Pancreatic cancer screening for high risk individuals: a clinical perspective

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ABSTRACT

Pancreatic cancer (PC) carries a poor prognosis with uniform fatality. The disease is often metastatic at the time of clinical diagnosis and survival rates have not improved over the past years. Due to lack of effective therapy, early detection has been proposed to reduce mortality, which remains elusive. Mass screening program for pancreatic cancer is not applicable to the general population. However, relatives of patients with PC and patients with certain other conditions are at higher risk of developing PC. Targeted screening for appropriately selected high-risk individuals for PC is being done at different centers. There is variation in the screening methodology and also in patient selection for screening. The purpose of this article is to review the available guidelines and the clinical studies of PC screening in high-risk individuals. For now, PC screening remains at the research level limited to patients with a high risk of PC; individuals with ≥3 first degree relatives with PC, those with FAMMM syndrome, Peutz-Jeghers syndrome and hereditary pancreatitis. Further larger studies are needed to evaluate the efficacy of suggested screening strategies before it can be implemented as standard practice.

Keywords: Pancreatic cancer; screening; endoscopic ultrasound; high-risk individuals.

INTRODUCTION

PC is the fourth leading cause of cancer death in men and women in western countries.[10] Despite improvements in surgical techniques and adjuvant therapies pancreatic cancer carries a dismal prognosis, with an overall 5-year relative survival of 5.8%.[10] In the recent years there has been tremendous growth in understanding different molecular and genetic events involved in the development and progression of pancreatic cancer. Several markers have been described for early detection of pancreatic cancer. In addition three well defined precursor lesions have also been identified. They include pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). However, no significant achievements have been made in translating new discoveries into routine clinical practice.

Screening and early diagnosis tools are lacking for PC and often patients are diagnosed with metastatic disease. For any screening program to be applicable to general population: in addition to being sensitive, safe, cost effective, acceptable to asymptomatic persons and should reduce morbidity and mortality. Ariyama et al.[19] from Japan reported 100% cure rates for patients resected for pancreatic tumors less than 1 cm, thus supporting the concept of screening for PC. Once clinically evident, PC has rapid disease progression and uniform fatality, hence the need for its early detection. There appears to be an opportunity of diagnostic and therapeutic window of many years between the initial mutation and development of non-metastatic pancreatic tumor. Screening for general population is not cost effective since the average
lifetime risk for PC in an individual without a family history of pancreatic cancer is about 1%. The age-adjusted yearly incidence of pancreatic cancer is below 10 in 100,000 both in Europe and America. However, the presence of family history of PC and certain well defined genetic tumor syndromes puts an individual to increased risk of PC. Screening such high risk individuals is being done in different centers but the optimal strategy is a matter of debate. The purpose of this article is to review the different studies of PC screening in targeted high risk individuals.

WHO ARE HIGH RISK INDIVIDUALS / RISK FACTORS FOR PC

Most pancreatic cancer cases are sporadic, however, certain risk factors are well described. They include increasing age, smoking, diabetes and chronic pancreatitis. The prevalence of PC in elderly, even in smokers is not high enough to justify mass screening program. The association of diabetes with pancreatic cancer is complex and is being further investigated. Chari et al. in a population-based cohort study reported that approximately 1% of patients newly diagnosed with diabetes 50 years of age or older were diagnosed with pancreatic cancer within first 3 years. Further research is needed to identify this subset of diabetic patients who go on to develop pancreatic cancer. There is wide variation in the risk of development of pancreatic cancer in patients with chronic pancreatitis and there are no formal guidelines in this regard.

About 10–15% of cases of PC are thought to be caused by inherited genetic factors. Some families have well defined genetic syndromes with known germ line mutations, such as hereditary nonpolyposis colorectal cancer (HNPCC), familial atypical multiple mole melanoma (FAMMM), hereditary breast and ovarian cancer, Li-Fraumeni syndrome and Peutz-Jeghers syndrome which are associated with increased risk of pancreatic cancer. More common are families with multiple family members with pancreatic cancer and no identifiable genetic mutation, known as familial pancreatic cancer (FPC). Another group of inherited risk factor for pancreatic cancer is the genetically driven chronic diseases such as hereditary pancreatitis and cystic fibrosis. These conditions increase the risk for pancreatic cancer several folds and have been the basis of targeted screening for pancreatic cancer.

Well defined cancer syndromes with increased risk for pancreatic cancer

Peutz-Jeghers syndrome characterized by hamartomatous polyps of gastrointestinal tract carries the highest lifetime risk of pancreatic cancer among these genetic syndromes. It is caused by autosomal dominant mutation of the STK11/LKB1 gene. The relative risk of pancreatic cancer in these patients is about 132-fold above that of the general population, with a cumulative risk of 36% by age 65 years. Familial atypical multiple mole melanoma characterized by dysplastic naevi and malignant melanoma is associated with increased risk of pancreatic cancer (9–12 fold). Mutations in the tumour suppressor CDKN2A are associated with FAMMM. Breast ovarian cancer syndrome characterized by germline mutations in the BRACA1 or BRACA2 genes is and is associated with a 10-fold increase in PC risk. BRACA2 mutation also appears to be the most common identified mutation in patients with FPC. There is also an associated increased risk of PC in patients with hereditary nonpolyposis colon cancer syndrome caused by mutations of DNA mismatch repair genes and in familial adenomatous polyposis syndrome due to mutation in APC tumor suppressor gene.

Genetic diseases that increase PC risk

This group of predisposing conditions includes diseases with genetic basis but not associated with multi organ cancers. Hereditary pancreatitis is the prototype in this group. It is an autosomal dominant disease resulting in acute pancreatitis in childhood with resultant progression to chronic pancreatitis. It is caused by mutations in the cationic trypsinogen gene, PRSS1 and has a lifetime pancreatic cancer risk of approximately 40%. and smoking increases the risk of PC in these patients. The two most common PRSS1 mutations are R122H and N29I. These result in premature activation of trypsinogen in the pancreas leading to pancreatitis. Cystic fibrosis is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane receptor (CFTR) gene. Increased risk of PC has been reported in patients with cystic fibrosis.

Familial pancreatic cancer (FPC)

PC has been noted to aggregate in families without evidence of other well defined genetic syndromes or cancers. It is generally defined as families in which two or more first-degree relatives with PC without any identifiable cause. The underlying genetic abnormality in FPC is not yet clearly established. The risk of PC increases with the number of family members affected. Data from the National Familial Pancreas Tumor Registry in the United States have shown that patients with two, or three and more affected first-degree relatives, had 6.4 to 32-fold higher risk of developing PC, respectively. Increase in risk of PC is less than 5-fold in patients with one first-degree relative with PC. Study from the Icelandic Cancer Registry estimates a 2.3-fold
increased risk\cite{19} whereas the US National Familial Pancreas Tumor Registry suggested 4.5-fold higher risk of PC in patients with single first-degree relative with PC.\cite{18}

**CLINICAL STUDIES OF PANCREATIC CANCER SCREENING**

Due to high mortality associated with PC, detection through screening offers an opportunity for early diagnosis and improved outcomes. The prevalence of PC is not high enough to justify mass screening in general population. However, with recognition of certain well defined risk factors of PC and improved imaging modalities, early detection of pancreatic neoplasia seems feasible. Screening of high risk individuals for PC has been reported from different centers utilizing different strategies. There is variability in both the criteria for patient inclusion as well as in the testing methodology.

The initial report of targeted screening for asymptomatic high risk individuals was by Brentnall et al.\cite{20} in 1999. The study included 14 patients from three large kindreds who had autosomal dominant inheritance of pancreatic cancer. They performed endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), spiral computed tomography, serum CEA and CA 19-9 levels. 7 patients underwent pancreatectomy on basis of abnormalities on EUS/ERCP and all 7 patients had histologic evidence of dysplasia (PanIN) in pancreatectomy specimens. EUS/ERCP findings seen were similar to those seen in chronic pancreatitis. Subsequently, experience was reported in 46 high risk patients by Kimmey et al.\cite{21} They evaluated patients in families with more than two first- or second-degree relatives with pancreatic cancer. EUS was used as the initial screening modality and those with abnormalities on EUS and no history of alcohol use were offered ERCP. Those with history of alcohol use and abnormal EUS underwent repeat EUS six months after abstinence. Patients with abnormal pancreatogram were offered surgical intervention. These asymptomatic patients were offered laproscopic distal pancreatectomy followed by completion pancreatectomy reserved for those with documented high-grade dysplasia. Twelve patients with abnormal EUS and ERCP underwent surgery (10 patients had total pancreatectomy and 2 had distal pancreatectomy). The resection specimens had no evidence of pancreatic cancer, but all specimens revealed widespread pre-cancerous (PanIN) lesions. Patients with abnormal EUS, but normal ERCP continued surveillance with EUS. 3 patients on follow up EUS had development of new changes and underwent pancreatectomy, again revealing ductal dysplasia. These findings on EUS are not specific for pancreatic dysplasia since similar findings are found in patients with chronic pancreatitis.\cite{21,22}

Similar PC screening experience was reported by Canto et al.\cite{23} in a cohort of 38 high risk patients. 31 were from kindreds with \(\geq 3\) affected with pancreatic cancer, 6 from kindreds with 2 affected relatives and 1 was a patient with Peutz–Jeghers syndrome. EUS was the initial screening procedure. If the EUS was abnormal (i.e., focal lesion such as mass, nodule, or cyst, or at least 3 of the 9 EUS features of chronic pancreatitis present), EUS-guided fine-needle aspiration (FNA) was performed. FNA was first obtained from pancreatic lesions and then random sampling of the pancreatic parenchyma was performed. Patients with abnormal EUS results also underwent dual-phase, multi-detector, spiral CT scan and were offered ERCP. Patients with suspicion of PC based on mass like finding or dysplastic changes on FNA cytology were offered surgical intervention. Pancreatectomy (total or distal) was performed based on the site distribution of the lesion in 7 out of 38 patients: 6 patients had a pancreatic neoplastic mass (1 invasive ductal adenocarcinoma, 1 benign intraductal papillary mucinous neoplasm, 2 serous cystadenomas, 2 nonneoplastic masses). The diagnostic yield for clinically significant lesions (adenocarcinoma and mucinous cystic lesion) from screening was 5.3% (2 of 38). Follow up EUS was performed a year later and in 4 patients on follow up there was increase in EUS abnormalities. However, FNA done in these 4 patients was negative for any atypia.

Subsequently, Canto et al.\cite{24} reported their experience in a larger cohort of 78 high risk patients; 6 had Peutz-Jeghers syndrome, and 72 were at-risk relatives from familial pancreatic cancer kindreds. EUS was the initial procedure and the pancreas was evaluated for changes of chronic pancreatitis as per previously described standard criteria.\cite{21,22} Chronic pancreatitis was defined on EUS as presence of \(\geq 3\) out of 9 sonographic features. Prominent finding on EUS was features of chronic pancreatitis in 78% of the study population. This finding was significantly more common than the control group. 8 patients with pancreatic neoplasia were found by surgery or FNA; 6 patients had benign intraductal papillary mucinous neoplasms (IPMN), 1 had an IPMN that progressed to invasive ductal adenocarcinoma, and 1 had PanIN changes. The diagnostic yield of screening was 10%.

A similar study utilizing EUS as the initial screening modality in Europe was published by Poley et al.\cite{25} in 2009. They screened 44 asymptomatic high-risk patients with EUS. 13 patients were from families with FAMMM syndrome, 21 with FPC, 2 hereditary pancreatitis, 2 were Peutz-Jeghers syndrome, 3 were BRCA1 and 2 were BRCA2 mutation carriers with familial clustering of PC, and 1 patient with Li-Fraumeni syndrome (p53 mutation). 3 patients (6.8%) were found to have a mass lesion and
underwent resection. Pathology showed moderately differentiated adenocarcinoma in all 3 patients with N1 disease in the 2 patients. In 7 patients small cystic lesions (Branch-IPMN) were found. They were small, unilocular and without any solid component, these patients did not undergo surgery and on 2 year follow up no change was reported. None of the patients in this group was reported to have EUS findings of chronic pancreatitis (≥3 criteria) as compared to 61 out of 78 patients with chronic pancreatitis changes reported by Canto et al.\(^\text{[25]}\)

Verna et al.\(^\text{[27]}\) reported their findings of yield of initial screening for PC in a cohort of 51 high-risk patients. They classified patients as average risk if they had only one family member affected by PC at an age >55 years; moderate risk if they had more than one family member with PC or one first-degree family member with the onset of disease at <55 years of age; high-risk patients were those who had a defined genetic cancer syndrome associated with PC (PJ, HNPCC, BRCa1/2, FAMMM, hereditary pancreatitis) and those with FPC. (FPC was defined as any three affected relatives, two first-degree relatives with pancreatic cancer, or one first-degree and at least one second-degree relative, one with onset at age <55). Their protocol of screening included EUS or MRI, CA 19-9 level and oral glucose tolerance test and patient were stratified into the risk categories as described. 6 out of 31 patients (19%) who underwent EUS had 3 or more pancreatic parenchymal changes suggestive of chronic pancreatitis. 2 patients were found to have pancreatic cancer (one resectable, one metastatic) and 5 patients with IPMN. 5 patients had surgical intervention. (1 total pancreatectomy for adenocarcinoma diagnosed on EUS-FNA and 4 patients had partial pancreatectomy. All four of these patients had branch type IPMN with multifocal PanIN2 lesions on pathology). Overall, 6 out of 51 patients (12%) had neoplastic lesions in the pancreas.

Ludwig et al.\(^\text{[28]}\) reported screening of PC in 109 at-risk relatives enrolled in their Familial Pancreatic Tumor Registry. Their initial screening intervention was MRCP followed by EUS if there were abnormalities on the imaging study. The criteria for at-risk relatives in this registry was defined as one or more first degree relative with PC before age 50 years, two or more relatives with PC (one of whom is first-degree), three or more second degree relatives with PC, or a known BRCa4 mutation with one or more relatives with PC. 18 out of 109 (16.5%) patients had abnormal finding on the initial imaging study. Based on imaging and subsequent EUS findings, 9 patients were determined to have clinically significant lesion and surgery was recommended. Out of these 9 patients 6 patients elected for pancreatic surgery (2 pancreaticoduodenectomies and 4 distal pancreatectomies). Pathology revealed two IPMNs, one PanIN3, one PanIN2, one T3N0 pancreatic cancer, and one serous cystadenoma. The overall diagnostic yield was 8.3% (9/109 patients).

Another European prospective screening study was reported by Langer et al.\(^\text{[29]}\). This was conducted by the National German Familial Pancreatic Cancer Registry on 76 asymptomatic high-risk individuals from 34 FPC and FAMMM kindreds over a period of 5 years. Diagnosis of FPC was based on the presence of two or more first-degree relatives with PC. The screening protocol included measuring serum CA 19-9, EUS, MRI/MRCP and these were repeated annually. FNA was performed in cases of detectable solid or cystic lesions or if there were diffuse parenchymal abnormalities. Their surgical intervention included intraoperative ultrasound and limited pancreatic resection which was evaluated by frozen section. If there was high grade PanIN or PC based on frozen section then the procedure was extended to total pancreatectomy. EUS revealed suspicious pancreatic and peripancreatic lesions in 25 of 76 (33%) individuals. 17 patients (22.4%) had EUS findings suggestive of chronic pancreatitis as evidenced by 3 or more standard criteria. Pancreatic resection surgery based on EUS abnormalities was performed in 6 patients. Pathology revealed serous cystadenomas (n = 3), PanIN1 lesion (n = 1), PanIN2 lesions (n = 1) and gastric type IPMN (n = 1). In this study no high grade lesion or cancer was detected and authors suggested that the current modality of screening for PC in high-risk individuals is not justified.

**DISCUSSION**

Screening for PC in the general population is not recommended with the current available tools and its relatively low incidence. However, there are these “high-risk” individuals who have varying degrees of increased risk of PC either due to family history of PC or certain genetic syndromes. Risk stratification of such individuals was addressed at the Fourth International Symposium of Inherited Diseases of the Pancreas.\(^\text{[30]}\) They classified their risk for PC into three categories: low (<5-fold), moderate (5 to10-fold) and high risk (>10-fold). As per the consensus conference it was felt to be appropriate to perform PC screening under research protocol for individuals who have >10-fold increased risk for developing PC. This group of high-risk individuals include: family members with ≥3 first-degree relatives with pancreatic cancer and people with FAMMM (p16 mutations), Peutz-Jeghers syndrome and hereditary pancreatitis. They also suggested screening for people who have ≥3 PC cases
among first-degree, second-degree and third-degree relatives, with at least one of these being a first-degree relative and for BRCA mutation carrier who have at least one case of PC within second-degree relatives.

The optimal screening strategy is unclear. There is no clear consensus on what age to start screening and what the surveillance interval should be. The studies of PC screening done so far have used different screening protocols. There is no consensus on the initial imaging modality of choice, however, it appears EUS is utilized by most centers. ERCP was used for PC screening in the initial study by Brennan et al., however, not in the later studies. Also, there is no recommendation regarding choice of CT scan or MRI/MRCP as the initial test for initial PC screening. Whether application of such EUS based screening programs in context of general clinical practice will translate into improved survival remains to be evaluated. There are no clear guidelines on how to manage patients once abnormalities are found on EUS or other imaging studies. There is variation in the method of histologic evaluation and surgical intervention for dysplastic lesions. Brennan et al. performed distal pancreatectomy followed by completion pancreatectomy if indicated, whereas Langer et al. utilized intraoperative ultrasound and frozen section to decide on total pancreatectomy.

There appear to be several unresolved issues in PC screening. The recent advances in understanding molecular events in PC pathogenesis and the emergence of biomarkers may translate into novel screening tools. The optimal screening test or strategy at this time is unclear. However, it appears EUS is utilized by most centers. ERCP was done so far have used different screening protocols. There is variation in the method of histologic evaluation and surgical intervention for dysplastic lesions. Brennan et al. performed distal pancreatectomy followed by completion pancreatectomy if indicated, whereas Langer et al. utilized intraoperative ultrasound and frozen section to decide on total pancreatectomy.

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