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Pancreatic Cancer Screening

Eun Ji Shin, MD and **Marcia Irene Canto, MD, MHS***
Department of Internal Medicine, Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, 1830 East Monument Street, Baltimore, MD 21205, USA

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PANCREATIC CANCER: WHY CONSIDER SCREENING?

Pancreatic cancer remains one of the most deadly diseases, despite significant advances in medicine over the past decade. Pancreatic adenocarcinoma is the fourth leading cause of cancer deaths in the United States for both males and females, with an estimated 44,030 new cases and 37,660 deaths in 2011.[1] In contrast to the death rates for other leading causes of cancer death (lung, colorectal, breast, and prostate), which have declined since 2003, the death rate from pancreatic adenocarcinoma has increased during the same time period.[1] Unfortunately, the majority of symptomatic patients are incurable. The prognosis for patients with pancreatic adenocarcinoma remains poor: a 5-year relative survival rate of 6% for all stages combined, most likely because of the late stage of disease at the time of diagnosis. Hence, there has been a strong interest in detecting precursor lesions or small asymptomatic cancers that are potentially curable. A widespread screening program does not seem feasible or cost effective given the relatively low incidence of the disease, accounting for 3% of all new cancer cases in the United States, and the lack of accurate, inexpensive, and noninvasive diagnostic tests for early lesions. However, screening may be desirable in the selected population at increased risk for developing pancreatic adenocarcinoma.

GENETIC PREDISPOSITION TO PANCREATIC CANCER

Although the great majority of pancreatic adenocarcinoma cases are thought to be sporadic in nature, up to 10% of cases can be attributed to genetic factors.[2–4] In fact, familial clustering of pancreatic cancer was noted as early as 1967, when Lynch and colleagues reported on an adenocarcinoma-prone family.[5] Familial pancreatic cancer (FPC) is characterized by two or more first-degree relatives (FDRs) with pancreatic adenocarcinoma in the absence of known cancer syndromes or other diseases with known genetic defect. Individuals from a family with a pair of affected FDRs have a higher risk (6.4-fold to 32-fold) of developing pancreatic cancer.[6–9] Thus far, the key causative gene or genes leading to the inherited predisposition in familial pancreatic cancer have not yet been fully elucidated. Complex segregation analysis suggests that this predisposition may be due to a novel rare major gene with an autosomal dominant inheritance with reduced penetrance.[10–13]

*Corresponding author: mcanto1@jhmi.edu.

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Initial linkage analysis suggested that the mutation of the palladin gene may be involved in the development of pancreatic cancer in a specific kindred.[14] However, the initial excitement has been tempered by the failure of population-based studies in Canada and Europe to demonstrate that mutations in the palladin gene are more common in those with FPC as compared to controls.[15–18] Further, a study evaluating the pattern of palladin protein expression in 177 cases of pancreatic adenocarcinoma determined that although the palladin protein is overexpressed in the stroma, it is not overexpressed in the neoplastic cells in pancreatic cancer.[19]

To date, germline breast cancer 2 (*BRCA2*) mutation appears to be the most common genetic abnormality in patients from FPC kindreds who develop pancreatic adenocarcinoma, but still have been reported in only 6% to 19% of all FPC kindreds.[20–22] Mutations in the *BRCA2* gene can be present even in the absence of breast or ovarian cancer, and in apparently sporadic pancreatic cancer. Recent studies have identified another associated inheritable gene mutation, partner and localizer for breast cancer 2 gene (*PALB2*), as a pancreatic adenocarcinoma susceptibility gene, which may be causative for 3% to 4% of FPC.[7,9] The PALB2 protein directly binds to the breast cancer 1 gene (*BRCA1*) and acts as a bridge between *BRCA1* and *BRCA2* to form a complex involved in double-strand break repair.[23] The *PALB2* gene is present in 1% to 2% of patients with familial breast cancer. Subsequent testing of patients with a personal history of breast and pancreatic cancer[24] and also of non-*BRCA1* and non-*BRCA2* breast cancer women with a personal or family history of pancreatic cancer[25] has shown the *PALB2* mutation to be a very uncommon mutation. The clinical utility of routine testing of FPC patients for *PALB2* has not been proven.

INHERITED CANCER SYNDROMES

Hereditary Pancreatitis

Hereditary pancreatitis is a rare inherited disorder characterized by recurrent attacks of acute pancreatitis in childhood or early adolescence, followed by the development of chronic pancreatitis in late adolescence or early adulthood.[26] It is transmitted as an autosomal dominant disorder with incomplete penetrance.[27] Most are due to germ-line gain-of-function mutations in a cationic trypsinogen gene (*PRSS1*) on chromosome 7q35.[28–30] Mutations in *PRSS1* cause premature trypsin activation and ineffective autodegradation of active trypsin mutants, leading to autodigestion and acute pancreatitis.[31] Hereditary pancreatitis is associated with one of the highest estimated lifetime risks for developing pancreatic cancer among the inherited pancreatic cancer syndromes, with a lifetime risk approaching 40%.[32,33] Particularly in those individuals with a paternal inheritance pattern, the cumulative risk for developing pancreatic cancer is approximately 75%.[32] Tobacco smoking increases the risk even further in this population, by approximately twofold, and decreases the age at onset of pancreatic cancer by approximately 20 years.[27,34]

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is an autosomal dominantly inherited polyposis syndrome with high penetrance. The reported frequency of Peutz–Jeghers syndrome is 1 in 8300 to 280,000 individuals.[35] It is characterized by hamartomatous polyps of the gastrointestinal (GI) tract and mucocutaneous pigmentation. It is caused by an inherited germline mutation of the *STK11/LKB1* tumor-suppressor gene.[36] Patients with Peutz–Jeghers syndrome have a significantly increased lifetime risk for multiple GI cancers, including esophageal (0.5%), stomach (29%), small intestinal (13%), and colon (39%).[37] These patients are also at increased risk for non-GI cancers, including breast (54%), lung (15%), ovarian (21%), cervical (10%), uterine (9%), and testicular (9%). The cumulative lifetime risk for developing pancreatic cancer is 36%, with a relative risk (RR) of 132.[37]

Familial Atypical Multiple Mole Melanoma

Familial atypical multiple mole melanoma is an autosomally dominant disease with variable penetrance. It is characterized by familial occurrence of multiple benign melanocytic nevi, dysplastic nevi, and melanoma.[38] It is associated with germline mutations in the *p16/CDKN2A* gene.[39,40] This syndrome is associated with an increased risk of sarcomas and endometrial, breast, and lung cancers.[41,42] There is an approximately 13-fold to 22-fold increased risk of pancreatic cancer in these patients compared to the general population.[42,43]

Lynch Syndrome

Patients with hereditary nonpolyposis colorectal cancer syndrome, also known as Lynch syndrome, have mutations in the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Lynch syndrome is characterized by early-onset colorectal cancer. Patients with Lynch syndrome are also prone to develop other types of cancers, including endometrial, gastric, renal, ureteral, and small intestinal cancers.[44] Lifetime risk of pancreatic cancer in patients with Lynch syndrome is 3.7% up to the age of 70, which is an 8.6-fold increased risk compared to the general population.[45]

Familial Breast–Ovarian Cancer

Familial breast–ovarian cancer syndrome is an autosomal dominantly inherited syndrome associated with germline mutations in *BRCA1* and *BRCA2* tumor-suppressor genes involved in repair of DNA damage. Carriers of the gene mutations are at a high risk for developing early-onset breast and ovarian cancers, as well as cancers of the gallbladder and bile duct (RR 4.97), prostate (RR 4.65), stomach (RR 2.59), and malignant melanoma (RR 2.58).[46] *BRCA1* mutation is associated with a 2.3-fold to 3.6-fold increased risk for pancreatic cancer,[47,48] and *BRCA2* mutation is associated with a 3-fold to 10-fold increased risk for pancreatic cancer.[46,49,50] In patients with sporadic pancreatic cancer, 7.3% had a germline *BRCA2* mutation.[51] Approximately 1% of the general Ashkenazi Jewish population carries each of the *BRCA1* and *BRCA2* founder mutations.[52, 53] Studies have shown that the *BRCA2* mutation is found in 5.5% to 10% of patients with pancreatic adenocarcinoma who are of Ashkenazi Jewish descent.[52–55]

TARGETS FOR SCREENING AND SURVEILLANCE

The ideal screening strategy for pancreatic cancer would target high-grade benign noninvasive precursor neoplastic lesions (pancreatic intraepithelial neoplasias [PanINs] or intraductal papillary mucinous neoplasms [IPMNs]) before malignant transformation or at an early stage that would allow for curative surgical resection.[56] Although IPMNs can be detected as cystic lesions or a dilated main pancreatic duct or both, PanINs are small branch ducts less than 5 mm in size, often microscopic, and not reliably visualized by clinical imaging tests. Hence, the optimal strategy for detection of early pancreatic neoplasia may need to involve biomarker tests alone or in combination with imaging.

AVAILABLE AND ANTICIPATED TUMOR MARKERS

Currently, there is no biomarker with adequate sensitivity and specificity that can be used for routine clinical screening.[57] Given the typical late stage of disease at the time of diagnosis, there has been much effort invested in identifying accurate tumor markers to aid in earlier diagnosis of pancreatic cancer.

The most widely used serum marker in patients with pancreatic cancer is sialylated Lewis blood group antigen on MUC-1 (Mucin 1, cell surface associated), carbohydrate antigen 19-9 (CA 19-9). It is a cell surface glycoprotein expressed by pancreatic cancer cells, but is

also found in normal pancreatic and biliary duct cells and gastric, colonic, endometrial, and salivary epithelia.[58] Consequently, CA 19-9 is not routinely used for diagnosis because of the unacceptably high rate of false-positive results, with specificity ranging from 33% to 100%.[59–61] CA 19-9 is also associated with imperfect sensitivity, ranging from 41% to 86%.[59,61] Approximately 4% to 15% of the general population do not express the Lewis antigen and therefore do not have detectable CA 19-9 levels.[61–65] In patients with resectable pancreatic cancer, only 65% exhibit an elevated level of CA 19-9.[61] The marker is also inadequate to differentiate reliably between pancreatic cancer and chronic pancreatitis, as up to 40% of patient with chronic pancreatitis can exhibit elevated levels of CA 19-9.[61,66] Given its performance characteristics as a biomarker in the general population, serum CA 19-9 is used primarily for monitoring responses to therapy in patients already diagnosed with cancer, rather than for early diagnosis.[61,67–69] A recent feasibility study of 546 individuals with one or more FDRs with pancreatic cancer used serum CA19-9 as a screening test. In the 27 patients with elevated CA 19-9 levels, endoscopic ultrasound (EUS) was performed, and one case of asymptomatic pancreatic ductal adenocarcinoma was detected.[70]

Carcinoembryonic antigen (CEA) was the first biomarker used in diagnostics. Several studies have demonstrated high levels of CEA in the pancreatic juice of patients with pancreatic cancer compared to those with benign pancreatic disease.[71–74] When the CEA cutoff level was set at 50 ng/mL, the positive predictive value, negative predictive value, and accuracy for diagnosing pancreatic cancer were 77%, 95%, and 85%, respectively.[71,75] The main limitation of CEA is its low sensitivity, ranging from 25% to 56%, with relatively high specificity, ranging from 82% to 100% in distinguishing pancreatic cancer from benign pancreatic diseases.[59,76–81]

Much of the initial efforts in identifying novel markers of pancreatic cancer focused on carbohydrate antigens of MUC1 in hopes of improving the performance of CA 19-9. PAM4 is an anti-MUC1 monoclonal antibody that appears to detect MUC1 expressed by pancreatic cancer more specifically than it detects MUC1 antigens derived from other cancers (eg, breast and ovarian).[82] Further, in comparison with CA 19-9, PAM4 demonstrated higher sensitivity and specificity in discriminating patients with pancreatic cancer from those with chronic pancreatitis ($P<.003$).[82] As expected, patients with advanced disease had significantly higher levels that those with early disease. Diagnostic sensitivity of PAM4 for stage 3 and stage 4 disease was 91%; for stage 2, 86%; and for stage 1, 62% (stage 1A, 54%; stage 1B, 75%).[83] Further supporting the potential role of PAM4 in detecting early-stage pancreatic cancer, PAM4 expression was detected in precursor lesions of pancreatic adenocarcinoma, positive in 89% of PanINs and 86% of IMPNs examined, including 94% of the earliest neoplastic lesions, PanIN-1A and 1B.[84]

Recent studies have identified other potential biomarkers for pancreatic cancer, including CA494,[85] carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1),[86] parathyroid hormone-related protein (PTHrP),[87] tumor M2-pyruvate kinase (TuM2-PK),[88] anti-mucin antibody CAM 17.1,[78] and serum beta-human chorionic gonadotropin (β-HCG).[89] Although their performance characteristics in initial studies are promising, larger studies are needed to confirm their clinical applicability and they are currently used only in research settings.

Pancreatic juice sample provides a rich medium for genetic and epigenetic marker analysis. Pancreatic juice samples can be obtained at the time of endoscopic ultrasound (secretin-stimulated) or endoscopic retrograde cholangiopancreatography (duodenal aspirate[90] or pure pancreatic juice).[57] Markers that have been studied in pancreatic juice include K-*ras* mutations, *p53* mutations, DNA methylation aberrations, and mitochondrial DNA

mutations.[61] Mutant K-*ras* is a marker of particular interest because these mutations are present in 90% of pancreatic adenocarcinomas and it has been measured in pancreatic juice samples. However, its sensitivity and specificity for pancreatic cancer are poor (sensitivity 38%–62%; specificity 88%–90%), most likely because mutant K-*ras* can also be found in chronic pancreatitis and in PanINs without pancreatic cancer.[57,90–96] Mutations at *p53* are found in approximately 70% of invasive pancreatic adenocarcinomas[91] and have been detected in 40% to 50% of pancreatic juice samples and brush cytology specimens of patients with pancreatic cancer.[97] DNA promoter methylation alterations have been investigated in multiple candidate genes, including *p16*,[98,99] *RELN*,[100] *DAB1*,[100] *ppENK*,[101,102] *Cyclin D2*,[103] *SOCS1*,[104] *SPARC*,[105] *TSLC1*,[106] and others.[61,102,107] DNA promoter hypermethylation status was quantified in a panel of candidate genes (*Cyclin D2*, *FOXE1*, *NPTX2*, *ppENK*, *p16*, and *TFP12*) in pure pancreatic juice obtained from patients with pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasms, chronic pancreatitis, and controls with no known pancreatic disease, as well as a from a cohort of high-risk individuals from FPC kindreds. This method demonstrated high sensitivity (82%) and specificity (100%) in identifying patients with pancreatic cancer.[108] Mitochondrial DNA mutations are commonly found in multiple cancers.[61,109–113] Using chip technologies, initial studies appear to suggest that mitochondrial mutations can be reliably detected in pancreatic juice samples from patients with pancreatic cancer.[61,111]

APPROACHES TO SCREENING

Currently, there is no sufficiently sensitive, specific, and reliable screening test for the early detection of pancreatic cancer. The great majority of pancreatic cancers, accounting for at least 90% of all patients, are considered sporadic.[2–4] The detection rate is low in average-risk individuals because pancreatic cancer is a rare disease, despite its significant death toll. In screening studies performed in Japan, 5 cancers were found in 2511 individuals.[114] Given the overall low incidence of disease and the current lack of accurate, inexpensive, and noninvasive screening tests, the consensus is that widespread population-based screening for pancreatic cancer in the general population or in those with only one affected FDR is neither feasible nor indicated in most countries.[56] However, selective screening has been performed in high-risk patients from FPC kindreds and in patients with inherited cancer syndromes.[56,115,116]

The various approaches to screening and results of screening tests for asymptomatic pancreatic neoplasms are summarized in Table 1. One approach is population-based screening, such as that formed in Japan with abdominal ultrasound (with[114] or without[117] MRI). A second approach uses a serum biomarker such as serum CA19-9 followed by a pancreatic imaging test.[70] A third approach uses only abdominal imaging tests, such as computed tomography (CT), magnetic resonance imaging (MRI), EUS, or endoscopic retrograde cholangiopancreatography (ERCP), in combination or in sequence (ie, EUS after MRI or magnetic resonance cholangiopancreatography [MRCP], or CT if abnormal).

Multidetector computed tomography (MDCT) is currently the abdominal imaging test of choice for pancreatic disease, particularly for diagnosis of solid tumors and staging of pancreatic cancer.[118,119] Despite its high accuracy for detecting and staging of pancreatic malignancies, the sensitivity of MDCT may be suboptimal, as MDCT misses lesions when used for screening for early pancreatic neoplasia.[115,116,119] The sensitivity of thin-section, triple-phase helical CT to detect lesions smaller than 2 cm is only 70% to 80%.[56,120] Recent studies have shown that MDCT has a negative predictive value of 87% for tumor resectability[121] and an accuracy rate of 85% to 95%.[75,122,123] Further, there is also a concern for radiation exposure if CT is used as part of a long-term screening or surveillance program, particularly in individuals with impaired DNA mismatch repair gene function due

to *BRCA1*, *BRCA2*, or *PALB2* gene mutation. Hence, CT is not the ideal screening or surveillance imaging test for high-risk individuals. Further, MDCP with a pancreatic protocol may not be as sensitive as EUS in at-risk individuals from FPC kindreds[115,116,124] (Canto MI, Hruban RH, Fishman EK, et al. Screening for prevalent early pancreatic neoplasia in high risk individuals: a prospective multicenter blinded study of EUS, CT, and MRI. Submitted for publication).

MRI may be an appropriate choice for noninvasive screening of high-risk patients because it is able to image the entire abdomen and pelvis, unlike EUS, while avoiding radiation exposure, unlike CT. MRCP is able to image pancreatic ductal anatomy noninvasively (unlike ERCP) and small cystic lesions such as IPMNs. Preliminary data from high-risk patients who underwent surgical resection suggest that MRI/MRCP may be superior to CT, particularly for detection of IPMNs (71% vs 14%, $P<.0001$).[56,124] A prospective MRI-based screening study of 79 patients aged 39 to 72 years with a *p16* Leiden mutation, which is associated with familial atypical multiple mole melanoma syndrome, has shown that early-stage pancreatic cancers can be detected at baseline and during follow-up.[125] After a median follow-up period of 4 years (range, 0–10 years), pancreatic cancer was diagnosed in seven patients (9%). The mean age at diagnosis was 59 years (range, 49–72 years). Three of the asymptomatic pancreatic cancers were present at the first examination, and four were detected after a negative result in the initial examination. All seven patients with cancer had resectable lesions; five underwent surgery, three had an R0 resection, and two had lymph node metastases. Further, possible precursor lesions (ie, duct ectasias or branch-duct IPMNs, based on MRCP) were found in nine individuals (11%).

EUS has been used to screen high-risk individuals in several screening programs.[60,115,116,126,127] It can provide high-resolution images of the pancreas without the risk of radiation exposure and can image mural nodules (focal thickening of the wall in branch duct IMPNs), which are associated with increased risk of malignancy.[57,119,128] The disadvantages of EUS are that it is operator dependent and is an endoscopic procedure with the inherent risks of procedure and sedation, which may limit its role in a widespread screening and surveillance program. Preliminary analysis of high-risk individuals enrolled in a screening program who underwent surgical resection suggests that EUS can detect almost twice as many neoplastic lesions as CT or MRI/MRCP.[56,124] Published studies using EUS-based screening for high-risk individuals have reported detection of asymptomatic precancerous branch duct IPMNs, large PanINs, incidental pancreatic endocrine tumors, and ductal adenocarcinomas. One Dutch study of *BRCA1*, *BRCA2*, or *p16* germline mutation carriers, patients with Peutz–Jeghers syndrome, and relatives of patients reported a high one-time yield of EUS-based screening. The authors found a 6.8% prevalence (n = 3 of 44 individuals screened) of asymptomatic pancreatic ductal adenocarcinomas (12, 20, and 50 mm in size).[126] All cancers were completely resected but two already had lymph node metastases at presentation. Further, the diagnostic yield of EUS-based screening for prevalent precursor branch duct IPMNs was 16%.

The clinical utility of ancillary studies such as fine-needle aspiration (FNA) and ERCP is not clear. EUS-guided FNA has been used to investigate pancreatic cystic lesions and can provide a cytologic diagnosis of IPMN in 71% of the cases.[129] The need for routine FNA of pancreatic cysts in a high-risk population has not been proven, given that the majority of cystic lesions detected are typically small branch duct IPMNs that do not require surgical treatment. EUS-guided FNA can also lead to false-positive results if cytologic aspirates show severe dysplasia or findings suspicious for ductal adenocarcinoma, which can lead to potentially unnecessary surgery.[115] ERCP has been used routinely in high-risk patients from FPC kindreds with abnormal EUS, but this resulted in a post-ERCP pancreatitis rate of 7% in one study.[115] Further, ERCP did not reliably demonstrate ductal communication of

branch duct IPMNs or lead to additional clinically relevant imaging findings. Hence, most formal screening programs around the world do not recommend routine ERCP for asymptomatic individuals.

SUMMARY

Accumulating data indicate that clinically available abdominal imaging tests such as EUS and MRI/MRCP can detect asymptomatic precursor benign (IPMN, PanIN) and invasive malignant pancreatic neoplasms, such as ductal adenocarcinoma, in individuals with an inherited predisposition. These asymptomatic FPCs detected have been more likely to be resectable, compared to symptomatic tumors. The most challenging part of screening high-risk individuals is the selection of individuals with high-grade precursor neoplasms for preventive treatment (ie, surgical resection before development of invasive cancer). Ongoing and future research should focus on formulating and validating a model for FPC risk and neoplastic progression using patient characteristics, imaging, and biomarkers. The comparative cost and effectiveness of various approaches for screening and surveillance of high-risk individuals also deserves study. For now, screening is best performed in high-risk individuals within the research protocols in academic centers with multidisciplinary teams with expertise in genetics, gastroenterology, radiology, surgery, and pathology.

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Table 1

Approaches to pancreatic screening

	Sequential Serum Biomarker + Imaging	Sequential Abdominal Imaging Tests	Single or Concurrent Imaging Tests
Sporadic population		Transabdominal US followed by noncontrast MRI/MRCP, prospective study in 2511 patients found 5 cancers (4 resectable)[130]	Transabdominal US in 130,951 patients found 3 PDA[117]
High-risk population	Serum CA19-9 followed by EUS if >37 U/mL detected in 546 individuals with ≥1 FDR with pancreatic cancer found pancreatic neoplasms in 5/546 (1 early cancer)	MRI/MRCP or CT followed by EUS in FPC relatives found IPMN and PDA in 8.3%[130] EUS followed by ERCP (when abnormal) detected PanINs[60]	MRI/MRCP only in 79 *p16* mutation carriers detected 5 cancers[125] EUS + MRI/MRCP in FPC relatives detected IPMNs or PDA or both[131] EUS + MDCT in FPC relatives detected IPMNs, PNET, and PDA[115,116] EUS only in FPC relatives and mutation carriers detected IPMNs and PDA[126]

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FDR, first-degree relative; FPC, familial pancreatic cancer; IPMNs, intraductal papillary mucinous neoplasms; MDCT, multi-detector computed tomography; MRI/MRCP, nagnetic resonance imaging/magnetic resonance cholangiopancreatography; PanINs, pancreatic intraepithelial neoplasias; PDA, pancreatic ductal adenocarcinoma; PNET, Pancreatic neuroendocrine tumors; US, ultrasound.