair of first-degree relatives in the kindred with pancreatic cancer), standardized incidence ratio (SIR) 6.79, 95% CI 4.54–9.75, as compared to children, parents and siblings of patients with sporadic pancreatic cancer (families without a pair of first-degree relatives with pancreatic cancer), SIR = 2.41, (95% CI = 1.04–4.74).

Several studies have examined if the risk of pancreatic cancer varies by age of onset of pancreatic cancer in the family, however, these studies have yielded inconsistent results, with some studies shown no association between age-of-onset and risk while others showing that the age-of-onset of pancreatic cancer may be slightly younger in patient with a family history. In a series of patients reported by James et al. 36.7% of patients with a family history of pancreatic cancer developed disease before the age of 50 compared with 18.3% of sporadic pancreatic cancer patients ($P < 0.017$). Conversely, several case-control studies have demonstrated that the age-of-onset of pancreatic cancer in the proband was not associated with having a family history of pancreatic cancer [23,24]. The PacGENE consortium, a consortia of familial pancreatic cancer registries compared the mean age-at-onset of 466 familial pancreatic cancer probands (64.1 ± 11.8 yr) and 670 affected relatives (65.4 ± 11.6 yr) to that in the general US SEER population (70.0 ± 12.1 yr, $P < 0.001$, for both groups). However, a portion of this difference may reflect ascertainment bias because families self-enroll in these high-risk family registries. Prospective data from the NFPTR, demonstrated that having a young-onset patient (<50 yr) in the family did not alter the risk of pancreatic cancer for sporadic pancreatic cancer kindred members, however, pancreatic cancer risk was higher among members of familial pancreatic cancer kindreds with a young-onset case (<50) in the kindred SIR = 9.31 (95% CI = 3.42–20.28) than those without a young-onset case in the kindred SIR 6.34 = (95% CI = 4.02–9.51) [25].

Segregation analysis provided statistical evidence that there is a major gene(s) responsible for the clustering of pancreatic cancer in families. Analysis of 287 pancreatic cancer families ascertained through a Johns Hopkins Hospital index case estimated that 6/1,000 individuals were estimated to carry a high-risk pancreatic cancer genotype and the lifetime risk of pancreatic cancer (age 85) was 32% [26].

In addition to the clustering of pancreatic cancer within a family, co-aggregation in families of cancers at other sites along with pancreatic cancer suggests the presence of a predisposition gene that is responsible for a cancer syndrome. Analysis of data from several large cohort studies and the Mayo clinic case-control study estimated odds of prostate cancer (OR 1.45, 95% CI 1.12–1.89) was higher among individuals with a family history of pancreatic cancer [21]. In addition, data from a large series of pancreatic cancer patients at the Mayo clinic suggested the relatives of pancreatic cancer patients were at an increased risk of liver carcinoma (SIR = 2.70, 95% CI = 1.51–4.46). Cote et al. reported an excess risk of lymphoma (OR = 2.83, 95% CI = 1.02–7.86) in the relatives of 247 pancreatic cancer patients compared to that in 420 controls. Data from the NFPTR at Johns Hopkins supported the finding of an increased risk of colon cancer among the relatives of young onset ($<age$ 50) pancreatic cancer probands, weighted standardized mortality ratio (wSMR) = 2.31 95% CI = 1.30–3.81. In addition, they reported that relatives of young onset pancreatic cancer patients were at higher risk of dying from cancers of the breast (wSMR = 1.98, 95% CI = 1.01–3.52), and prostate (wSMR = 2.31, 95% CI = 1.14–4.20). Additionally, in the NFPTR the relatives of familial pancreatic cancer probands had a significantly increased risk of dying from breast (wSMR 1.66, 95% CI 1.15–2.34), ovarian (wSMR = 2.05, 95% CI 1.10–3.49), and bile duct cancers (wSMR = 2.89, 95% CI 1.04–6.39), whereas the relatives of sporadic probands were at increased risk of dying from bile duct cancer (wSMR = 3.01, 95% CI 1.09–6.67) [27].

PANCREATIC CANCER SUSCEPTIBILITY GENES

While the genetic basis of the majority of the familial clustering of pancreatic cancer has yet to be elucidated, several important pancreatic cancer susceptibility genes have been identified. Recent advances in genome sequencing and array genotyping have accelerated the pace at which new pancreatic cancer susceptibility genes are being identified and have

lead to the discovery of several new pancreatic cancer genes in the past 2 years and ongoing studies using these new methods are likely to identify many more pancreatic cancer genes in the coming years.

There is a wide spectrum of genetic variation involved in pancreatic cancer. This is similar to what is observed for most complex diseases (diseases due to both environmental and genetic basis). On one end of the spectrum is rare genetic variation that is often associated with a very high lifetime risk of developing diseases, high penetrance genes. On the opposite end of the spectrum is common genetic variation that typically confers only a minor or modest increase risk of disease, low penetrance genes. Genome-wide association studies in which the prevalence of common genetic variants is compared among cases and controls have great potential to identify these common genetic changes associated with pancreatic cancer risk. Conversely, family-based studies using linkage or genome-sequencing approaches are better suited to the identification of rare high penetrance genes. A list of established pancreatic cancer susceptibility genes is presented in Table 1.

HIGH PENETRANCE GENES

BRCA2

Mutations in the *BRCA2* have been shown to be associated with an increased risk of breast, ovarian, prostate, and pancreatic cancer. Analysis of a large series of *BRCA2* mutation positive families ascertained for young onset breast and/or ovarian cancer estimated that *BRCA2* mutations carriers have a 3.5-fold (95% CI 1.9–6.6) increased risk of pancreatic cancer compared with non-carriers [28]. Several studies have estimated the prevalence of mutations in the *BRCA2* gene among pancreatic cancer patients. The first report of mutation in the *BRCA2* gene among patients with pancreatic cancer was by Goggins et al. who reported that 7% (4/41) Johns Hopkins Hospital surgical patients with adenocarcinomas of the pancreas were found to have a germline deleterious mutation in the *BRCA2* gene [29]. Subsequent studies indicate the prevalence of *BRCA2* mutations in unselected pancreatic cancer patients may in fact be lower, ranging up to 4% among pancreatic cancer patients of Ashkenazi Jewish descent [30]. However, the prevalence of mutations may be significantly higher among individuals with a family history of pancreatic cancer. Murphy et al. [15] reported that 16% of patients with familial pancreatic cancer from kindreds where there were 3 or more pancreatic cancers harbor germline mutations in *BRCA2*. Similarly, Hahn et al. reported 12% of patients from familial pancreatic cancer kindreds had deleterious *BRCA2* mutations and Couch et al. reported a large series of 180 pancreatic cancer patients who reported pancreatic cancer in a first- or second-degree relative identified 10 (6%) germline deleterious *BRCA2* mutations. Of note, not all pancreatic cancer families with germline *BRCA2* mutations also report a family history of breast and/or ovarian cancer and some sporadic pancreatic cancer kindreds with germline *BRCA2* defects report no family cancer history at all.

PALB2

Mutations in the *PALB2* gene, partner and localizer of *BRCA2*, have been shown to confer and increased risk of breast and pancreatic cancer. The *PALB2* protein binds with *BRCA2* protein stabilizing it in the nucleus, the *BRCA2/PALB2* complex is part of the Fanconi Anemia DNA repair pathway and acts in double-stranded DNA repair. Approximately 1% of non-*BRCA1/BRCA2* deficient familial breast cancers are caused by germline defects in *PALB2* [31]. In 2009, using a whole-exome sequencing approach Jones et al. identified a truncating mutation in *PALB2* in a patient with familial pancreatic cancer. Analysis of 96 additional familial pancreatic cancer patients from families with two or more pancreatic cancers identified three additional truncating mutations in the *PALB2* gene [18]. Subsequent

studies have identified additional *PALB2* mutations in 1–3% of familial pancreatic cancer kindreds [32,33].

BRCA1

While there is strong evidence supporting an increased risk of pancreatic cancer among carriers of the *BRCA2* gene, the role of *BRCA1* gene mutation in pancreatic cancer susceptibility is less clear. While some large studies have estimated that there is a 2.26-fold (95% CI 1.26–4.06) increased risk of pancreatic cancer in *BRCA1* mutation carriers [34], other studies have reported no increased in the prevalence of *BRCA1* mutations in pancreatic cancer patients [30]. A study of 145 Ashkenazi Jewish pancreatic cancer patients did not detect an excess frequency of *BRCA1* mutations, whereas the risk of *BRCA2* mutations was significantly elevated OR = 3.85; 95% CI = 2.1–10.8 [30]. In addition analysis of 66 familial pancreatic cancer patients from NFPTK kindreds with three or more pancreatic cancer failed to identify any deleterious *BRCA1* mutations despite the fact approximately half of the kindreds reported a family history of breast or ovarian cancer in addition to pancreatic cancer [35].

p16/CDKN2A

Germline mutations in the *p16/CDKN2A* gene are most commonly associated with familial melanoma. While only a portion of the familial aggregation of melanoma is due to germline defects in *p16/CDKN2A*, individuals with germline defects in *p16/CDKN2A* have been shown to have an increased risk of pancreatic cancer. It has been estimated that individuals from familial melanoma kindreds have a 13- to 22-fold increased risk of developing pancreatic cancer [36] and individuals who carry *p16/CDKN2A* mutations have a 38-fold increased risk of developing pancreatic cancer compared to the general population [37]. Pedigree analysis of *p16/CDKN2A* gene in 27 Dutch familial melanoma kindreds demonstrated that 19 of the 27 families harbored specific mutation, the p16-Leiden founder mutation, which is a 19 bp deletion in exon 2 of the *p16/CDKN2A* gene. The lifetime risk of pancreatic cancer in carriers of the p16-leiden founder mutation was estimated to be 17% by the age of 75 [38]. In addition to pancreatic cancer and melanoma, a variety of cancers have been reported to be increased familial melanoma kindreds, including carcinoma of the lung, and breast as well as sarcoma [17,36].

LYNCH SYNDROME

Lynch syndrome is an autosomal dominant hereditary disease characterized by early onset of colorectal cancer [39]. Patients with Lynch syndrome have germline mutations in genes coding for proteins associated with DNA mismatch repair genes *hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*, and *hMSH6/GTBP* [39]. The lifetime risk (age 70) of colon cancer among mutation carriers is estimated to be 68.7% (95% CI = 58.6–78.9%) for men and 52.2% (95% CI = 37.6–66.9%) for women. Women who carry mutations in these genes are also at a very high lifetime risk of developing endometrial cancer, 54% (95% CI = 41.9–66.1%) [40]. In addition to colorectal and endometrial cancer, mutation carriers are also at an increased risk of developing cancers of the ovary, stomach, bile duct, kidney, bladder, ureter, and skin [39].

Lynch et al. [41] first reported that families with Lynch syndrome have an increased risk of developing pancreatic cancer. A recent study by Kastrinos et al., examined 147 families that carried a mutation a mismatch repair gene. These families had an 8.6-fold (95% CI = 4.7–15.7) increased risk of pancreatic cancer compared with the general population and an estimated 3.68% (95% CI = 1.45–5.88%) lifetime (age 70) risk of pancreatic cancer [42]. While Geary et al. [43] also reported an increased rate of pancreatic cancer HNPCC families

another study by Barrow et al. [44] observed no excess risk. Adenocarcinomas of the pancreas in patients with HNPCC typically show microsatellite instability (MSI⁺) and a distinct medullary histopathology [45].

HEREDITARY PANCREATITIS

Hereditary pancreatitis, which typically manifests as repeated attacks of acute pancreatitis beginning in childhood and often leads to pancreatic insufficiency, is a rare inherited form of chronic pancreatitis [46]. Mutations in two genes have been found to cause hereditary pancreatitis. Mutations in the cationic trypsinogen (*PRSS1*) gene, causes an autosomal dominant form of hereditary pancreatitis [47,48] while mutations in the serine protease inhibitor gene (*SPINK1*) causes an autosomal recessive form of hereditary pancreatitis [49].

Individuals with hereditary pancreatitis have been shown to have a 53-fold (95% CI 23–105) increased risk for developing pancreatic cancer [50] and a lifetime risk (age 70) of pancreatic cancer of 30–40% [50,51]. The risk is even higher among smokers with hereditary pancreatitis who tend to develop disease 20 yr before non-smokers [51].

PEUTZ-JEGHERS SYNDROME [*STK11*]

Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by hamartomatous polyps in the gastrointestinal tract and pigmented macules of the lips, buccal mucosa, and digits. Most cases of Peutz-Jeghers syndrome (>80%) are caused by mutations in the *STK11* tumor suppressor gene, on chromosome 19p13, which encodes for a serine-threonine kinase. Individuals with Peutz-Jeghers syndrome have been shown to be at an increased risk of several gastrointestinal cancers including esophageal, stomach, small intestine, colon, lung, breast, uterine, ovarian, and pancreatic cancer [52]. Overall, individuals with Peutz-Jeghers syndrome have a lifetime (age 70) risk of cancer of 93% [53]. Giardiello et al. examined 210 individuals with Peutz-Jeghers syndrome and observed a 132-fold (95% CI 44–261) increased risk of pancreatic cancer compared to the general population. The lifetime risk of pancreatic cancer in Peutz-Jeghers patients had been estimated to be 11–32% [53].

Recent studies have suggested that pancreatic cancers that arise in Peutz-Jeghers patients may due to through the intraductal papillary mucinous neoplasm (IPMN) precursor pathway. IMPNs are cystic lesions of pancreas and therefore are detectable via computed tomography (CT) or endoscopic ultrasonography (EUS).

SUSCEPTIBILITY VARIANTS

Genome-wide association studies (GWAS) are powerful tools aimed at identifying relatively common variants that may increase risk of disease. Unlike candidate gene studies, in which a priori knowledge is used to identify plausible cancer susceptibility genes, GWAS have the advantage of examining common genetic variation (variation that occurs at frequencies >5–10%) in an unbiased manner. Through this approach we have been able to identify susceptibility genes for a wide variety of diseases including breast cancer, colon cancer, and pancreatic cancer [19,54]. The first GWAS for pancreatic cancer have just been completed, the PanScan I and II studies which jointly examined 550 K variants in 3,851 affected individuals (cases) and 3,934 unaffected controls drawn from 12 prospective cohort studies and eight case-control studies, with the majority of PanScan sites from North American or Europe and a smaller GWAS of 991 pancreatic cancer patients and 5,209 controls from Japan. It is important to note that the associated variants identified in association studies may not be causal, but only in linkage disequilibrium with the causal genetic variation. Additional functional and fine-mapping studies are necessary to identify the causal variants.

In the sections below, the results of the GWAS as well as some candidate gene studies are detailed.

ABO

The ABO gene encodes $\alpha(1,3)$ -*N*-acetylgalactosaminyl transferase α catalyzing attachment of the A antigen and $\alpha(1,3)$ -galactosyl transferase attachment of the B antigen on oligosaccharide chains on the surface of erythrocytes, gastrointestinal mucosa and elsewhere. In the PanScanI study, 1,896 cases and 1,939 controls from 12 cohort studies and one case-control study were genotyped using an Illumina 550 K SNP panel and genome-wide significant evidence of association was reported to rs505922, a SNP in the *ABO* gene. This finding was replicated in an independent sample of 2,457 affected individuals and 2,654 controls from eight case-control studies from the PanScan II study. Joint analysis of these two phases yielded multiplicative per-allele OR 1.20 (95% CI = 1.12–1.28, combined $P = 5.37 \times 10^{-8}$) [19]. The SNP rs505922 is in complete linkage disequilibrium with the O/non-O blood group allele, such that individuals with non-O blood groups are at an increased risk of developing pancreatic cancer. Additional epidemiological studies, using reported ABO blood group and ABO serotype support the associated between ABO blood group and pancreatic cancer risk pancreatic cancer risk. Using SNP genotype data to determine serotype status, Wolpin et al. reported that compared to individuals with O blood type, the OR of pancreatic cancer for individuals with A, AB, and B blood type were 1.38 (95% CI = 1.18–1.62), 1.47 (95% CI = 1.07–2.02), and 1.53 (95% CI = 1.21–1.92), respectively [55]. In addition, a recent study by Risch et al. reported an association between non-O blood group and pancreatic risk. Furthermore, risk among non-O individuals was even higher if they were also seropositive for CagA-negative *H. pylori* (OR 2.78; 95% CI 1.49–5.20). Interestingly, no increased risk was observed for CagA-negative *H. pylori* individuals of O blood type (OR 1.28, 95% CI 0.62–2.64) [56]. ABO blood group has also been shown to be associated the several other GI diseases, most notably gastric cancer.

1q32.1

Combined analysis ~550 K SNPs in the PanScan I and II studies provided evidence of association to five SNPs in the *NR5A2* region on 1q32.1, including one intronic SNP in this gene [57]. The SNP with the strongest association was rs3790844 multiplicative per-allele OR = 0.77, 95% CI 0.71–0.84 ($P = 2.45 \times 10^{-10}$) [58]. *NR5A2* is a nuclear receptor subfamily 5, group A, member 2, also known as liver receptor homolog 1. Studies have suggested *LRH-1/NR5A2* is involved in the initiation of intestinal tumors by influencing inflammation and cell cycle regulation [59]. Furthermore, decreased LRH-1 expression is related to a decrease in TNF-alpha levels [59].

13q22.1

In a large gene desert located on chromosome 13q22.1, two SNPs rs9543325 and rs9564966 with strong inter-marker LD $R^2 = 0.85$ and $R^2 = 0.6$ provided evidence of association in joint analysis of the PanScanI and II data. The multiplicative per-allele OR were 1.26, (95% CI = 1.18–1.35, $P = 3.27 \times 10^{-11}$) for rs9543325 and 1.21 (95% CI = 1.13–1.30, $P = 5.86 \times 10^{-8}$) [58].

CLPTM1/TERT

The CLPTM1/TERT region on 5p15.33 has been shown to be important in several cancers. In particular, recent genome-wide association studies of lung and other cancers provide strong evidence of association in this region [60,61]. In this region, there was evidence of association to rs401681 multiplicative per-allele OR 1.19 (95% CI = 1.11–1.27, $P = 3.66 \times 10^{-7}$) in the joint analysis of the PanScanI and II data [58]. *TERT* is a telomere maintenance

gene, and abnormal telomere length has been demonstrated in many cancers including pancreatic cancer. In particular, the majority of pancreatic adenocarcinomas show chromosome ends lacking telomeric repeat sequences [62].

FOXQ1

Genome-wide association analysis of 991 pancreatic cancer patients and 5,209 controls from Japan provided evidence of association to rs9502893, multiplicative per-allele OR 1.29 (95% CI 1.17–1.43, $P = 3.30 \times 10^{-7}$) [63]. This SNP is located on 6q25.3 and is in a large LD block with the *FOXQ1* gene. *FOXQ1* is one of the 43 members of the Fox family of transcription factor genes. *FOXQ1* protein is under-expressed in pancreatic cancers.

BICD1

Evidence of association was also reported for rs708224 on 12p11 multiplicative per-allele OR 3.30 (95% CI = 1.19–1.47, $P = 3.30 \times 10^{-7}$) in the Japanese genome-wide association study [63]. This SNP is located in the second intron of the *BICD1* gene. Some studies have suggested a role for *BICD1* in telomere length.

DPP6

DPP6 gene had been shown to be somatically altered in pancreatic cancers and it has been suggested that this genes plays a role in pancreatic cancer invasion. Several SNPs in the *DPP6* gene provided some evidence of association in the Japanese population, the strongest evidence was for rs6464375 when examined using a recessive model of inheritance, OR 3.73 (95% CI = 2.24–6.21, $P = 4.41 \times 10^{-7}$). However, it is important to note there was limited evidence of association under an additive genetic model ($P = 0.01$) and given the small size of the study population, addition studies are needed to replicate these findings [63].

CFTR

Cystic fibrosis (CF) is an autosomal recessive condition caused by a defect in protein cystic fibrosis transmembrane conductance regulator (CFTR) which regulates mucus in the lung and gastrointestinal tract. Most patients with CF develop pancreatic insufficiency. There is some evidence supporting an increased risk of pancreatic cancer among *CFTR* mutation carriers. A study of 949 pancreatic cancer patients and 13,340 controls reported 5.3% of patients and 3.8% of controls carried a mutation in the *CFTR* gene (OR = 1.40, 95% CI = 1.04–1.89) [64]. However, other smaller studies have failed to detect and association between CFTR mutation and pancreatic cancer risk [65] (Table 1).

CANDIDATE SUSCEPTIBILITY VARIANTS

In addition to the findings from genome-wide associations studies, there have been numerous candidate gene studies conducted to identify pancreatic cancer susceptibility variants. Many of these studies focus on biological pathways known to be important in pancreatic cancer risk such as tobacco metabolism, DNA repair, inflammation, and folate metabolism as well as others. In addition, to the main effects of these genes, variation in these genes may also interact with environmental exposures to influence risk. While some of these studies have reported positive findings, the results are inconsistent across studies and further replication is needed to determine if variation in these genes influence pancreatic cancer risk. For example, cigarette exposure accounts for an estimated 26% of pancreatic cancers [4] therefore the genes involved in tobacco metabolism may be involved in pancreatic cancer susceptibility. Variation in the *NAT1*, *NAT2*, *GSTM1*, *GSTT1*, and *GSTP1* genes have been studied to examine there association with pancreatic cancer, while

some studies have suggested variation in the *NAT1* many be involved in pancreatic cancer risk other have reported no association [66–68].

MULTIGENETIC CAUSALITY AND GENE/ENVIRONMENT INTERACTION

In addition to the direct effect of genetic factors on pancreatic cancer, it is likely that gene–gene interactions and gene–environment interactions may also play an important role in pancreatic cancer risk. While many studies have looked for interactions between candidate genes or between candidate genes and environmental factors, the results of these studies have been inconsistent. Given the individual effects of these genes and/or environmental factors on pancreatic cancer risk may be quite modest (OR ~1.5 or less) large studies are needed with both genetic data and detailed environmental risk factor profiles.

RISK ASSESSMENT AND SCREENING IN HIGH RISK POPULATIONS

Family history is a strong predictor of pancreatic cancer risk because it is suggestive of the presence of a genetic predisposition to pancreatic cancer, although shared environmental factors also play a role. As we have discussed above, risk increases with the number of affected relatives, however, family size, current age, or age of onset of pancreatic cancer and the exact relationship between affected family members are also important indicators of risk. Quantitative risk models have been developed for many types of cancers, including the Gail [69] and BRCAPRO [70] models for breast cancer. In April 2007, the first risk prediction tool for pancreatic cancer, PancPRO was released [71]. PancPRO builds on the foundation developed in BRCAPRO. In brief, this model predicts the probability that an individual has a pancreatic cancer susceptibility gene and their associated lifetime risk of pancreatic cancer using family history information provided by the proband and family. The PancPRO model has been shown to provide accurate risk assessment for familial pancreatic cancer kindreds with an observed to predicted pancreatic cancer ratio of 0.83 (95% CI = 0.52–1.20) and high discriminatory ability, with an area under the curve of 0.75 (95% CI = 0.68–0.81) [71] and a user-friendly version is freely available as part of the CaGene package (www4.utsouthwestern.edu/breasthealth/cagene) and the R software implementation at (<http://astor.som.jhmi.edu/BayesMendel>).

An example risk assessment using the PancPRO model is presented in Figure 1. Panel 1A displays a familial pancreatic cancer kindred. The proband is a 50-yr-old female whose grandfather developed pancreatic cancer at age 64 and paternal aunt at age 72, the other family members are pancreatic cancer free at the ages shown. Using the family history data provided, the PancPRO model estimates the probability of carrying a high-penetrance pancreatic cancer susceptibility gene of 18% and their risk of developing pancreatic cancer is 1.0%, 2.9%, and 4.9% by ages 60, 70, and 80, respectively. In contrast, general population age-averaged SEER rates for whites, a pancreatic cancer-free 50-yr-old has a risk of 0.14%, 0.45%, and 1.2% of developing pancreatic cancer by age 60, 70, and 80, respectively. If we permute the family history of the proband such that the father is affected with pancreatic cancer at age 65 and the paternal aunt is unaffected at age 72, the proband's carrier probability increases to 41% and their risk of pancreatic cancer increases to 2.3%, 6.5%, and 10.3% by age 60, 70, and 80, respectively, as shown in panel 1B. Similarly, the proband in the original pedigree was diagnosed with pancreatic cancer at age 50, as shown in panel 1C, the proband's probability of carrying a pancreatic cancer gene is estimated to be 96%.

SCREENING IN HIGH-RISK FAMILIES

The development of a successful early detection screening program for pancreatic cancer is needed to reduce the mortality of this disease. With current technologies, screening of the general population given the low incidence of pancreatic cancer is not practicable. However,

there are currently several ongoing clinical trials evaluating the usefulness of screening of high-risk populations, including individuals with a strong family history of pancreatic cancer or individuals who carry a mutation in a established high-penetrance pancreatic cancer susceptibility gene (such as *STK11*, *BRCA2*, etc.). The majority of these studies have evaluated the use of EUS, CT, and/or magnetic resonance imaging (MRI) to detect small lesions in the pancreas. In the second phase of the “Cancer of the Pancreatic Screening Study (CAPS)” study Canto et al. examined seventy-eight patients with a strong family history of pancreatic cancer or with Peutz-Jeghers Syndrome, using EUS and CT, 8 of which were found to have a confirmed pancreatic neoplasia [72]. Vasen et al. [73] screened 79 patients with the p16-Lieden mutation with MRI and magnetic cholangiopancreatography (MRCP), after a median of 4 yr follow-up (range 0–10), seven individuals were found to have pancreatic cancer. These studies along with others [74] demonstrate that the early detection of pancreatic cancer is possible. Identification of pancreatic cancer susceptibility genes can help identify high-risk population who may benefit from the early detection screening tests currently under evaluation.

DISCUSSION

Over the past decade many important pancreatic cancer susceptibility genes have been identified, these include high-penetrance genes *BRCA2*, *PALB2*, *PRSS1*, *SPINK1*, *STK11*, and DNA mis-match repair genes and low penetrance genes *CFTR*, *ABO*. However, the genetic basis of the majority of pancreatic cancer remains unclear, as these established high-penetrance genes explain only 10–15% of the familial aggregation of pancreatic cancer. Recent technological improvements in genotyping and genome sequencing have accelerated the pace at which new pancreatic cancer genes have been discovered, including the recent discovery of *PALB2* as a pancreatic cancer susceptibility gene. These new technologies will facilitate the discovery of additional pancreatic cancer genes in the coming years.

Identification of the inherited genetic basis of pancreatic cancer can not only lead to a better understanding of the etiology of this disease but can aid in the early detection of pancreatic cancer through the identification of high-risk populations who are most likely to benefit from the early detection screening programs currently under development.

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Abbreviations

OR	odds ratio
NFPTR	National Familial Pancreatic Tumor Registry
SIR	standardized incidence ratio
wSMR	weighted standardized mortality ratio
MSI+	microsatellite instability
IPMN	intraductal papillary mucinous neoplasm
CT	computed tomography

EUS	endoscopic ultrasonography
GWAS	genome-wide association studies
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
EUS	endoscopic ultrasonography
MRI	magnetic resonance imaging
CAPS	Cancer of the Pancreatic Screening Study
MRCP	magnetic cholangiopancreatography

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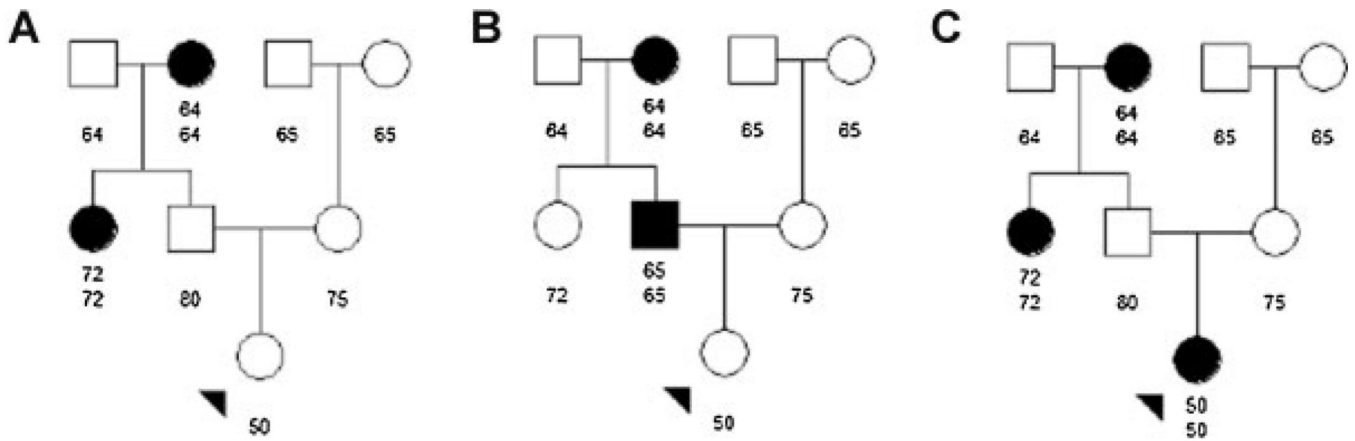
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	Probability of Carrying Pancreatic Cancer Gene	Risk of Pancreatic Cancer by Age		
		60	70	80
General Population (SEER 2005-2007)	.7%	0.14%	0.45%	1.2%
A: Paternal Grandmother and Maternal Aunt affected	18%	1.0%	2.9%	4.9%
B: Paternal Grandmother and Father Affected	41%	2.3%	6.5%	10.3%
C: Paternal Grandmother and Maternal Aunt and Proband affected	96%	N/A	N/A	N/A

Figure 1.
Example of risk assessment in a pancreatic cancer family using the PancPRO model.

Table 1

Established and Suggested Pancreatic Cancer Susceptibility Gene

	Gene(s)	Genetic syndrome	Risk of pancreatic cancer
High penetrance genes	BRCA2	Hereditary breast and ovarian cancer	OR = 3.5 (95% CI 1.87–6.58) [28]
	STK11/LKB1	Peutz-Jeghers	SIR = 132 (95% CI 44–261) [75]
	<i>PALB2</i>	Familial breast cancer	Increased [18]
	PRSS1	Hereditary pancreatitis	SIR = 53 (95% CI 23–105) [50]
	SPINK1		
	CDKN2A	Familial melanoma	SIR = 13–38 [76]
	Unknown	Familial pancreatic cancer	SIR = 6–32 [25,77]
Possible high to moderate penetrance genes	Mismatch repair genes	Hereditary non-polyposis colorectal cancer	No effect up to SIR 8.6 (95% CI, 4.7–15.7) [42–44]
	BRCA1	Hereditary breast and ovarian cancer	No effect up to OR = 2.26 (95% CI 1.26 to 4.06) [30,34,35]
Low penetrance genes	ABO		OR = 1.20 (95% CI 1.12–1.28, per allele) [19]
	CFTR		OR = 1.40; 95% CI, 1.04–1.89 [78]
Genomic regions with genome-wide significant evidence of association ($P < 5 \times 10^{-8}$)	1q32.1		OR = 0.77, 95% CI 0.71–0.84 [58]
	<i>13q22.1</i>		OR = 1.26, 95% CI 1.18–1.35 [58]