World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i32.11182

World J Gastroenterol 2014 August 28; 20(32): 11182-11198
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (14): Pancreatic cancer

Pancreatic ductal adenocarcinoma: Risk factors, screening, and early detection

Andrew E Becker, Yasmin G Hernandez, Harold Frucht, Aimee L Lucas

Andrew E Becker, Yasmin G Hernandez, Aimee L Lucas, Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States
Harold Frucht, Division of Digestive and Liver Diseases, Columbia University College, New York, NY 10032, United States
Author contributions: All authors were involved in the design of the manuscript; Becker AE wrote the manuscript; Lucas AL, Hernandez YG and Frucht H reviewed and revised the manuscript.
Correspondence to: Aimee L Lucas, MD, MS, Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, One Gustave L Levy Place, Box 1069, New York, NY 10029, United States. aimee.lucas@mssm.edu
Telephone: +1-212-2410101 Fax: +1-646-5378647
Received: November 1, 2013 Revised: February 15, 2014
Accepted: April 15, 2014
Published online: August 28, 2014

Abstract

Pancreatic cancer is the fourth most common cause of cancer-related deaths in the United States, with over 38000 deaths in 2013. The opportunity to detect pancreatic cancer while it is still curable is dependent on our ability to identify and screen high-risk populations before their symptoms arise. Risk factors for developing pancreatic cancer include multiple genetic syndromes as well as modifiable risk factors. Genetic conditions include hereditary breast and ovarian cancer syndrome, Lynch Syndrome, familial adenomatous polyposis, Peutz-Jeghers Syndrome, familial atypical multiple mole melanoma syndrome, hereditary pancreatitis, cystic fibrosis, and ataxia-telangiectasia; having a genetic predisposition can raise the risk of developing pancreatic cancer up to 132-fold over the general population. Modifiable risk factors, which include tobacco exposure, alcohol use, chronic pancreatitis, diet, obesity, diabetes mellitus, as well as certain abdominal surgeries and infections, have also been shown to increase the risk of pancreatic cancer development. Several large-volume centers have initiated such screening protocols, and consensus-based guidelines for screening high-risk groups have recently been published. The focus of this review will be both the genetic and modifiable risk factors implicated in pancreatic cancer, as well as a review of screening strategies and their diagnostic yields.

Key words: Pancreatic neoplasms; Pancreas cancer screening; Genetic predisposition to disease; Hereditary breast and ovarian cancer syndrome; Lynch syndrome; Peutz-Jeghers; *BRCA*; *PALB2*; *p16*; Pancreatitis

Core tip: Risk factors for developing pancreatic cancer include multiple genetic syndromes as well as modifiable risk factors. These factors can raise the risk of developing pancreatic cancer up to 132-fold over the general population. Several large-volume centers have initiated screening protocols, and consensus-based guidelines for screening high-risk groups have recently been published. The focus of this review will be both the genetic and modifiable risk factors implicated in pancreatic cancer, as well as a review of screening strategies and their diagnostic yields.

Becker AE, Hernandez YG, Frucht H, Lucas AL. Pancreatic ductal adenocarcinoma: Risk factors, screening, and early detection. *World J Gastroenterol* 2014; 20(32): 11182-11198 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i32/11182.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i32.11182

INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer-related deaths in the United States, with an estimated over 45000 diagnoses and 38000 deaths in 2013[1]. Pancreatic ductal adenocarcinomas (PDAC) arise from the exocrine pancreas and account for 95% of pancreatic cancers. The lifetime risk of developing pancreatic cancer

Table 1 Selected pancreatic ductal adenocarcinoma genetic risk factors

Risk factor	Gene	Increased PDAC risk	Other associated cancers
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2, PALB2*	2-3.5	Breast, ovarian, prostate
Lynch syndrome (hereditary non-polyposis colorectal cancer)	*MLH1, MSH2, MSH6, PMS2, EPCAM*	8.6	Colon, endometrium, ovary, stomach, small intestine, urinary tract, brain, cutaneous sebaceous glands
Familial adenomatous polyposis	*APC*	4.5-6	Colon, desmoid, duodenum, thyroid, brain, ampullary, hepatoblastoma
Peutz-Jeghers syndrome	*STK11/LKB1*	132	Esophagus, stomach, small intestine, colon, lung, breast, uterus, ovary
Familial atypical multiple mole melanoma pancreatic carcinoma syndrome	*P16INK4A/CDKN2A*	47	Melanoma
Hereditary pancreatitis	*PRSS1, SPINK1*	69	
Cystic fibrosis	*CFTR*	3.5	
Ataxia-telangiectasia	*ATM*	Increased	Leukemia, lymphoma
Non-O blood group		1.3	
Familial pancreatic cancer	Unknown	9 (1 FDR) 32 (3 FDRs)	

PDAC: Pancreatic ductal adenocarcinomas; FDR: First-degree relative.

Table 2 Selected pancreatic ductal adenocarcinoma modifiable risk factors

Risk factor	Increased PDAC risk
Current cigarette use	1.7-2.2
Current pipe or cigar use	1.5
> 3 alcoholic drinks per day	1.2-1.4
Chronic pancreatitis	13.3
BMI > 40 kg/m^2, male	1.5
BMI > 40 kg/m^2, female	2.8
Diabetes mellitus, type 1	2.0
Diabetes mellitus, type 2	1.8
Cholecystectomy	1.2
Gastrectomy	1.5
Helicobacter pylori infection	1.4

PDAC: Pancreatic ductal adenocarcinomas; BMI: Body mass index.

is 1.49%, or 1 in 67, with incidence increasing with age[2]. Epidemiologically, the incidence rates of PDAC are higher in males, African Americans, and lower socioeconomic status groups[1].

Both genetic and modifiable risk factors contribute to the development of PDAC. A hereditary component has been identified in approximately 10% of cases, with a specific germline mutation being implicated in 20% of those cases[3,4]. These genetic conditions, including the hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome (HNPCC), familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), familial atypical multiple mole melanoma syndrome (FAMMM), hereditary pancreatitis (HP), cystic fibrosis (CF), and ataxia-telangiectasia (AT), have been shown to raise the risk of PDAC anywhere from 2 to 132-fold (Table 1)[5-7]. Modifiable risk factors, which include tobacco exposure, alcohol use, chronic pancreatitis, diet, obesity, diabetes mellitus, as well as certain abdominal surgeries and infections have also been identified as increasing the risk of PDAC (Table 2).

PDAC is nearly universally lethal: less than 20% of patients are surgical candidates at the time of presentation, and the median survival for non-resected patients is 3.5 mo[8]. Even among those patients who are candidates to undergo pancreatectomy, the median survival is 12.6 mo[8]. However, by identifying and screening patients at an increased risk of developing PDAC, detection of precursor and early-stage lesions may allow diagnosis at a still surgically-resectable stage. Several large-volume centers have initiated screening protocols, and consensus-based guidelines for screening high-risk groups have recently been published[3,9]. The focus of this review will be both the genetic and non-genetic risk factors implicated in PDAC, as well as screening strategies and their diagnostic yields.

PDAC RISK FACTORS

PDAC risk factors: Genetic

It has been reported that up to 10% of PDAC have a hereditary component[4]. A 2009 meta-analysis demonstrated that having just one affected relative resulted in an 80% increased risk of developing PDAC[10]. Specific mutations in multiple genes have been implicated in causing roughly 10% of PDAC, with varying penetrance and degree of increased cancer risk for each mutation (Table 1)[11,12]. Identification and stratification of individuals at increased risk of having genetic mutations may allow for a group of patients that will benefit from early detection of these pancreatic neoplasms, as well as targeted, gene-specific therapy.

Hereditary breast and ovarian cancer syndrome and other fanconi anemia genes: *BRCA1*, *BRCA2/FANCD1*, *PALB2/FANCN*, *FANCC*, and *FANCG*: Fanconi anemia is an autosomal recessive disease characterized by multiple congenital anomalies, bone-marrow failure, and increased susceptibility to malignancy, including acute myeloid leukemia and head and neck squamous cell carcinoma[13,14]. There are 15 Fanconi anemia genes, and products of these genes are involved in multiple DNA repair

mechanisms, including the *BRCA1/2* pathway[13,14]. The incidence of the disease is 1 in 100000 live births, and the carrier rate of Fanconi anemia mutations is estimated at 1 in 300[13,15].

HBOC is characterized by early-onset breast and ovarian cancers resulting from monoallelic germline mutations in the *BRCA1* or *BRCA2* (also known as *FANCD1*) genes. These tumor suppressor genes code for proteins that repair double-stranded DNA breaks. While *BRCA2* codes for a Fanconi anemia protein, the *BRCA1* protein directly interacts with the FANCA protein[16]. *BRCA1/2* mutations have been shown to have a population frequency of 1.0%, with a higher concentration within the Ashkenazi Jewish population (2.3%)[17,18]. These genes have high penetrance with respect to female breast cancer (cumulative risk by age 70 of 57% for *BRCA1* and 49% for *BRCA2*) and ovarian cancer (cumulative risk by age 70 of 40% for *BRCA1* and 18% for *BRCA2*), and lower rates for male breast cancer (cumulative risk by age 70 of 1.2% for *BRCA1* and 6.8% for *BRCA2*) as well as PDAC[19]. While a few large studies have indicated that *BRCA1* mutations are associated with a roughly 2-fold increased risk of PDAC, the mutation is rarely seen in PDAC families without a strong history of breast cancer[6,7,20]. Additionally, not all studies have found an increased risk of PDAC among the *BRCA1* cohort[21]. On the other hand, the evidence for an association between *BRCA2* germline mutations and PDAC is more clearly defined. With a relative risk of at least 3.5, *BRCA2* mutations have been identified as the most common known inherited cause of PDAC: studies have found deleterious mutations in the *BRCA2* gene in 17%-19% of familial pancreatic cancer families and 7.3% of apparently sporadic pancreatic cancers[22-25]. Our group has demonstrated an increased prevalence of *BRCA1* mutations (8.3%) and *BRCA2* mutations (10.8%) in a cohort of unselected Ashkenazi Jewish patients who underwent surgical resection for PDAC and IPMN; half of those *BRCA1/2*-associated tumors demonstrated loss of heterozygocity[26]. In a registry study of *BRCA1* and *BRCA2* families, there was a significantly earlier age of onset (age 63 for each) for PDAC, compared to that found in the SEER database (age 70)[27].

PALB2, or partner and localizer of *BRCA2* (also known as *FANCN*), is a gene that codes for a protein which stabilizes the *BRCA2* protein as it repairs DNA. *PALB2* is known to be a breast cancer susceptibility gene and has been found to be mutated in up to 3% of familial PDAC[28,29]. While some large registry cohort studies have not found *PALB2* mutations to increase the relative risk of PDAC, other groups have identified *PALB2* mutations in multiple familial pancreatic cancer families[30-33]. Additionally, it has been demonstrated that relatives of *PALB2* mutation carriers have a 6-fold increased risk of PDAC compared to relatives of those with the wild-type gene[34].

Mutations in two other Fanconi anemia proteins, specifically *FANCC* and *FANCG,* have shown loss of heterozygosity in young-onset (< 55 years of age) PDAC[35,36]. No studies to date have found an increased risk of PDAC associated with mutations in these genes.

Targeted therapy is a promising area of research for genes in this pathway. Cells deficient in *BRCA1, BRCA2/FANCD1*, *PALB2/FANCN*, *FANCC* or *FANCG* must use DNA repair mechanisms that are more error prone and resultant mutations are more likely to result in cell death. Thus, agents that induce DNA damage or inhibit other repair mechanisms may affect deficient cells more than fully-functional cells[37]. *In vitro* cells deficient in these proteins and *in vivo* cells in mice were shown to be hypersensitive to alkylating agents such as mitomycin C, cisplatin, chlorambucil, and melphalan, whereas normal cells were unaffected[38,39]. Additionally, poly (ADP-ribose) polymerase (PARP) inhibitors have been shown to have anti-tumor activity in multiple other human cancers[40]. There have been case reports of complete pathological response of *BRCA2*-associated PDAC to PARP inhibitors, and clinical trials are currently underway[41].

Lynch syndrome (or HNPCC): *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*: Lynch syndrome, the most common inherited colorectal cancer syndrome, is characterized by early-onset colorectal cancer as well as a predisposition to cancer of the endometrium, ovary, stomach, small intestine, urinary tract, brain, pancreas and cutaneous sebaceous glands[42]. The incidence of this syndrome has been postulated to be between about 1:660 to 1:2000[43]. The *MSH2*, *MSH6*, *MLH1*, *PMS2*, and *EPCAM* genes, which are mutated in this syndrome, normally code for proteins involved in the DNA mismatch repair pathway which bind to mismatched double-stranded DNA and microsatellites to target and prepare them for repair[42]. Patients with Lynch syndrome have an 8.6-fold increased risk of developing PDAC compared to the general population[44]. These pancreatic tumors often have a characteristically medullary appearance, with prominent lymphocytic infiltration and microsatellite instability[44,45].

FAP: *APC*: FAP is characterized by the early development of hundreds to thousands of colorectal adenomatous polyps; some of these polyps inevitably progress to malignancy, conferring an almost 100% risk of colorectal cancer by age 40[46]. There is also an increased risk of extracolonic cancers including desmoid, duodenum, thyroid, brain, ampullary, pancreas, and hepatoblastoma tumors[47]. The incidence of FAP in the Northern European population is 1 in 13000-18000 live births in the Northern European population[48,49]. FAP is caused by a mutation in the *APC* gene, a tumor suppressor gene which codes for a scaffolding protein responsible for targeting β-catenin for destruction, as well as acting as a control on progression of the cell cycle and a microtubule stabilizer[47]. Specifically, the relative risk of PDAC in FAP is reported to be 4.5 to 6-fold, although it is uncertain if this represents a true increased risk of PDAC or reflects misclassification

of ampullary carcinomas[50,51]. There also exists a subset of the FAP population with an attenuated phenotype, known as attenuated FAP (AFAP) that is also caused by a mutation in the *APC* gene; this population has fewer colorectal adenomatous polyps (10-100) and a fifteen-year delay in the onset of colorectal cancer compared to those with FAP[52]. Compared to FAP, AFAP is associated with a lower risk of extracolonic cancers[53].

PJS: *STK11/LKB1*: PJS is characterized by hamartomatous gastrointestinal polyposis and distinctive mucocutaneous pigmentation found most commonly on the lips or perioral region[45,54]. PJS, with an estimated frequency of 1:8300 to 1:280000, is associated with an inherited mutation in the *STK11/LKB1* gene, a tumor suppressor gene which encodes for a serine/threonine kinase[45]. While the exact mechanism by which the *LKB1* gene acts as a tumor suppressor is unknown, PJS tumors have shown less activated AMP-kinase, which results in mammalian target of rapamycin hyperactivation[55]. Additionally, *LKB1* haploinsufficiency has been shown to cooperate with *K-ras* to cause PDAC in the mouse model, through a decrease in growth arrest[56]. A 2000 meta-analysis demonstrated that PJS is associated with a relative risk of 15.2 for all cancers and a 93% overall rate of cancer by age 64[5]. The study found a statistically significant increased risk of esophageal, stomach, small intestine, colon, pancreas, lung, breast, uterus, and ovarian cancers, including a relative risk of 132 for PDAC.

FAMMM: *p16INK4A/CDKN2A*: FAMMM is characterized by malignant melanoma in one or more first-degree relatives (FDRs) or second-degree relatives (SDRs) and multiple, atypical melanocystic nevi[55]. The prevalence of FAMMM is unknown. While there is variability in the underlying genetics of this syndrome, a germline mutation in the *p16INK4A* (also known as *CDKN2A* or *MTS1*) gene has been found in approximately 38% of the cases of this syndrome[57,58]. FAMMM with this particular mutation, which confers a 60%-90% risk of melanoma by age 80, is called FAMMM pancreatic carcinoma syndrome (FAMMM-PC) because those with the *p16INK4A* mutation have also demonstrated an increased risk of PDAC[59-62]. This gene, which codes for the *p16* protein, is a tumor suppressor gene involved in the regulation of cell cycle progression. A study following 19 FAMMM families over seventy years found a 13 to 22-fold increased risk of developing PDAC in those with this *p16INK4A* mutation; conversely, they found no cases of PDAC in those without this mutation[63]. More recently, a relative risk of PDAC of 47 was demonstrated among those with this *p16INK4A* mutation compared to the general population[64]. The risk of PDAC was even more apparent when looking at those under 55 years of age: a Swedish study found the relative risk to be 65-fold for *p16* mutation carriers[61].

HP and CF: *PRSS1*, *SPINK1* and *CFTR*: HP is characterized by recurrent attacks of acute pancreatitis starting in childhood, which can lead to pancreatic failure[65]. About 80% of HP is caused by a germline mutation in the *PRSS1* gene, which codes for the prodigestive enzyme trypsinogen[66]. Defective mutations result in either premature activation or reduced deactivation of the enzyme, leading to pancreatic injury. The *SPINK1* gene codes for a serine protease inhibitor that inhibits active trypsin; mutations in this gene have also been associated with various forms of pancreatic disease, including pancreatitis[67]. HP has an 80% penetrance rate[68]. A 2010 meta-analysis found a relative risk of 69 for PDAC for patients with HP compared to the general population[69].

Additionally, homozygous mutations in the autosomal recessive *CFTR* gene cause cystic fibrosis, which is associated with both a younger age of onset (median age of 35 years) and 5.3-fold greater risk of the development of PDAC[70]. However, even when a *CFTR* gene mutation is inherited in a heterozygous fashion, it has been demonstrated that this confers a 4-fold greater chance of developing chronic pancreatitis[66,71,72].

The presence of chronic inflammation in pancreatitis is thought to be the primary mechanism by which PDAC develops. A few mechanisms have been suggested as methods by which inflammation leads to PDAC[73]. Inflammatory cytokines such as IL-6 and IL-11 may induce the proliferation and facilitate survival of malignant and premalignant cells through the activation of multiple transcription factors, including STAT3 and NF-κB. Additionally, chronic inflammation may suppress immunosurveillance as well as inhibit oncogene-induced senescence, which would allow the lesion to develop unchecked. It has been suggested that increased activation of pancreatic stellate cells leads to fibrosis *via* increased cell proliferation and inflammation[74].

AT: *ATM*: AT is an autosomal recessive, progressive neurologic disorder characterized by early ataxia and later telangiectasias of the blood vessels on exposed areas of the skin and eyes, with cerebellar ataxia, varied immune dysfunction, an extreme sensitivity to ionizing radiation, and an increased risk of cancers, particularly leukemias and lymphomas[75-77]. The estimated incidence of AT is 1 in 40000-300000 live births, and the disease is caused by a homozygous mutation in the *ATM* gene, which codes for a serine/threonine kinase involved in DNA repair[77]. Monoallelic A*TM* mutation carrier status, an estimated 1.4% of the United States population, is also associated with an increased risk of cancer, especially that of the female breast[78,79]. Among the families of those with AT, the rate of PDAC is at least twice that of the general population[80,81]. A 2012 study of a familial pancreatic cancer cohort found monoallelic ATM mutations in 2.4% of the PDAC probands, and that number increased to 4.6% of the patients with at least 3 FDRs with PDAC. Loss of heterozygosity of the *ATM* gene was found in the only patient with available tumor tissue in the study[77].

Non-O blood group: Non-O blood groups have also been associated with a higher risk of PDAC[82-84]. Multiple prospective and case-control studies across different countries as well as a genome-wide association study demonstrated an increased risk of PDAC among those with non-O blood groups; additionally, a 2010 meta-analysis found that having an O blood group was associated with a relative risk of 0.79 for the development of PDAC[83,85]. In fact, it was demonstrated that each additional non-O allele conferred a larger risk of PDAC[86]. Interestingly, it was shown that the association between non-O blood groups and PDAC was largest in individuals colonized by CagA-negative *Helicobacter pylori* (*H. pylori*)[84]. While it has been postulated that the increased cancer risk is related to a chronic host inflammatory state, it has been found in one study that non-O blood groups do not increase the risk of chronic pancreatitis[83,87].

FPC: Unknown gene: Familial pancreatic cancer (FPC), defined as having 2 or more FDRs with PDAC with no known genetic cause, is responsible for up to roughly 80% of clustering PDAC[3]. The National Familial Pancreas Tumor Registry at Johns Hopkins demonstrated a nine-fold greater risk of developing PDAC among individuals with an FDR with PDAC in the setting of FPC, compared to a 1.8-fold greater risk for those with an FDR with sporadic PDAC[12]. Additionally, among FPC kindreds, having two or three FDRs with PDAC was associated with a 6.4-fold and 32-fold greater risk of developing PDAC, respectively.

Additionally, studies of the European Registry of Hereditary Pancreatitis and FPC as well as the German National Case Collection for FPC Registries have described anticipation (developing PDAC roughly 10 years earlier than their affected parent) in 59%-80% of over 100 FPC families[33,88]. Finally, segregation analyses have shown evidence for a yet-unidentified autosomal dominant, high-risk allele influencing the onset age of PDAC present in 7/1000 individuals[89]. The *palladin* gene, a proto-oncogene overexpressed in some sporadic pancreatic tumors has also been found to be mutated in affected members of one PDAC family[90-92]. This gene codes for a cytoskeleton protein that promotes tumor invasion in fibroblasts[90].

PDAC risk factors: Modifiable

Multiple modifiable risk factors are associated with an increased risk of developing PDAC (Table 2). Since PDAC has such a low incidence rate and most of the associated relative risks (with the exception of chronic pancreatitis) are low, greater improvements in PDAC morbidity and mortality may be possible with lifestyle modification.

Tobacco use: Smoking is the largest identifiable and modifiable risk factor for PDAC, contributing to 20%-35% of PDAC cases[93-95]. A 2008 meta-analysis of 82 studies demonstrated an increased risk of PDAC development for both current cigarette (relative risk of 1.74) and pipe or cigar (1.47) users[93]. A 2012 pooled analysis found the risk of current cigarette use to be 2.2-fold[96]. Additionally, both studies found increased smoking intensity and cumulative smoking dose to increase the risk for development of PDAC. Even after 10 years of smoking cessation, a modestly elevated relative risk of 1.48 remains[93]. However, multiple studies have demonstrated a risk of PDAC among former smokers to be similar to non-smokers after up to 15-20 years of cessation[96-100]. Finally, exposure to second-hand tobacco smoke has been found to increase the risk of PDAC by 21%[101].

It is likely that PDAC develops from exposure to tobacco-related carcinogens through circulating blood, especially given a similar rate of tobacco-related neoplasm in the kidney and stomach[93]. These carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons, as well as their metabolites, cause mutations in both protoncogenes (K-ras) and tumor suppressors (p53)[102,103]. Tobacco smoke also directly contributes to pancreatic inflammation[103].

Smoking is particularly harmful in certain cohorts. For patients with HP, smoking has been demonstrated to more than double the risk of PDAC and lower the age of cancer onset by 20 years[95]. For members of FPC families, one study found cigarette smoking resulted in a 4-fold increased risk over non-smokers, as well as lowering the age of onset of PDAC by 10 years[104]. Another study demonstrated an incidence ratio of 19.2 for members of PDAC families who had ever smoked cigarettes *vs* 6.25 for those who had never smoked at all[12].

Alcohol use: While alcohol has been found to be associated with PDAC, the current evidence indicates that it is limited to heavy alcohol usage only: pooled data and meta-analyses have found three or more drinks per day to be associated with a 1.22 to 1.36-fold increased risk of developing PDAC, with a dose-response relationship[105,106]. It is known that heavy alcohol usage does contribute to pancreatitis, which may be a method by which it increases the risk of PDAC[107]. Additionally, metabolites of alcohol, including acetaldehyde (a carcinogen) and fatty acid ethyl esters, as well as ethanol itself (a carcinogen) can cause pancreatic inflammation as well as directly contribute to carcinogenesis[103].

Chronic pancreatitis: A 2010 meta-analysis demonstrated a relative risk of 13.3 for developing PDAC in those with chronic pancreatitis, with a ten to twenty year lag between the incidences of pancreatitis and pancreatic malignancy[69]. As with hereditary pancreatitis, chronic inflammation seen in chronic pancreatitis is thought to be the mechanism by which PDAC develops. Far and away, the most common cause of chronic pancreatitis is alcohol abuse, which is responsible for 60%-90% of cases[108]. As with HP, chronic inflammation is thought to be the mechanism by which PDAC develops in chronic pancreatitis. Inflammatory cytokines may induce cellular proliferation, as well as reduce immunosurveillance and inhibit

senescence, allowing the lesion to continue to grow[73].

Diet and obesity: Meta-analyses have demonstrated an increased risk of PDAC associated with a diet including red meat in men (relative risk of 1.29), and processed meat in both men and women (1.19)[109]. Another meta-analysis found that there was a relative risk of 1.12 for developing PDAC for each 5kg/m^2 increase in body mass index (BMI)[110]. A large 2003 study found a BMI of over 40 to be associated with a relative risk of PDAC of 1.49 for men and 2.76 for women[111]. Interestingly, a 2009 study found being overweight or obese at a younger age to be associated with a younger age of onset of PDAC; the study also found those who had a BMI over 25 from ages of 30 to 79 had reduced PDAC survival[112]. The method by which fat consumption may lead to PDAC includes pancreatic hypertrophy and hyperplasia in response to cholecystokinin-mediated lipase secretion from the presence of fat in the duodenum, which puts the pancreatic exocrine glands at an increased risk of carcinogenesis[102]. Additionally, hyperglycemia, abnormal glucose levels, and insulin resistance are all associated with an increased risk of PDAC[112-117].

Diabetes mellitus: type 1, type 2, type 3c: Meta-analyses have demonstrated associations between both type 1 and type 2 diabetes mellitus (DM) and pancreatic cancer, with odds ratios of approximately 2.0 and 1.8, respectively[109,118,119]. Twenty-five to 50% of patients with PDAC will have developed DM 1-3 years prior to their PDAC diagnosis; however, the relative risk of pancreatic cancer drops as time from type 2 DM diagnosis increases, indicating that DM may in fact be an early manifestation of the cancer[118,120,121]. Also, while new-onset DM is not specific for PDAC (less than 1% of adult-onset DM patients will develop PDAC within 3 years), large cohort studies in the United States and Sweden have demonstrated differing relative risks for those with a long history of DM *vs* those with new-onset DM: having DM for a longer time is associated with a decreased PDAC risk compared to newly-diagnosed DM[121-124]. In addition, associated new-onset DM has been shown to resolve after tumor resection[114,125,126].

A different diabetes diagnosis, type 3c (pancreatogenic) DM, or diabetes associated with acute or chronic disease of the pancreas, which is up to 8% of all diabetes, may confer an even higher risk of pancreatic cancer, especially in those patients with chronic pancreatitis[121,127-129]. Type 3c DM occurs in up to 30% of patients with PDAC and is associated with deficiencies in islet hormones such as insulin, glucagon, and pancreatic polypeptide[121]. Most frequently, the insulin resistance is actually hepatic resistance, with relatively normal peripheral insulin sensitivity; this is thought to be a result of a deficiency of pancreatic polypeptide, which has been shown to affect hepatic insulin receptors[128,130]. In patients with pancreatic polypeptide deficiency, this hepatic insulin resistance has been shown to return to normal with the replacement of the hormone[128,131,132].

Insulin is growth promoting, and thus chronic insulinemia may result in increased cellular proliferation and decreased apoptosis, a mechanism by which PDAC may eventually develop[110,112,117]. This is mediated through both increased levels of insulin, as well as insulin-like growth factor-1, which also results from hyper-insulinemia[102]. Additionally, the oxidative stress from hyperglycemia may be the cause of cell damage that could lead to the development of neoplasm.

DM treatment choice has been demonstrated to modulate pancreatic risk. One case-control study found a relative risk of 2.89 for pancreatic cancer in those with DM; this risk decreased to 2.12 with treatment by oral hypoglycemic agents and increased to 6.49 by treatment with insulin[98]. This is consistent with evidence that insulin can promote pancreatic cancer cell proliferation[133]. In particular, treatment with metformin has been shown to decrease overall cancer risk in diabetic patients[134,135]. Multiple studies have demonstrated a decreased risk of pancreatic cancer among diabetics treated with metformin[135-137]. Specifically, one study demonstrated that treatment with metformin conferred a relative risk of pancreatic cancer of 0.30, *vs* 2.78 with treatment with insulin[135].

Surgery and infection: A meta-analysis found a relative risk of PDAC of 1.23 for those with a history of a cholecystectomy[138]. The mechanisms suggested by which cholecystectomy increases the risk of PDAC include increased cholecystokinin levels, which have been shown to stimulate the growth of human pancreatic cancer cell lines and promote pancreatic carcinogenesis in hamsters, as well as increased degradation of bile salts to secondary bile acids, which have a pancreatic carcinogenic effect in hamsters[138-142].

Another meta-analysis has demonstrated a relative risk of 1.54 for developing PDAC post-gastrectomy, with a higher risk found for Billroth Ⅱ resections than Billroth Ⅰ resections[143,144]. The reasons postulated for higher rates of pancreatic carcinogenesis include a post-gastrectomy environment favorable for bacteria that increase levels of DNA-damaging N-nitrosamine carcinogens, increased rates of *H. pylori* seropositivity, and increased rates of recurrent acute pancreatitis in Billroth Ⅱ resections[144].

Evidence suggests *H. pylori* infection is associated with PDAC: a 2011 meta-analysis found an increased odds ratio of 1.38[145]. The definitive method by which *H. pylori* infection contributes to the development of PDAC is unknown, but may be related to the inflammatory mediators and angiogenic factor secretion associated with chronic infection[145]. There is some evidence for a link between hepatitis B infection and pancreatic cancer, as well as possibly hepatitis C; however, the method by which these infections contribute to PDAC is unknown[146,147].

Hydrocarbon exposure: While studies have shown correlations between pancreatic cancer and various expo-

sures, the most consistent exposures linked to development of pancreatic neoplasm are chlorinated hydrocarbons and polycyclic aromatic hydrocarbons[148]. However, it is important to note that consistently statistically significant results have not been found with either of these two occupational exposures.

PDAC STAGING, RISK STRATIFICATION AND SCREENING

Staging, prognosis, and the case for screening

The five-year PDAC survival rate of 6% is dismal, largely because the majority of patients are diagnosed at an advanced stage[1]. Surgical resection is the only curative treatment for pancreatic cancer. However, only pre-cancerous or early-stage (Ⅰ-Ⅱ) PDAC is surgically resectable. Since five-year survival rate for patients diagnosed with Stage Ⅰ A disease is 19 times that of those diagnosed with Stage Ⅳ disease (13.6% *vs* 0.7%), greater improvements in survival may be seen if we focus on shifting the diagnosis of PDAC from a late stage to an early or pre-cancerous stage[8]. Unfortunately, early-stage PDAC is usually clinically silent, highlighting the need for improved methods of early detection of precursor and early stage lesions. This provides the rationale for screening programs to detect precursor and early stage lesions.

PDAC precursors

World Health Organization guidelines suggest that in order to screen for a cancer, there must be a recognizable latent or early stage of the disease that can be tested for and managed effectively[148]. Several pancreatic lesions meet the criteria for a precursor to PDAC: pancreatic intraepithelial neoplasms (PanINs), mucinous cystic neoplasms (MCNs), and intraductal mucinous cystic neoplasm (IPMNs)[149,150].

PanIN: PanINs are non-invasive, non-mucin-producing, small epithelial neoplasms[150,151]. There are 3 grades of PanINs, classified by degree of atypia: PanIN-1, PanIN-2, and PanIN-3. A 2003 study found PanIN lesions in 82% of pancreata with invasive cancer compared to just 28% of normal pancreata, as well as an increased number of high-grade PanIN lesions compared to low-grade PanIN lesions[152]. Multiple studies have found PanIN-3 lesions only in pancreata harboring other malignancies[152-154]. For PanIN lesions, there are three broad subsets of germline or somatic mutations that are usually found in concert in a pancreatic malignancy: (1) activation of oncogenes (*K-Ras, HER2*); (2) inactivation of tumor suppressor genes (*TP53*, *p16/CDKN2A*, *SMAD4/DPC4, BRCA1, BRCA2*); and (3) inactivation of genome maintenance genes (*MLH1*, *MSH2*)[151,155,156]. While PanINs are not visible on cross-sectional imaging, a 2006 study suggests that endoscopic ultrasound (EUS) may be able to detect lobular parenchymal atrophy associated with PanINs, particularly multifocal PanIN, and IPMNs[157].

Pancreatic cystic neoplasms: MCN and IPMN: Autopsies indicate that the prevalence of patients with a pancreatic lesion at death is about 24%; studies have found that magnetic resonance imaging (MRI) picks up incidental pancreatic cysts in patients with no pancreatic history in up to 13.5% of patients, and computed tomography (CT) in 2.6%[158-160]. The ability to detect precursor lesions before they invade and progress to pancreatic cancer is of the utmost importance. MCNs are cystic, mucin-producing epithelial neoplasms with ovarian-type stroma, detectable on cross-sectional imaging[150]. MCNs are much more common in females than males (95% female), and a significant percentage of the stroma cells stain positive for estrogen or progesterone receptors[161,162]. With a mean age of diagnosis of 45-50, MCNs usually arise in the body or tail of the pancreas (> 90%) and do not communicate with the larger pancreatic ducts[161-165]. Compared to non-invasive MCNs, malignant MCNs are diagnosed in older patients and are significantly larger, indicating that they most likely grow slowly over time[163,166]. The five-year survival rate for margin-negative, surgically resected non-invasive MCNs is close to 100%, but roughly 50% for invasive MCNs; however, their low frequency of invasion (12%) highlights the need for better characterization of tumor progression[161-163,166].

IPMNs, which include branch duct (BD-IPMN), main duct (MD-IPMN), and mixed types, are mucin-producing epithelial neoplasms that are also detected by cross-sectional imaging[167]. They are more common in the head of the pancreas, affect men more than women and have a mean age of diagnosis of about 65 years of age[166,168]. While BD-IPMNs and MD-IPMNs have the same age of presentation, BD-IPMNs are more common and frequently multifocal (21%-41% of cases) and less likely to progress to malignancy (11%-17% *vs* 44%-48% *vs* 45% for mixed IPMNs)[166,169-173]. Patients with resected BD-IPMNs also have a higher five-year survival rate (91%) than both MD-IPMNs (65%) and mixed IPMNs (77%)[166].

Patients with both MCNs and IPMNs have improved survival when lesions are resected before developing an invasive component: a study of 851 consecutive resected patients at Massachusetts General Hospital showed a five-year survival rate of 87% for those with invasive and non-invasive cystic lesions and just 62% in those with malignancy[172].

While it is important to continue to better our ability to identify these PDAC precursor lesions, this must be matched by an improvement in the capacity to accurately predict which of those lesions will progress to malignancies. Characterizing how these precursor lesions develop will help better guide future screening and subsequent treatment.

Screening modalities: Imaging and biomarkers

Imaging: EUS and MRI have demonstrated the most accuracy as screening modalities for PDAC in terms of detecting small, cystic lesions, while magnetic resonance

Table 3 Pancreatic ductal adenocarcinomas screening efforts and diagnostic yields *n* (%)

Ref.	Number screened	High-risk group	Initial imaging (if abnormal screening)	Diagnostic yield	Definition of diagnostic yield
Brentnall *et al*[182]	14	FPC	EUS + ERCP + CT	7 (50)	Dysplasia
Rulyak *et al*[183]	35	FPC	If symptomatic: EUS + ERCP If asymptomatic: EUS (ERCP)	12 (34.3)	Dysplasia
Kimmey *et al*[184]	46	FPC	EUS (ERCP)	12 (26)	Dysplasia
Canto *et al*[185]	38	FPC, PJS	EUS (CT, ERCP, EUS-FNA)	2 (5.3)	PDAC, IPMN
Canto *et al*[186]	78	FPC, PJS	EUS + CT (ERCP, EUS-FNA)	8 (10.3)	IPMN, PanIN1-2
Poley *et al*[187]	44	FPC, BRCA, PJS, FAMMM, p53, HP	EUS (CT, MRI)	10 (23)	PDAC, IPMN on imaging
Langer *et al*[188]	76	FPC, BRCA, FAMMM	EUS + MRCP (EUS)	1 (1.3)	IPMN
Verna *et al*[181]	51	FPC, PJS, FAMMM, BRCA, HP, HNPCC	EUS and/or MRCP (EUS-FNA, ERCP)	6 (12)[1]	PDAC, IPMN, multifocal PanIN2-3
Ludwig *et al*[189]	109	FPC, BRCA	MRCP (EUS)	9 (8.3)	PDAC, IPMN, PanIN2-3, SCA on imaging
Vasen *et al*[190]	79	p16	MRI/MRCP, EUS if unable	7 (8.9)	PDAC
Al-Sukhni *et al*[191]	262	FPC, FDR of double-primary cancer, BRCA, PJS, HP, p16	MRI (ERCP, EUS, CT)	3 (1.1)[2]	PDAC
Schneider *et al*[33]	72	FPC, BRCA, PALB2, p16	EUS + MRCP (EUS)	4 (5.5)	MD-IMPN, multifocal PanIN23
				9 (12.5)	MD-IMPN, multifocal PanIN2-3, BD-IPMN
Canto *et al*[174]	216	FPC, BRCA, PJS	CT + MRI/MRCP + EUS (ERCP)	92 (42.6)	Pancreatic lesion

[1]Only 41 patients had imaging, resulting in yield of 14.6% (6/41); [2]Only 175 patients had imaging, resulting in yield of 1.7% (3/175). PDAC: Pancreatic ductal adenocarcinomas; HNPCC: Lynch syndrome; FAP: Familial adenomatous polyposis; PJS: Peutz-Jeghers syndrome; FAMMM: Familial atypical multiple mole melanoma syndrome; HP: Hereditary pancreatitis; FPC: Familial pancreatic cancer; endoscopic retrograde MRI: Magnetic resonance imaging; CT: Computed tomography; EUS: Endoscopic ultrasonography; ERCP: Endoscopic retrograde cholangiopancreatography; MCN: Mucinous cystic neoplasms ; IPMN: Intraductal mucinous cystic neoplasm; FNA: Fine needle aspirate.

cholangiopancreatography (MRCP) provides the best visualization of possible communication with the main pancreatic duct[9,174]. CT subjects patients to radiation and has a suboptimal detection rate compared to EUS and MRI. Abdominal ultrasound and endoscopic retrograde cholangiopancreatography are not used as screening modalities for PDAC[9].

Biomarkers: Due to high cost, relative inability of non-invasive imaging modalities to detect small and solid tumors, and the modest risks associated with screening techniques like EUS, the use of biomarkers for the early detection of PDAC is an important frontier[175].

Carbohydrate antigen 19-9 (CA 19-9) is the only FDA approved blood biomarker test for PDAC[176]. However, due to the low prevalence of PDAC in the population, CA 19-9 is recognized as a poor screening tool: a screening of over 10000 patients found only 4 cases of PDAC based on CA 19-9 levels; additionally, 3 of those cases were not resectable at diagnosis[176]. The sensitivity (70%), specificity (87%), positive predictive value (59%), and negative predictive value (92%) are still not high enough to be used regularly in healthy patients[176,177]. CA 19-9 levels do appear to be informative as a predictor of disease recurrence post-resection[176,178].

The literature surrounding pancreatic cancer biomarkers is vast: a 2009 analysis found over 2500 genes overexpressed at the mRNA or protein level[179]. There is ongoing research that suggests a future for gene expression profiling, proteomics, metabolomics, and microRNA as diagnostic PDAC biomarkers.

Current screening guidelines

The low absolute risk of developing PDAC precludes population-wide screening at the current time, both from a cost-benefit and absolute harm perspective. Assuming a lifetime risk of developing PDAC of 1.49%, a hypothetical screening test with 90% sensitivity and specificity would have a positive predictive value (PPV) of just 12%, meaning that almost nine in ten positive screening results would be incorrect, with those patients subject to unnecessary stress and further testing[3]. Even a screening test with 95% sensitivity and specificity would result in a PPV of just 22%. Notwithstanding, the identification of genetic and environmental risk factors may provide opportunities to enrich the screening population with high-risk cohorts, which would drastically increase the PPV of screening results, with the hopes of identifying precursor or early-stage lesions in some high-risk individuals before the lesions progress to inoperable pancreatic cancer.

Brand *et al*[180] published recommendations for PDAC screening in 2007. They suggested that potential candidates for screening included: (1) *BRCA1, BRCA2*, *p16* mutation carriers with at least one FDR or SDR with PDAC; (2) a PJS family member (preferably confirmed germline mutation carrier); (3) HP patients; (4) a patient with 2 relatives in same lineage with PDAC, at least one of whom is an FDR of the patient; and (5) patients with $\geqslant$ 3 FDR, SDR or third-degree relatives with PDAC. They suggested that screening of these individuals

Table 4 Selected highlights

Selected recent advances	Genetic risk factors
	In 2009, the use of gene sequencing identified PALB2, which had previously been implicated in breast cancer, as a susceptibility gene for PDAC[28]
	Expression of the palladin gene has been shown to be upregulated by cohabitance of normal fibroblasts with epithelial cells expressing the K-Ras oncogene. In 2012, it was shown that the palladin gene, which codes for a cytoskeletal protein, promotes mechanisms for metastasis and outgrowth of tumerogenic cells[90]
	Also in 2012, gene sequencing indicated that ATM mutations result in a predisposition to PDAC; LOH was demonstrated in 2 kindreds with PDAC[77]
	Therapy
	For patients with diabetes, treatment with metformin is associated with a lower relative risk of pancreatic cancer[127,136,137]
	A 2011 case report detailing a complete pathological response of a BRCA2-associated pancreatic tumor to gemcitabine plus iniparib showed the potential for PARP inhibitors in the treatment of BRCA2-associated pancreatic cancer[41]. Similar clinical trials are currently underway
Screening	Screening goals
	The goal of PDAC screening is the detection and treatment of (1) resectable PDAC; (2) PanIN-3 lesions; and (3) IPMN with high-grade dysplasia
	Low prevalence and high risk cohort enrichment
	The low absolute risk of PDAC development precludes population-wide screening from a cost-benefit and absolute harm perspective. The opportunity to screen high-risk cohorts will vastly increase the PPV of a screening test
	Screening efforts
	Past screening efforts, using patients cohorts at a high risk of developing PDAC, have demonstrated diagnostic yields from 1.1% to 50%, depending on their definition of yield (Table 3). Current screening modalities may be costly and invasive, and therefore associated with some patient risk. Furthermore, the long-term implications for detection of small and clinically insignificant lesions are uncertain. Further studies are needed to determine appropriate surveillance
Anticipated future advances and screening possibilities	Risk stratification
	Personal, family, genetic and environmental history will allow risk stratification and development of tailored screening and surveillance programs
	Biomarkers
	Ongoing research that suggests a future for gene expression profiling, proteomics, metabolomics, and microRNA as diagnostic PDAC biomarkers
	Targeted therapy
	As with BRCA2-associated tumors and PARP inhibitors, tumor biology will increasingly dictate the subsequent therapy

PDAC: Pancreatic ductal adenocarcinomas; IPMN: Intraductal mucinous cystic neoplasm.

should occur only under research protocol conditions, and required a threshold of at least 10-fold increased risk of PDAC. However, there was no consensus on the approach to screening, when to begin screening, and frequency of surveillance.

In 2011, the International Cancer of the Pancreas Screening (CAPS) Consortium held a conference with a panel of 49 experts from multiple disciplines, with the goal "to develop consortium statements on screening, surveillance and management of high-risk individuals with an inherited predisposition to PC [pancreatic cancer]"[9]. There was agreement that detecting and treating invasive resectable PDAC as well as multifocal PanIN-3 and IPMN with high-grade dysplasia should be considered a successful outcome of a screening or surveillance program.

The CAPS consortium suggested guidelines for PDAC screening, based on evidence of increased PDAC risk[9]. The statements agreed upon (> 75% consensus) were to screen candidates with: (1) two FDRs with PDAC; (2) two blood relatives with PDAC and at least one FDR; (3) PJS; (4) *BRCA2* mutation carriers with either one FDR with PDAC or at least two affected family members; (5) *PALB2* mutation carriers with at least one FDR with PDAC; (6) *p16* mutation carriers (FAMMM) with at least one FDR with PDAC; and (7) lynch syndrome and one FDR with PDAC. While they agreed that initial screening should include EUS and/or MRI/MRCP, there was no consensus about when to start or end screening.

Risk stratification

Based on personal and family history and genetic testing, patients can be stratified into risk categories. Verna *et al*[181] defined average risk patients as having one family member with PDAC, diagnosed at age 55 or older; these patients do not receive screening with EUS or MRI. Moderate risk patients were defined as those with two or more first, second, or third-degree relatives with PDAC, or an FDR with PDAC diagnosed earlier than age 55; these patients are screened with EUS or MRI. Finally, high risk patients had three or more first, second, or third-degree relatives with PDAC, two or more FDRs with PDAC, one FDR and one SDR with PDAC one of whom was diagnosed before age 55, or a genetic syndrome with PDAC associated with it; these patients receive both EUS and MRI. For all of the risk groups, any abnormal testing is followed by EUS if not already done. Following this screening, if no malignant or premalignant

disease is found, the patient is surveilled based on their risk factors. If malignant or premalignant disease is suspected or diagnosed, surgery must be considered.

Past PDAC screening efforts

A number of PDAC screening programs directed at various high-risk groups have been published, largely focusing on EUS as a screening modality. While each group screened individuals only at elevated risk of PDAC, inclusion criteria, screening modalities, and definition of diagnostic yield varied across groups, resulting in a wide range of reported yields. Their results, with diagnostic yields ranging from 1.1% to 50%, can be found in Table 3[3,9].

CONCLUSION

PDAC is the fourth most common cause of cancer-related deaths in the United States and a major health issue[1]. With dismal five-year survival rates, significant advances in the understanding of the etiology and tumor biology, as well as early detection, screening and treatment of PDAC are needed (Table 4). Given that only those diagnosed at an early or precancerous stage have a reasonable expectation of low morbidity and mortality, increased efforts are needed to improve risk stratification and identify early stage disease or premalignant conditions while they are still resectable. PDAC screening efforts in these enriched cohorts may also allow us to identify more effective modalities for early detection and screening, which could be then modified and instituted in the general population.

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P- Reviewer: Westgaard A **S- Editor**: Zhai HH
L- Editor: A **E- Editor**: Wang CH

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ISSN 1007-9327