The American Journal of Pathology, Vol. 189, No. 1, January 2019

ELSEVIER

The American Journal of PATHOLOGY

ajp.amjpathol.org

Pancreatic Cancer Theme Issue

REVIEW

Familial Pancreatic Ductal Adenocarcinoma

Kelly E. Diaz* and Aimee L. Lucas*†

From the Samuel Bronfman Department of Medicine and the Henry D. Janowitz Division of Gastroenterology,† Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York*

Accepted for publication June 11, 2018.

Address correspondence to Aimee L. Lucas, M.D., M.S., Henry D. Janowitz Division of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1069, New York, NY 10029. E-mail: aimee.lucas@mssm.edu.

Pancreatic ductal adenocarcinoma (PDAC), although a rare disease, has a poor prognosis. With 5-year overall survival of 8%, there is a critical need to detect PDAC early or at a premalignant stage. Current screening methods are largely imaging based, but a more focused screening approach based on modifiable and nonmodifiable risk factors may improve the efficacy and likely outcomes of screening. In addition, the pathologic mechanisms that lead to the development of PDAC are discussed in an effort to further understand the targets of pancreatic cancer screening. The focus of this article will be inherited pancreatic cancer syndromes and familial pancreatic cancer, which together compose up to 10% of PDAC. Understanding the methods and targets of PDAC screening in high-risk individuals may translate to improved morbidity and mortality. *(Am J Pathol 2019, 189: 36–43; https://doi.org/10.1016/j.ajpath.2018.06.026)*

Pancreatic cancer (PC) affected 2.4% of the world in 2012 and has a high morbidity and mortality.[1] It is the fourth most common cause of cancer death in the United States, with an estimated 43,090 deaths in 2017,[1,2] and has been projected to be the second leading cause of cancer death in 2020.[3] Of the cases of PC, 94% are pancreatic ductal adenocarcinoma (PDAC) that develop in the exocrine tissue of the pancreas.[2] PDAC arises in the sporadic setting, associated with a known inherited cancer syndrome, or in familial PC (FPC)[4]; this article will focus on the latter two categories. Approximately 10% of PDACs have a hereditary component, and of the cases of familial PDAC, 20% have an identifiable germline mutation.[5,6]

Because of low prevalence in the general population, population-based screening programs for PDAC do not exist. However, certain risk factors may increase the utility and outcome of screening methods. With 29% 1-year survival and 7% 5-year survival rates across all stages, strategies to safely and effectively screen for PDAC in high-risk individuals are increasingly important.[7] The survival rate significantly decreases as tumor size increases, reinforcing the need for early effective screening methods.[8] We will focus on the risk factors, pathology, screening methods, and intervention for PDAC in inherited cancer syndromes and FPC.

Risk Factors

Nonmodifiable Risk Factors (Genetics)

Inherited cancer syndromes, in order of highest to lowest increased risk of PDAC, include Peutz-Jeghers syndrome (PJS), hereditary pancreatitis (HP), familial atypical multiple mole melanoma syndrome, Lynch syndrome (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis, hereditary breast and ovarian cancer syndrome, and ataxia telangiectasia (Table 1).[9–11] However, a germline mutation is not identified in most PDACs that appear to have a hereditary component.

FPC is defined by consensus as families with at least two first-degree relatives with PDAC who do not meet criteria for a known PDAC-associated hereditary syndrome.[12–14] In individuals with two first-degree relatives with pancreatic cancer, the relative risk and lifetime risk are 6.4% and 9% to

Supported by the American Cancer Society grant 129387-MRSG-16-015-01-CPHPS (A.L.L.).

Disclosures: None declared.

This article is a part of a review series on benign and neoplastic pancreatic lesions from their pathologic to molecular profiles and diagnoses.

https://doi.org/10.1016/j.ajpath.2018.06.026

Table 1 Cancer Syndromes and PDAC Risk

Cancer syndrome	Gene mutation	Increased PDAC risk	PDAC lifetime risk, %	Age to initiate surveillance, years
Familial pancreatic cancer	Unknown			50 (or 10 years younger than youngest diagnosed age of PDAC)
2 FDR		SIR, 6.4		
3+ FDR		SIR, 32.0		
Peutz-Jeghers syndrome	*STK11 (LKB1)*	132%	11–32	30–35
Hereditary pancreatitis	*PRSS1*	RR, 69	25–40	40
Familial atypical multiple mole melanoma syndrome	*P16INK4A/CDKN2A*	RR, 46	17	50 (or 10 years younger than youngest diagnosed age of PDAC)
Lynch syndrome (HNPCC)	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*		8.6	50 (or 10 years younger than youngest diagnosed age of PDAC)
FAP	*APC*		1.7	50 (or 10 years younger than youngest diagnosed age of PDAC)
Cystic fibrosis	*CFTR*	5.3-fold increased risk	<5	50 (or 10 years younger than youngest diagnosed age of PDAC)
HBOC syndrome	*BRCA1*, *BRCA2/FANCD1*, *PALB2/FANCN*, *FANCC*, *FANCG*	*BRCA2*: 4.6-fold increased risk *BRCA1*: 2-3-fold increased risk	3–8	50 (or 10 years younger than youngest diagnosed age of PDAC)
Ataxia telangiectasia	*ATM*	Twofold increased risk		50 (or 10 years younger than youngest diagnosed age of PDAC)

FAP, familial adenomatous polyposis; FDR, first degree relative; HBOC, hereditary breast and ovarian cancer; HNPCC, hereditary nonpolyposis colorectal cancer; PDAC, pancreatic ductal adenocarcinoma; RR, relative risk; SIR, standardized incidence ratio.

18%, respectively. Furthermore, individuals with three affected first-degree relatives have a relative risk and lifetime risk of 32% and 38%, respectively.[15] The gene mutation causing FPC, likely functioning in an autosomal dominant manner with reduced penetrance, has not yet been determined.[16]

PJS, a result of a germline mutation in the *STK11 (LKB1)* gene, is associated with hamartomatous polyps throughout the gastrointestinal tract and characteristic mucocutaneous pigmentation often found on the perioral or buccal mucosa.[17] *STK11* is a tumor suppressor gene; when a second somatic mutation in the *STK11* allele is acquired, disease manifestations are noted.[18] PJS is associated with a significantly increased risk of many extraintestinal cancers (ie, breast, ovarian, and cervical) and gastrointestinal cancers, including a 132% increased risk and 11% to 36% lifetime risk of developing PDAC.[9,19] Given this increased risk, National Comprehensive Cancer Network Guidelines recommend screening for pancreatic cancer in individuals with PJS starting at the age of 30 to 35 years.[12]

Mutations in both *PRSS1* and *SPINK1* can cause HP. However, mutations in *PRSS1* lead to an autosomal dominant form of inheritance. They are present in 80% of patients with HP.[20] *SPINK1* mutations are inherited in complex inheritance patterns, and <1% of patients with these mutations develop pancreatitis.[6] HP is characterized by recurrent episodes of acute pancreatitis in adolescents, leading to chronic pancreatitis by early adulthood.[20] *PRSS1* encodes trypsinogen, which is cleaved to its active form in the small intestine. With this mutation, there is premature activation of pancreatic enzymes within the pancreas that are thought to cause the recurrent inflammatory responses in acute pancreatitis. Although the relative risk of PDAC in HP was 69%, the risk was noted to be higher in patients who had additional modifiable risk factors, like tobacco use and diabetes, as discussed below.[21]

Familial atypical multiple mole melanoma syndrome is associated with a mutation in *CDKN2A/p16INK4A* and is characterized by a history of malignant melanoma in one or more first-degree relatives and multiple atypical melanocytic nevi.[22] Mutations in the *CDKN2A* gene disrupt the p16INK4 protein, allowing cells to inappropriately progress from the G_1 to the S phase with uncontrolled cell growth. There is a 47% relative risk of PDAC in this population.[10]

Lynch syndrome, or hereditary nonpolyposis colon cancer, is caused by a germline mutation in one of the DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*.[23] These patients are at increased risk of multiple

types of cancers: colorectal, endometrial, ovarian, stomach, small intestine, hepatobiliary system, urinary tract, brain, and pancreatic cancer. The lifetime risk of PDAC in hereditary nonpolyposis colorectal cancer has been estimated as high as 8.6%; however, other studies have found that mismatch repair genes have a lifetime risk of 3.7% of developing PDAC.[24,25]

Familial adenomatous polyposis is characterized by multiple colorectal adenomatous polyps and involves a germline inactivating mutation in the tumor suppressor *APC* gene. In addition to an increased risk of pancreatic cancer, these patients are at increased risk of extracolonic tumors, such as desmoid, duodenal, ampullary, thyroid, hepatoblastoma, and brain.[12] The *APC* gene encodes β-catenin, which interacts with E-cadherin. When the *APC* gene is mutated, the cell division process is unchecked and cells cannot suppress overgrowth, leading to malignancy. Mutation in the *APC* gene can also cause altered cell migration and chromosomal instability, predisposing the cell to mutations in other genes leading to tumor progression and proliferation. Even after colectomy, these patients remain at increased risk of cancer in the anal transition zone, the ileal pouch, and other gastrointestinal organs.[12] There is a 4.5% increased risk of developing PDAC and a lifetime risk of 1.7%.[26]

Cystic fibrosis is an autosomal recessive disease resulting from a mutation in the *CFTR* gene. In cystic fibrosis, it is thought that the pancreatic exocrine dysfunction predisposes patients to chronic pancreatitis, and this chronic inflammation leads to the development of PDAC.[27] In patients with cystic fibrosis, there is a 5.3-fold increased relative risk of PDAC.[28] Individuals with cystic fibrosis are at increased risk of many other cancers as well: colon cancer, small-bowel cancer, and lymphoid leukemia.[29] These individuals may also be at increased risk of gastrointestinal cancer after organ transplant.

Hereditary breast and ovarian cancer syndrome and other Fanconi anemia genes involve mutations in *BRCA1*, *BRCA2/FANCD1*, *PALB2/FANCN*, *FANCC*, and *FANCG*. *BRCA1* and *BRCA2* encode proteins involved in repairing double-stranded DNA breaks. Fanconi anemia genes are similarly involved in multiple DNA repair mechanisms, including the *BRCA1/BRCA2* pathway. Hereditary breast and ovarian cancer syndrome presents with early-onset breast and ovarian cancers. Although *BRCA2* mutations are associated with a fourfold to sixfold increased risk of PDAC, the association of *BRCA1* mutations is less well defined, with some finding a twofold to threefold increased risk and others finding no association.[11,30–35] *BRCA2* is associated with an increased risk of melanoma, whereas both *BRCA1* and *BRCA2* are associated with an increased risk of male breast cancer and prostate cancer.

PALB2 binds to the *BRCA2* protein; this interaction allows for repair and checkpoint functions and tumor suppression activity.[36] *PALB2* mutations are known to increase susceptibility to PDAC, a relatively new disease association. In patients with familial pancreatic cancer, the prevalence of the *PALB2* mutation is between 1% and 4%.[37,38]

Ataxia telangiectasia is an autosomal recessive disorder attributable to a homozygous mutation in the *ATM* gene and is characterized by cerebellar ataxia, oculocutaneous telangiectasias, abnormal eye movements, and immunodeficiency. However, monoallelic carriers of *ATM* mutations are at increased risk of breast, pancreatic, lymphoid, and central nervous system cancers. There is a twofold increased risk of PDAC.[39] Interestingly, the incidental discovery of the association of *ATM* gene and PDAC was made with unbiased genome-wide sequencing.[39]

Modifiable Risk Factors

In addition to multiple genetic risk factors, modifiable risk factors may also be important in prevention of PDAC. Tobacco use doubles the risk of pancreatic cancer relative to the general population and may accelerate the onset of illness.[40,41] The inflammatory response to carcinogenic chemicals in tobacco (N-nitrosamines, polycyclic aromatic hydrocarbons, aromatic amines, and free radicals) is thought to be the mechanism of PDAC development by increasing DNA synthesis, DNA lesions, inflammatory cytokines, like IL-8 and transcription factor NF-κB, and ultimately inflammatory pancreatic tissue damage.[42] Smokeless tobacco also increases the risk of PDAC.[1]

Even among individuals with a family history of PDAC, the standardized incidence ratio of PDAC in smokers was 19.2 compared with 6.25 in nonsmokers.[15] Prolonged exposure corresponds with increased risk.[42] Tobacco use can increase the risk of familial pancreatic cancer in patients and decreases the age of onset by approximately 10 years.[41] In addition, in individuals with HP, smoking lowered the age of onset of PDAC and led to double the risk of PDAC development.[43]

Heavy alcohol use (nine or more drinks per day) is associated with a 60% increased risk of PDAC and reduced survival from PDAC.[44,45] In a meta-analysis, in which heavy alcohol use was defined as three or more drinks per day, the relative risk of PDAC was 1.16 in females and 1.19 in males.[46] In studies with heavy alcohol use defined as seven or more drinks per day, the relative risk was 0.78 (95% CI, 0.43−1.44) in females compared with 1.27 (95% CI, 1.03−1.56) in males.[46] Light and moderate alcohol use has not been found to increase risk of PDAC, and the effects of specific types of alcohol have not been well studied. There are no data on the impact of heavy alcohol use in the setting of FPC or gene mutations predisposing to PDAC. The association between alcohol and PDAC is thought to be because of the functional impairment of the pancreas and pancreatic enzyme dysfunction.[47] Similar to the effect of toxins in tobacco, alcohol has many carcinogenic compounds, like ethanol, acetaldehyde, and N-nitrosodimethylamine, that trigger an inflammatory response, contributing to the development of cancer.[48] Studies are confounded by

the fact that alcohol use is a significant risk factor for pancreatitis and the association of heavy alcohol use with obesity and tobacco use.

The inflammatory response is a key mechanism in pancreatitis that can lead to pancreatic cancer. In pancreatitis, the premature activation of digestive enzymes in the pancreatic enzymes leads to autodigestion and the release of further inflammatory cells.[49,50] The acute inflammatory response includes stroma formation, infiltrating granulocytes, monocytes, pancreatic stellate cells, and macrophages. The pancreatic stellate cells then trigger further inflammation and development of pancreatic fibrosis, which is a known risk factor for pancreatic cancer. The inflammatory response is thought to suppress immune surveillance and inhibit oncogene-induced senescence.[51,52] Studies have found that patients with a history of chronic pancreatitis have up to a 13-fold increased risk of developing PDAC because of chronic inflammation.[21,53]

Obesity also significantly increases the risk of PDAC, likely because of more frequent inflammation and hormonal disruption in obesity. A comparison of those with a body mass index of $\geq$30 kg/m^2 and those with a body mass index of $<$23 kg/m^2 found a significantly increased risk of pancreatic cancer, with an relative risk of 1.72.[54] One study found a body mass index of $>$40 kg/m^2 associated with a relative risk of PDAC of 1.49 for men and 2.76 for women.[55] The mechanism of the development of PDAC in obese individuals is multifactorial, thought to be because of both inflammation and cell proliferation. The excess adipose tissue in obesity can release proinflammatory cytokines that promote tumor progression and metastasis.[56] In addition, obesity is thought to increase the risk of PDAC attributable to pancreatic hypertrophy and hyperplasia attributable to fat in the duodenum.[57] Data are limited regarding the impact of obesity on FPC and PDAC risk in the setting of a germline mutation.

Diabetes has a bidirectional relationship with PDAC, because diabetes can be both a risk factor for and a complication of PDAC. Individuals with diabetes have a twofold increased risk of developing PDAC.[56] Some studies have suggested the possibility of screening for PDAC in older patients with recently diagnosed diabetes.[58] In fact, recent data have suggested that the development of glucose intolerance may develop years before the diagnosis of PDAC.[59] However, diabetes can also be a consequence of the resection of PC, because of the loss of islet cells.

The mechanism of the development of PDAC in individuals with diabetes is thought to be associated with cell proliferation and decreased apoptosis. In diabetes, the environment of hyperglycemia, hyperinsulinemia, and changes in the insulin/insulin-like growth factor receptor pathways is thought to promote pancreatic ductal cell proliferation.[56,60] Typically, these environments have to be prolonged to increase the risk of pancreatic cancer. Insulin is thought to increase cell proliferation as well as increase glucose use by activating mitogen-activated protein kinase and phosphatidylinositol 3-kinase.[61] Metformin may decrease the risk of PDAC and improve survival in patients with PDAC by lowering insulin and insulin-like growth factor 1 levels.[56,62] Further studies are required to determine the impact of diabetes in FPC and germline mutations that predispose to PDAC.

Targets of Screening

To consider screening for a disease, several qualities must be met on the basis of the criteria established by Wilson and Jungner[63]: i) the disease must be an important public health issue, ii) facilities for diagnosis and treatment must be available, iii) there must be an identifiable precursor lesion in the latent or early asymptomatic stage, iv) treatments must be available, v) treatments should be acceptable to patients, and vi) testing must be suitable to the medical community and population to be screened.

PDAC has several well-defined precursor lesions, including pancreatic intraepithelial neoplasms (PanINs), mucinous cystic neoplasms (MCNs), and intraductal mucinous cystic neoplasms (IPMNs).[64–66] PanIN lesions are the most common and well characterized of the precursor lesions. PanIN lesions are typically noninvasive and nonmucinous, and they are graded on a two-tiered system (low versus high grade). Grading is based on architecture and nuclear atypia, including loss of polarity and nuclear crowding, and they may demonstrate a range of morphologies, including papillary, flat, and cribriform.[67] Early PanINs do not have known clinical significance, and only some PanIN lesions progress to invasive cancer.[6] However, PanIN lesions may be an important target in hereditary syndromes because they are found with a 2.75-fold increased frequency in familial PDAC cases.[68] A 2009 study found that noninvasive precursor lesions are more commonly identified in the surgical resection specimens of individuals with a family history of pancreatic cancer compared with the specimens of individuals with sporadic disease.[68] PanINs are challenging to identify in the absence of surgical resection, although an association with lobulocentric atrophy on endoscopic ultrasound (EUS) has been proposed.

MCNs typically occur in the body or tail of the pancreas and do not communicate with the pancreatic ductal system.[69] Given the absence of ductal involvement, patients with MCNs are less likely to present with jaundice, new-onset diabetes, or pancreatitis.[69] MCNs occur more often in females than males (approximately 20:1). The key feature distinguishing them from IPMNs is the underlying spindle cell ovarian-type stroma seen on histology.[67] It is estimated that 15% to 30% of MCNs may evolve into invasive PDAC.[69] An increased incidence of MCNs has not been reported in the familial setting.

IPMNs are grossly visible mucinous cystic neoplasms that typically occur throughout the pancreas.[67] Classified by location of ductal involvement within the gland, IPMNs are classified into a two-tiered system (low versus high grade) on the basis of histology. Different subtypes of IPMNs

include branch-duct, main-duct, and mixed-duct types. Involvement of the main duct is associated with a greater risk of progression to cancer. On EUS, identification of mucin excretion from the ampulla of Vater is strongly indicative of IPMN.[69] Small branch-duct IPMNs are not recommended for surgical resection given a low risk of progression of disease.[69] The degree of dysplasia helps predict the risk of progression. IPMNs are frequently identified in the setting of FPC or germline mutations predisposing to PDAC, and they may be multifocal.[68,70–72]

Recommendations for resection of IPMN in the sporadic setting vary by guidelines but overall are based on the type of cyst, severity of dysplasia, and imaging characteristics. Fukuoka Guidelines strongly recommend surgical resection of any IPMN involving the main pancreatic duct if the individual is surgically fit, whereas branch duct IPMNs are resected if there are high-risk stigmata, such as cyst size $\geq$3 cm, main pancreatic duct of 5 to 9 mm, thickened, enhanced cyst walls, lymphadenopathy, or nonenhanced mural nodules.[73] Recently published recommendations for asymptomatic pancreatic cysts conditionally recommend patients with both a solid component and a dilated pancreatic duct and/or concerning features on EUS and fine-needle aspiration undergo surgery.[2] Significant changes, such as development of a solid component, increasing size of the pancreatic duct, or diameter >3 cm may prompt an EUS for further evaluation.[2] These guidelines are based on expert consensus and may not necessarily apply to pancreatic neoplasia found in the background of FPC or a germline mutation.

Screening Methods

Many pancreatic cancers occur in the head of the pancreas, presenting with symptoms of obstructive jaundice and pancreatitis.[66] However, 52% of patients are diagnosed at a distant stage, with symptoms of weight loss, abdominal discomfort radiating to the back, and sometimes new-onset diabetes.[74] In these distant stages of the disease, 5-year survival is 3%. To detect PDAC at an earlier stage or before onset, improved screening methods are critical.

Because of low prevalence, it would not be effective or cost-effective to screen for pancreatic cancer in the general population. However, given the high mortality of PDAC, screening high-risk individuals may improve disease morbidity and mortality. Consensus-based screening recommendations suggest screening those individuals with increased risk of PDAC, such as individuals with FPC, PJS, HP, or familial atypical multiple mole melanoma syndrome. For those with *BRCA1*, *BRCA2*, *PALB2*, *ATM*, or Lynch syndrome mutations, screening may be considered in individuals with first- or second-degree relatives affected with pancreatic cancer.[12]

The current screening methods are largely imaging based and may use a combination of EUS and/or magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (Figure 1). EUS and MRI/magnetic resonance cholangiopancreatography are preferred because of the absence of ionizing radiation compared with computed tomography and accuracy in finding pancreatic

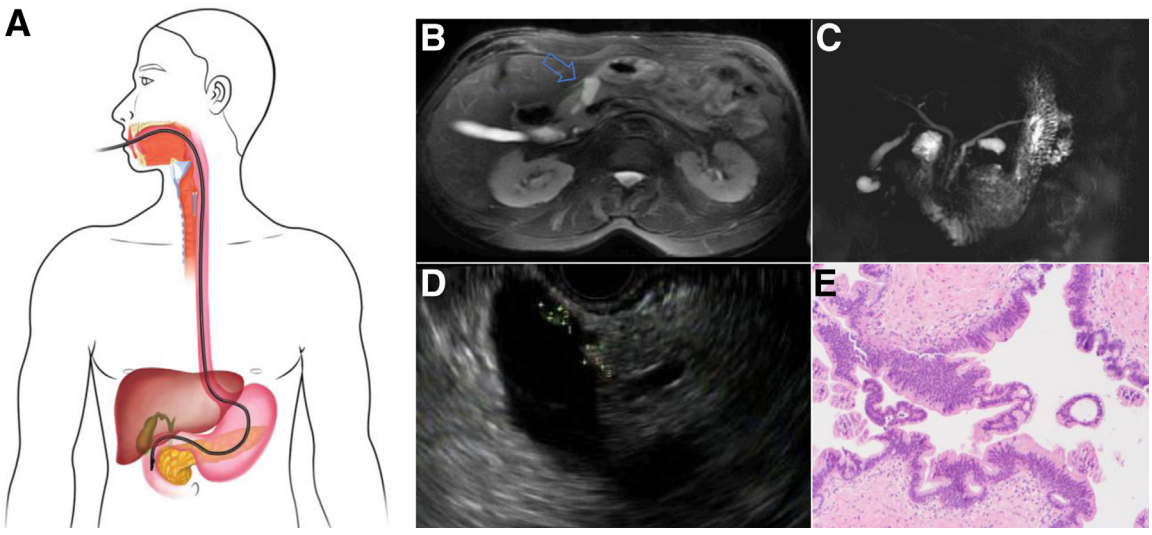

Figure 1 Screening for pancreatic ductal adenocarcinoma in high-risk individuals. **A**–**D:** Screening for pancreatic ductal adenocarcinoma may include endoscopic ultrasound (EUS; **A** and **D**) or magnetic resonance imaging (MRI; **B**) with magnetic resonance cholangiopancreatography (MRCP; **C**). **A:** During an EUS, an endoscope with an ultrasound probe at its tip is placed in the oropharynx and passed through the esophagus into the stomach and small intestine (image from Ni-ka Ford, printed with permission from Mount Sinai Health System). From various stations in the stomach and small bowel, pancreatic lesions may be visualized and sampled, as appropriate. **B: Arrow** indicates 3 cm pancreatic cyst. **B** and **C:** Representative MRI and MRCP images, respectively, from a familial pancreatic cancer patient are shown. **D:** A representative EUS image from the same patient, noting a 3 cm cystic lesion in the pancreas with two small nodules (printed with permission from Christopher DiMaio). **E:** The patient ultimately underwent surgical resection, which demonstrated an intraductal papillary mucinous neoplasm lined by gastric foveolar-type epithelium with up to severe dysplasia (hematoxylin and eosin staining; printed with permission from Hongfa Zhu). Original magnification, ×100 (**E**).

lesions.[70] Although EUS is more invasive than MRI, MRI can detect lesions outside of the pancreas. However, some individuals with claustrophobia or metallic implants cannot tolerate MRI. Magnetic resonance cholangiopancreatography may have increased sensitivity to detect the connection of lesions to the main pancreatic duct, whereas EUS may demonstrate improved sensitivity for solid lesions. Endoscopic retrograde pancreatography is not recommended because of the risk of pancreatitis.

Current guidelines recommend screening with EUS and/or MRI of the pancreas at the age of 50 years, with an exception for PJS, for which screening may begin at the age of 30 to 35 years, and *PRSS1*, for which screening may begin at the age of 40 years.[12,75] Given limited evidence of anticipation in successive generations, guidelines also recommend screening at 10 years younger than the earliest age of pancreatic cancer in the family.[41]

Ideally, screening programs target a disease with an effective treatment.[63] Unfortunately, <20% of pancreatic cancer patients are candidates for surgery, given the late stage of diagnosis; thus, early detection is key to implementation of effective treatment strategies.[74] Goals of a successful PDAC screening program, therefore, may include detection and treatment of high-grade PanIN, high-grade IPMN, and any early invasive cancer (ie, T1N0M0) or an invasive resectable cancer.[76]

Conclusion

Although screening and treatment methods have improved, further research will be necessary to find more effective methods of screening to improve PDAC survival. Focused screening of individuals that are at high risk of developing PDAC because of modifiable and nonmodifiable risk factors may improve timing of detection, disease morbidity, and mortality. A better understanding of the pathologic mechanisms of inflammation, cell proliferation, and decreased apoptosis that lead to PDAC in high-risk individuals may help guide the development of screening methods and thus improve outcomes.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015, 136:E359–E386
2. Vege SS, Ziring B, Jain R, Moayyedi P; Clinical Guidelines Committee; American Gastroenterology Association: American Gastroenterological Association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015, 148:819–822
3. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM: Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014, 74:2913–2921
4. Welinsky S, Lucas AL: Familial pancreatic cancer and the future of directed screening. Gut Liver 2017, 11:761–770
5. Bartsch DK, Gress TM, Langer P: Familial pancreatic cancer: current knowledge. Nat Rev Gastroenterol Hepatol 2012, 9:445–453
6. Hruban RH, Canto MI, Goggins M, Schulick R, Klein AP: Update on familial pancreatic cancer. Adv Surg 2010, 44:293–311
7. American Cancer Society: Cancer Facts and Figures 2016. Atlanta, GA, American Cancer Society, 2016
8. Hur C, Tramontano AC, Dowling EC, Brooks GA, Jeon A, Brugge WR, Gazelle GS, Kong CY, Pandharipande PV: Early pancreatic ductal adenocarcinoma survival is dependent on size: positive implications for future targeted screening. Pancreas 2016, 45:1062–1066
9. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME: High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol 2010, 105:1258–1264
10. de Snoo FA, Bishop DT, Bergman W, van Leeuwen I, van der Drift C, van Nieuwpoort FA, Out-Luiting CJ, Vasen HF, ter Huurne JA, Frants RR, Willemze R, Breuning MH, Gruis NA: Increased risk of cancer other than melanoma in CDKN2A founder mutation (p16-Leiden)-positive melanoma families. Clin Cancer Res 2008, 14:7151–7157
11. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL: Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 2002, 94:1358–1365
12. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology: ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015, 110:223–262
13. Hruban RH, Petersen GM, Goggins M, Tersmetter AC, Offerhaus GJA, Falatko F, Yeo CJ, Kern SE: Familial pancreatic cancer. Ann Oncol 1999, 10:S69–S73
14. Brand RE, Lerch MM, Rubinstein WS, Neoptolemos JP, Whitcomb DC, Hruban RH, Brentnall TA, Lynch HT, Canto MI; Participants of the Fourth International Symposium of Inherited Diseases of the Pancreas: Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut 2007, 56:1460–1469
15. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJA, Griffin C, Cameron JL, Yeo CJ, Kern SE, Hruban RH: Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004, 64:2634–2638
16. Klein AP, Beaty TH, Bailey-Wilson JE, Brune KA, Hruban RH, Petersen GM: Evidence for major gene influencing risk of pancreatic cancer. Genet Epidemiol 2002, 55:252–258
17. Jeghers H, McKusick VA, Katz KH: Generalized intestinal polyposis and melanin spots of the oral mucosa, lips, and digits: a syndrome of diagnostic significance. N Engl J Med 1949, 241:1031–1036
18. Jenne DE, Reimann H, Nezu J, Friedel W, Loff S, Jeschke R, Müller O, Back W, Zimmer M: Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet 1998, 18:38–43
19. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz-Correa M, Offerhaus JA: Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000, 119:1447–1453
20. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, Truninger K, Ammann R, Cavallini G, Charnley RM, Uomo G, Delhaye M, Spicak J, Drumm B, Jansen J, Mountford R, Whitcomb DC, Neoptolemos JP; European Registry of Hereditary Pancreatitis and Pancreatic Cancer: Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2004, 2:252–261
21. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R: Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol 2010, 24:349–358
22. Eckerle Mize D, Bishop M, Reese E, Sluzevich J: Familial atypical multiple mole melanoma syndrome. Cancer Syndromes [Internet]. Edited by Riegert-Johnson DL, Boardman LA, Hefferon T,

Roberts M. Bethesda, MD: National Center for Biotechnology Information (US), 2009
23. Kastrinos F, Stoffel EM: History, genetics, and strategies for cancer prevention in Lynch syndrome. Clin Gastroenterol Hepatol 2014, 12: 715−727
24. Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, Bandipalliam P, Stoffel EM, Gruber SB, Syngal S: Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009, 302: 1790−1795
25. Win AK, Young JP, Lindor NM, Tucker KM, Ahnen DJ, Young GP, Buchanan DD, Clendenning M, Giles GG, Winship I, Macrae FA, Goldblatt J, Southey MC, Arnold J, Thibodeau SN, Gunawardena SR, Bapat B, Baron JA, Casey G, Gallinger S, Le Marchand L, Newcomb PA, Haile RW, Hopper JL, Jenkins MA: Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol 2012, 30:958−964
26. Galiatsatos P, Foulkes WD: Familial adenomatous polyposis. Am J Gastroenterol 2006, 101:385−398
27. Cohn JA, Mitchell RM, Jowell PS: The impact of cystic fibrosis and PSTI/SPINK1 gene mutations on susceptibility to chronic pancreatitis. Clin Lab Med 2005, 25:79−100
28. Maisonneuve P, Marshall BC, Lowenfels AB: Risk of pancreatic cancer in patients with cystic fibrosis. Gut 2007, 56:1327−1328
29. Maisonneuve P, Marshall BC, Knapp EA, Lowenfels AB: Cancer risk in cystic fibrosis: a 20-year nationwide study from the United States. J Natl Cancer Inst 2013, 105:122−129
30. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I, Tang J, Li S, Zhang S, Shaw PA, Narod SA: Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 2006, 98:1694−1706
31. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HF, Ausems MG, Menko FH, Gomez Garcia EB, Klijn JG, Hogervorst FB, van Houwelingen JC, van't Veer LJ, Rookus MA, van Leeuwen FE; Netherlands Collaborative Group on Hereditary Breast Cancer: Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005, 42:711−719
32. Thompson D, Easton DF; Breast Cancer Linkage Consortium: Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002, 94: 1358−1365
33. Moran A, O'Hara C, Khan S, Shack L, Woodward E, Maher ER, Lalloo F, Evans DG: Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Fam Cancer 2012, 11:235−242
34. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE; Breast Cancer Linkage Consortium: Risks of cancer in BRCA1-mutation carriers. Lancet 1994, 343:692−695
35. Breast Cancer Linkage Consortium: Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999, 91:1310−1316
36. Xia B, Sheng Q, Nakanishi K, Ohashi A, Wu J, Christ N, Liu X, Jasin M, Couch FJ, Livingston DM: Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell 2006, 22:719−729
37. Tischkowitz MD, Sabbaghian N, Hamel N, Borgida A, Rosner C, Taherian N, Srivastava A, Holter S, Rothenmund H, Ghadirian P, Foulkes WD, Gallinger S: Analysis of the gene coding for the BRCA2-interacting protein PALB2 in familial and sporadic pancreatic cancer. Gastroenterology 2009, 137:1183−1186
38. Hofstatter EW, Domchek SM, Miron A, Garber J, Wang M, Componeschi K, Boghossian L, Miron PL, Nathanson KL, Tung N: PALB2 mutations in familial breast and pancreatic cancer. Fam Cancer 2011, 10:225−231
39. Roberts NJ, Jiao Y, Yu J, Kopelovich L, Petersen GM, Bondy ML, Gallinger S, Schwartz AG, Syngal S, Cote ML, Axilbund J, Schulick R, Ali SZ, Eshleman JR, Velculescu VE, Goggins M, Vogelstein B, Papadopoulos N, Hruban RH, Kinzler KW, Klein AP: ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov 2012, 2:41−46
40. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, Negri E, Li D, Risch HA, Olson SH, Gallinger S, Miller AB, Bueno-de-Mesquita HB, Talamini R, Polesel J, Ghadirian P, Baghurst PA, Zatonski W, Fontham E, Bamlet WR, Holly EA, Bertuccio P, Gao YT, Hassan M, Yu H, Kurtz RC, Cotterchio M, Su J, Maisonneuve P, Duell EJ, Boffetta P, La Vecchia C: Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012, 23:1880−1888
41. Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA: Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. Gastroenterology 2003, 124:1292−1299
42. Duell EJ: Epidemiology and potential mechanisms of tobacco smoking and heavy alcohol consumption in pancreatic cancer. Mol Carcinog 2012, 51:40−52
43. Lowenfels AB, Maisonneuve P: Epidemiology and prevention of pancreatic cancer. Jpn J Clin Oncol 2004, 34:238−244
44. Islami F, Tramacere I, Rota M, Bagnardi V, Fedirko V, Scotti L, Garavello W, Jenab M, Corrao G, Straif K, Negri E, Boffetta P, La Vecchia C: Alcohol drinking and laryngeal cancer: overall and dose-risk relation–a systematic review and meta-analysis. Oral Oncol 2010, 46:802−810
45. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, Bosetti C, Li D, Gallinger S, Miller AB, Bueno-de-Mesquita HB, Talamini R, Polesel J, Ghadirian P, Baghurst PA, Zatonski W, Fontham E, Bamlet WR, Holly EA, Gao YT, Negri E, Hassan M, Cotterchio M, Su J, Maisonneuve P, Boffetta P, Duell EJ: Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol 2012, 23:374−382
46. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, Corrao G, Bravi F, Boffetta P, La Vecchia C: Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. Int J Cancer 2010, 126:1474−1486
47. Zhang S, Wang C, Huang H, Jiang Q, Zhao D, Tian Y, Ma J, Yuan W, Sun Y, Che X, Zhang J, Chen H, Zhao Y, Chu Y, Zhang Y, Chen Y: Effects of alcohol drinking and smoking on pancreatic ductal adenocarcinoma mortality: a retrospective cohort study consisting of 1783 patients. Sci Rep 2017, 7:9572
48. Seitz HK, Stickel F: Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer 2007, 7:599−612
49. Shah AU, Sarwar A, Orabi AI, Gautam S, Grant WM, Park AJ, Shah AU, Liu J, Mistry PK, Jain D, Husain SZ: Protease activation during in vivo pancreatitis is dependent on calcineurin activation. Am J Physiol Gastrointest Liver Physiol 2009, 297:G967−G973
50. Manohar M, Verma AK, Venkateshaiah SU, Sanders NL, Mishra A: Pathogenic mechanisms of pancreatitis. World J Gastrointest Pharmacol Ther 2017, 8:10−25
51. Guerra C, Collado M, Navas C, Schuhmacher AJ, Hernandez-Porras I, Canamero M, Rodriguez-Justo M, Serrano M, Barbacid M: Pancreatitis-induced inflammation contributes to pancreatic cancer by inhibiting oncogene-induced senescence. Cancer Cell 2011, 19: 728−739
52. Inman KS, Francis AA, Murray NR: Complex role for the immune system in initiation and progression of pancreatic cancer. World J Gastroenterol 2014, 20:11160−11181
53. Kirkegard J, Mortensen FV, Cronin-Fenton D: Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. Am J Gastroenterol 2017, 112:1366−1372
54. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS: Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001, 286:921−929
55. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003, 348:1625−1638
56. Cui Y, Andersen DK: Diabetes and pancreatic cancer. Endocr Relat Cancer 2012, 19:F9−F26

57. Jarosz M, Sekula W, Rychlik E: Influence of diet and tobacco smoking on pancreatic cancer incidence in Poland in 1960-2008. Gastroenterol Res Pract 2012, 2012:682156
58. Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, Petersen GM: Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology 2008, 134:95−101
59. Sharma A, Smyrk TC, Levy MJ, Topazian MA, Chari ST: Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. Gastroenterology 2018, 155: 490−500.e2
60. Li J, Cao G, Ma Q, Liu H, Li W, Han L: The bidirectional interaction between pancreatic cancer and diabetes. World J Surg Oncol 2012, 10:171
61. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D: Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 2005, 294:2872−2878
62. Amin S, Mhango G, Lin J, Aronson A, Wisnivesky J, Boffetta P, Lucas AL: Metformin improves survival in patients with pancreatic ductal adenocarcinoma and pre-existing diabetes: a propensity score analysis. Am J Gastroenterol 2016, 111:1350−1357
63. Wilson JM, Jungner YG: [Principles and practice of mass screening for disease] Spanish. Bol Oficina Sanit Panam 1968, 65:281−393
64. Hruban RH, Maitra A, Kern SE, Goggins M: Precursors to pancreatic cancer. Gastroenterol Clin North Am 2007, 36:831−849
65. Esposito I, Konukiewitz B, Schlitter AM, Kloppel G: Pathology of pancreatic ductal adenocarcinoma: facts, challenges and future developments. World J Gastroenterol 2014, 20:13833−13841
66. Corbo V, Tortora G, Scarpa A: Molecular pathology of pancreatic cancer: from bench-to-bedside translation. Curr Drug Targets 2012, 13:744−752
67. Kamisawa T, Wood LD, Itoi T, Takaori K: Pancreatic cancer. Lancet 2016, 388:73−85
68. Shi C, Klein AP, Goggins M, Maitra A, Canto M, Ali S, Schulick R, Palmisano E, Hruban RH: Increased prevalence of precursor lesions in familial pancreatic cancer patients. Clin Cancer Res 2009, 15: 7737−7743
69. Pittman ME, Rao R, Hruban RH: Classification, morphology, molecular pathogenesis, and outcome of premalignant lesions of the pancreas. Arch Pathol Lab Med 2017, 141:1606−1614
70. Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, Topazian M, Takahashi N, Fletcher J, Petersen G, Klein AP, Axilbund J, Griffin C, Syngal S, Saltzman JR, Mortele KJ, Lee J, Tamm E, Vikram R, Bhosale P, Margolis D, Farrell J, Goggins M; American Cancer of the Pancreas Screening Consortium: Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology 2012, 142:796−804
71. Verna EC, Hwang C, Stevens PD, Rotterdam H, Stavropoulos SN, Sy CD, Prince MA, Chung WK, Fine RL, Chabot JA, Frucht H: Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. Clin Cancer Res 2010, 16:5028−5037
72. Ludwig E, Olson SH, Bayuga S, Simon J, Schattner MA, Gerdes H, Allen PJ, Jarnagin WR, Kurtz RC: Feasibility and yield of screening in relatives from familial pancreatic cancer families. Am J Gastroenterol 2011, 106:946−954
73. Tanaka M, Fernandez-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K; International Association of Pancreatology: International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012, 12:183−197
74. American Cancer Society: Cancer Facts and Figures 2017. Atlanta, GA, American Cancer Society, 2017
75. Ulrich CD; Consensus Committees of the European Registry of Hereditary Pancreatic Diseases; Midwest Multi-Center Pancreatic Study Group, International Association of Pacreatology: Pancreatic cancer in hereditary pancreatitis: consensus guidelines for prevention, screening and treatment. Pancreatology 2001, 1:416−422
76. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, Nio Y, Schulick RS, Bassi C, Kluijt I, Levy MJ, Chak A, Fockens P, Goggins M, Bruno M; International Cancer of Pancreas Screening Consortium: International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013, 62:339−347