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Screening for Pancreatic Cancer

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INTRODUCTION

Pancreatic cancer (PC) is a highly fatal disease. In the United States, approximately 53,070 new cases of PC were projected to occur in 2016, accompanied by an estimated 41,780 cancer deaths.[1] PC can only be cured by complete surgical resection. However, most patients with PC have unresectable disease at the time of diagnosis. Therefore, there is a need to detect PC and its precursor lesions earlier in asymptomatic patients before disease progression so that a cure can more likely be achieved.

Because of the low incidence of PC, screening is not cost-effective for population-based screening. Individuals with genetic risk factors for PC based on their family history or known PC-associated genetic syndromes are at high risk to develop PC. Thus, these high-risk individuals (HRIs) can be a potential target for PC screening programs. This article provides an overview of the epidemiology and genetic background of familial PC and discusses the diagnostic and management approaches for these patients.

EPIDEMIOLOGY AND RISK FACTORS FOR FAMILIAL PANCREATIC CANCER

About 5% to 10% of individuals with PC have a family history of the disease.[2,3] Hereditary risk for PC can be categorized into 2 groups: (1) hereditary cancer syndromes and (2) familial pancreatic cancer. The former refers to patients with defined inherited cancer syndromes in which patients are at increased risk for a number of malignancies, including pancreatic cancer. On the other hand, familial PC is defined as those having at least a pair of affected first-degree relatives (FDRs) with PC (Box 1).

Nongenetic factors also contribute to the increased risk associated with a family history of PC. Smoking is an independent risk factor for familial PC (odds ratio [OR], 3.7; 95%

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confidence interval [CI], 1.8–7.6). The age of onset of familial PC is similar to that of sporadic PC (>60 years).[4] Smoking lowers the age of onset by approximately 20 years in hereditary pancreatitis and decreases age of onset of PC in familial kindreds.[5,6] Members of familial PC kindreds should be counseled not to smoke.[7]

GENETIC PREDISPOSITION FOR PANCREATIC CANCER

Several genetic predispositions have been described to be associated with PC. Although most genetic defects causing hereditary PC remain to be discovered, several genetic cancer syndromes associated with PC have been described.

Patients with inherited cancer syndromes such as hereditary pancreatitis, Peutz-Jeghers syndrome (PJS), familial atypical multiple mole melanoma, Lynch syndrome (hereditary nonpolyposis colorectal cancer), ataxia telangiectasia, and Li-Fraumeni syndrome have an increased risk of developing PC (Table 1). It should be noted that individuals with PC gene mutations susceptible to PC may not have a family history of PC.[8] Germline mutations in the BRCA2, PALB2, p16, STK11, ATM, PRSS1, PALB2 genes, and the hereditary colon cancer genes, are associated with significantly increased risk of PC. Among these, BRCA1 and BRCA2 mutations are the most common known mutations in familial PC (12%–19%).[9,10]

Hereditary Pancreatitis

Hereditary pancreatitis is an autosomal-dominant disorder with incomplete penetrance. It is commonly associated with mutations in serine protease 1 gene (PRSS1) on chromosome 7q35, which encodes cationic trypsinogen. The International Hereditary Pancreatitis Study Group reported that the risk of PC is approximately 50 to 60 times greater than expected compared with the background population.[5] In a French case series, the standardized incidence ratio (SIR) of PC was 87 (95% CI 42–113). The cumulative risk of PC at age 50 and 75 years was 11% and 49% for men and 8% and 55% for women, respectively. Smoking and diabetes mellitus were the main associated risk factors.[11] Despite the high risk of PC, patients with hereditary pancreatitis have similar mortality risk compared with the general population.[12] The diagnostic yield and outcomes of screening for PC in this subgroup of HRIs have not been well studied.

Hereditary Breast Cancer

BRCA2 mutations are frequently found (5%–17%) in patients with familial PC.[10,13,14] The risk of PC in those with BRCA2 gene mutation is increased 3.5-fold (range 1.87–6.58).[15,16] Approximately 1% of all Ashkenazi Jews carry BRCA2 genes. Therefore, individuals with Jewish ancestry and a diagnosis of PC should be referred for BRCA gene mutation screening (6174delT), which is present in 1% of Ashkenazi Jewish individuals[17] and 4% of patients with PC.[18]

About 1% of BRCA1/BRCA2-negative breast cancer cases with PC are caused by germline defects in the PALB2 (partner and localizer of BRCA2) gene.[19,20] PALB2 mutations have been identified in 2.1% to 4.9% of familial PC kindreds.[3,21,22] PALB2 gene mutations confer an increased risk of both breast and pancreatic cancer. The lifetime risk of PC in

affected individuals remains unknown. It is assumed that the risk in PALB2 mutation carriers may be comparable to that in BRCA1/BRCA2 carriers.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal-dominant syndrome associated with mutations of STK11 gene. This condition is at high risk of cancers of the gastrointestinal tract, lung, breast.[23] The risk of developing PC is very high, with lifetime risk of 11% to 36% by the age of 70.[24,25]

Familial Atypical Multiple-Mole Melanoma Syndrome

Familial atypical multiple-mole melanoma (FAMMM) syndrome is caused by mutation of CDKN2A (so-called p16 or multiple tumor suppressor-1 gene). The syndrome is characterized by multiple nevi, cutaneous and ocular malignant melanomas, and PCs. A variant syndrome, so called “the FAMMM-pancreatic carcinoma syndrome,” carries a cumulative risk of PC up to 17% by age 75.[26–31]

Lynch Syndrome

Individuals with the DNA mismatch repair gene mutations (MLH1, MSH2, MSH6, PMS2) have a cumulative risk of 3.7% to develop PC by the age 70 and 8.6-fold increased risk compared with the general population.[32–34] Medullary histology is a characteristic feature of a mismatch repair-deficient cancer, and individuals with PC who have this history should have further testing for Lynch syndrome.[35]

Familial Pancreatic Cancer

Familial PC (FPC) is defined as a genetic predisposition in individuals with at least a pair of FDRs with pancreatic ductal adenocarcinoma, in the absence of a known genetic susceptibility syndrome. The literature has suggested that the risk of developing PC among an individual with family history of pancreatic cancer ranges from 1.5- to 30-fold.[10–12,20,36–40] Data from a prospective registry-based study revealed that the overall risk of PC in member of FPC kindreds was a ninefold increase (95% CI: 4.5–16.1). This risk increases with the number of affected relatives: 4.6-fold increased risk (95% CI, 0.5–16.4) for 1 FDR with PC; 6.4-fold increased risk (95% CI: 1.8–16.4) for 2 FDRs with PC, and 32.0-fold increased risk (95% CI: 10.2–74.7) for 3 or more FDRs with PC.[2]

A statistical risk assessment model “PancPRO” has been developed to estimate the risk of a future PC for asymptomatic individuals based on the individual’s family history.[41] In an Italian prospective study, the lifetime risk of PC was calculated by PancPro. The pedigrees of 570 families of patients presenting with pancreatic ductal adenocarcinoma were collected. Considering a tenfold risk over the general population as a threshold for including a subject in a surveillance program, 19 families (3.3%) involving 92 FDRs with age greater than 40 years would be selected in a surveillance program.[42]

SCREENING AND SURVEILLANCE OF PANCREATIC CANCER

Most PC is believed to arise from pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasms (IPMNs). A pathologic study has suggested that PC developing in familial cancer kindreds arises from PanIN.[43] Patients who have curative surgery for noninvasive and small, margin-negative PC have a significantly improved long-term survival.[44]

The goal of screening and surveillance of PC is to detect and curatively resect pre-invasive lesions with high-grade dysplasia (HGD). These lesions mainly are PanIN3 and IPMN with HGD, which are at high risk of malignant transformation into PC. Noninvasive precursor lesions are more common and of a higher grade (PanIN 3 and IPMN with HGD) in familial PC patients than in patients with sporadic disease.[45–47] Rate of progression of these preinvasive lesions to invasive cancer in HRIs remains to be determined. However, data from nonfamilial PC patients suggest that sporadic noninvasive IPMN takes 3 to 5 years to become an invasive PC.[48] About 2% to 7% of small branch duct IPMNs progress to invasive PC over 5 year follow-up.[49,50]

Several cohort studies have reported a diagnostic yield of screening programs for PC in HRIs ranging from 3.9% to 50%, varying depending on study populations and study endpoints.[51–60] Small pancreatic cysts, likely representing branch duct IPMNs, are the most common abnormal finding and are found in 34% to 53% of HRIs within the screening program.[60] Solid lesions are less common.

Age Initiate to Screening

The age to initiate screening and age to end screening of pancreatic lesions in HRIs remain unclear. For patients with hereditary pancreatitis, a consensus conference recommended that screening should be offered to patients who are at least 40 years of age due to young age onset of PC in affected individuals.[61] Similarly, patients with Peutz-Jeghers syndrome should begin screening earlier, at about 30 years of age or older because of younger age of onset of PCs (about 45 years). For HRIs with familial PC, a multidisciplinary international consortium recommended starting screening at age 50.[62] Some centers start screening at age 55, because the median age of onset of familial PC is 65 years, similar to that in sporadic PC. Most familial PCs are diagnosed in patients 60 years or older.

Imaging Modalities

Imaging modalities such as computed tomography (CT), endoscopic ultrasonography (EUS), and MRI with cholangiopancreatography (MRCP) have been studied for screening and surveillance of PC in HRIs.

The initial screening should include EUS and/or MRI/MRCP but not CT.[62] Pancreas protocol-enhanced CT provides high-resolution imaging of the pancreas; however, it has a lower detection rate of small pancreatic lesions in the high-risk population compared with EUS or MRI.[51,54,60,63] CT scan can be used to further characterize the solid lesion if it is found on the screening imaging.[62] MRI and CT scan also allow examination of other

abdominal organs, which is important for certain genetic syndromes with elevated risk of multiple organ malignancy.

In a multicenter study involving 225 asymptomatic HRIs who underwent screening for PC, CT, MRI, and EUS detected a pancreatic lesion in 11%, 33%, and 42% of patients, respectively. The detected pancreatic lesions included 82 IPMNs and 3 pancreatic endocrine tumors.[60] In the study of patients with sporadic IPMNs, EUS was superior to transabdominal ultrasound, CT scan, and MRI in detection of IPMN-derived and -concomitant PC at diagnosis and during follow-up.[64]

Cost-Effectiveness of Screening

A few studies on cost-effectiveness of screening for PC in HRIs have been reported. In patients with Peutz-Jeghers syndrome who are at increased risk of PC, screening would cost more than $35,000 per life saved.[65] In a decision analysis comparing 1-time screening for pancreatic dysplasia with EUS versus no screening, endoscopic screening was cost-effective, with an incremental cost-effectiveness ratio of $16,885/life–year saved.[66]

Serologic Testing

It is known that serum CA 19-9 is neither sensitive nor specific for PC, and it is not appropriate for mass screening. Data on blood tests for biomarkers of PC such as serum CA19-9 in HRIs are limited. In a prospective cohort study using serum CA 19-9 in 546 individuals who had at least 1 FDR with PC, CA 19-9 was elevated in 4.9% of cases. Neoplastic or malignant findings were detected in 5 patients (0.9%), and pancreatic adenocarcinoma was detected in 1 patient (0.2%).[67]

Pancreatic Juice and Pancreatic Cyst Fluid Biomarkers

Prevalence of genetic alterations that contribute to familial PC such as mutant KRAS2 and inactivation of TP53 or SMAD4 is similar to that of sporadic PC.[68] Thus, genetic markers of sporadic pancreatic adenocarcinomas can be used to detect familial PC. Genetic markers for PC in pancreatic juice and/or pancreatic cyst fluid may improve early diagnosis of and screening for high-risk lesions that are not detectable by imaging, thus improving identification of lesions that require surgery.[69]

EUS-guided fine needle aspiration (EUS-FNA) allows sampling of the pancreatic cyst fluid and cyst wall, which can be sent for a range of tests including molecular testing. In a multicenter, retrospective study of 130 patients with resected pancreatic cystic neoplasms, cyst fluid was analyzed in order to

- Identify gene mutations in pancreatic cysts (BRAF, CDKN2A, CTNNB1, GNAS, KRAS, NRAS, PIK3CA, RNF43, SMAD4, TP53, and VHL)
- Identify loss of heterozygosity at CDKN2A, RNF43, SMAD4, TP53, and VHL tumor suppressor loci
- Identify aneuploidy

A panel of molecular markers and clinical features can classify cyst type with 90% to100% sensitivity and 92% to 98% specificity.[69] The clinical benefit of these molecular markers in pancreatic cyst fluid in HRIs has not been well studied.

EUS-FNA is generally safe procedure; however, it can rarely cause bleeding, pancreatitis, and infection. In addition, in patients with multiple pancreatic lesions, sampling of all lesions may not be feasible. Furthermore, cytologic analyses of the FNA specimens may lead to false-positive diagnoses of pancreatic neoplasia. Routine EUS-FNA is not performed unless there is a solid lesion of any size or a mural nodule in a cyst of any size. To avoid potential adverse events and limitation related to EUS-FNA, there have been increasing interests in analysis of molecular markers in pancreatic juice collected from duodenum.

In a study of secretin-stimulated pancreatic juice collected from the duodenum during upper endoscopy by Kanda and colleagues,[70] GNAS mutations were found in 66% of IPMNs, a rate similar to that observed in cyst fluid aspirated during EUS. The same group further examined TP53 mutations, a known tumor suppressor gene that has been implicated in progression of IPMNs, in duodenal samples of pancreatic juice.[71] They identified TP53 mutations in pancreatic juice in 67% of patients with pancreatic ductal adenocarcinoma and PanIN-3 or IPMN with HGD, but not in individuals without advanced lesions. These studies suggested that pancreatic juice collected from the duodenum can potentially be used as a screening modality for PC.

MANAGEMENT OF DETECTED PANCREATIC LESIONS IN ASYMPTOMATIC HIGH-RISK INDIVIDUALS

Most pancreatic lesions in asymptomatic HRIs undergoing screening can be observed and do not require surgery.[60] Prophylactic pancreatectomy is not recommended for asymptomatic HRIs without pancreatic lesions because of morbidity and mortality related to surgery.[62] Discussions regarding the need for surgery in asymptomatic high-risk individuals with screening-detected pancreatic lesions should ideally occur in a multidisciplinary setting, similar to tumor board. Surgery should be performed in a high-volume center with expertise in pancreatic surgery.

Solid pancreatic lesions are found in 1.4% of asymptomatic HRIs.[60] According to consensus guidelines, solid lesions, particularly those seen by multiple imaging modalities, are ominous, and the threshold for surgical resection is much lower. There was no consensus on management of indeterminate smaller solid lesions (<1 cm diameter). EUS-FNA of these lesions can be considered, although the diagnostic yield is usually low.[62]

Cystic pancreatic lesions were found in 39% of HRIs within a screening program.[60] Most of these lesions appear to be low-risk branch-duct IPMNs.[62] International consensus guidelines for the management of IPMNs can be applied to HRIs with IPMNs to assess risk of HGD or malignancy.[72] In asymptomatic HRIs, surgery for suspected branch duct IPMNs can be considered for lesions 2 cm or larger or the presence of mural nodules or solid component.[62] The patient with a cyst without worrisome features of HGD or malignancy should be

monitored with imaging after 6 to 12 months.[23,62] Shorter follow-up (≤3 months) should be considered for indeterminate lesions.

If main pancreatic duct strictures/dilations are detected without associated lesions in the imaging study, repeat imaging within 3 months is recommended.[62] When main pancreatic duct dilation is associated with any cystic lesion, a concern for main duct involvement should be raised, even with duct size less than 5 mm.

SUMMARY

Screening and surveillance of HRIs for early pancreatic neoplasia, including high-grade, preinvasive precursor lesions and early PC, is currently recommended. The outcomes of surveillance and treatment of screening-detected lesions remain under evaluation. Optimization of surgical criteria for resection and development and validation of biomarkers in pancreatic juice, cyst fluid, and blood are needed.

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KEY POINTS

- Individuals with an inherited predisposition for pancreatic cancer (high-risk individuals) based on their family history or known pancreatic cancer-associated genetic mutation are at higher risk to develop pancreatic cancer.
- Noninvasive precursor lesions for pancreatic cancer are more common and of a higher grade in familial pancreatic cancer patients than in patients with sporadic disease. High-grade precursor duct lesions and small early stage pancreatic cancer are the targets for screening.
- Screening should include endoscopic ultrasonography and/or MRI/magnetic resonance cholangiopancreatography, ideally in a multidisciplinary setting. Computed tomography scan can be used to further characterize a solid lesion if it is found on the screening imaging.
- Surgery should be performed at centers with expertise in pancreatic surgery when there is a concerning solid lesion, cysts that are 2 cm or larger, mural nodule or solid component, or a dilated main pancreatic duct.

Box 1

High-risk individuals for pancreatic cancer screening

- Individuals with 3 or more affected blood relatives with PC, including at least 2 related by first degree (familial PC), with at least one of the affected related to the at-risk relative by first degree (parent, sibling, child)
- Individuals with at least 2 affected FDRs with PC
- All patients with Peutz–Jeghers syndrome should be screened, regardless of family history of PC
- *p16* (CDKN2A) gene mutation carriers with 1 affected FDR
- *BRCA2* gene mutation carriers with 1 affected FDR
- *BRCA2* gene mutation carriers with 2 affected family members (no FDR) with PC
- *PALB2* gene mutation carriers with 1 affected FDR
- ATM gene mutation carriers
- Mismatch repair gene mutation carriers (Lynch syndrome) with 1 affected FDR

Data from Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62(3):339–47.

Table 1

Inherited cancer syndromes associated with increased risk of pancreatic cancer

Syndrome	Gene(s)	Locus	Lifetime Risk of PC, Percent
Hereditary breast/ovarian cancer	BRCA2, BRCA1	13q	3–5
	PALB2	16p	Unknown
Familial atypical multiple mole melanoma syndrome	CDKN2A	9p	10–19
Peutz-Jeghers syndrome	STK 11	19p	11–36
Familial adenomatous polyposis	APC	5q	Unknown
Hereditary nonpolyposis colon cancer (Lynch II)	DNA mismatch repair genes	2p, 3p, 7p	4
Hereditary pancreatitis	PRSS1, SPINK1	7q, 5q	25–40
Ataxia telangiectasia	ATM	11q	Unknown
Li-Fraumeni syndrome	P53	17p	Unknown

Adapted from Brentnall TA. Management strategies for patients with hereditary pancreatic cancer. Curr Treat Options Oncol 2005;6:437; with permission.