Screening and early detection of pancreatic cancer in high risk population

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Abstract
Pancreatic cancer is a serious growing health issue in developed countries. For patients diagnosed with pancreatic cancer, the five year survival rate is below 5%. One major important reason leads to the poor survival rate is lack of early detection of pancreatic cancer. Over 80% of the patients are diagnosed in advanced disease stages. Screening for pancreatic cancer is a desirable option for high risk individuals to allow early detection and treatment of curable pancreatic neoplasms at a pre-invasive stage. This article highlights the need, endpoint, population, method, diagnostic yield, and the problems of current screening programs.

INTRODUCTION
Pancreatic cancer is one of the most lethal diseases despite marked improvement in medical and cancer care over the past years. The number of newly diagnosed pancreatic cancer patients has increased significantly in recent years[1]. The most common histological subtype of pancreatic cancer is adenocarcinoma, which comprises 87% of the pancreatic malignancies. Among the pancreatic cancer patients, there were only 15%-20% diagnosed as “resectable” and surgery was the only way to treat the disease. The majority of the pancreatic cancer patients were diagnosed as unresectable and chemotherapy was the standard treatment to control the incurable disease. The prognosis for patients with pancreatic cancer remains poor. The overall survival rate was 5% combining all stages, 20% for patient with localized disease and 1%-2% for those with distant metastasis. In most cases, pancreatic cancer has progressed before clinical manifestation. Many patients initially thought to have localized and resectable cancer succumb to recurrent or metastatic disease. Hence, there is an urgent need to detect small asymptomatic cancers or precursor lesions, which are potentially curable for the most devastating disease.
OPPORTUNITY AND POTENTIAL WINDOW OF SCREENING

A recent study suggested that there may be a large window and good opportunity for detecting pancreatic cancer when the disease is in earliest and most treatable stages[3,5]. Quantitative analysis of the timing of the genetic evolution of sporadic pancreatic cancer indicated a time span of at least 10 years between the occurrence of cancer-initiating mutations and the formation of parental nonmetastatic founder cell[5]. Indeed, patients with pancreatic tumors diagnosed incidentally had longer median survival[3] than those with tumors discovered after symptoms appeared, suggesting that early detection of small asymptomatic cancers or precursors lesions may improve the outcome. Identification of high risk populations of pancreatic cancer for screening becomes essential. Distinct clinical and genetic features are thought to increase the risk of pancreatic cancers. It has been estimated about 10% of pancreatic cancer has a familial basis. Hereditary pancreatic cancer includes inherited cancer syndromes with a recognized known germline mutation associated with an increased risk of pancreatic cancer and familial pancreatic cancer with two or more cases of pancreatic cancer in their families. Screening pancreatic cancer in these high risk individuals might be recommended for early detection to improve the prognosis of pancreatic cancer. A multidisciplinary international consortium met to discuss pancreatic screening was held recently[8] and some statements regarding to pancreatic cancer screening were made and voted to guide the pancreatic cancer screening.

DEFINITION OF “SUCCESS” OF SCREENING

A very recent effort made by international cancer of the pancreas screening (CAPS) has proposed to define “successful screening” by detection and treatment of T1N0M0 margin negative pancreatic cancer and high grade dysplastic precursor lesions, including pancreatic intraepithelial neoplasia-3 (PanIN-3), intraductal papillary mucinous neoplasm (IPMN) with high grade dysplasia, and mucinous cystic neoplasm (MCN) with high grade dysplasia[8].

WHO TO SCREEN?

Not all populations with risk of pancreatic cancer need to be screened because there is no evidence that screening for pancreatic cancer is effective in reducing mortality and the harms of screening for pancreatic cancer exceed any potential benefits[8]. Clinical risk factors include age, obesity, smoking, diabetes, and non-genetic chronic pancreatitis are associated with pancreatic cancer. However, the specificity of these factors to pancreatic cancer is low. For example, the risk for developing pancreatic cancer increases with age, mostly in individuals at age over 45. Overweight and obese individuals have an increased risk (odds ratio: 1.8 and 1.22 in males and females, respectively) and earlier disease onset[6]. Current cigarette smokers and former smokers who had quit for less than 5 years also have a higher risk of pancreatic cancer than non-smokers (odds ratio: 1.71 and 1.78 for current smokers and recent past smokers, respectively)[7]. Patients with diabetes are at higher risk for pancreatic cancer (odds ratio: 1.76)[8], and new onset of diabetes may be an early indicator of pancreatic cancer[9]. Several studies have indicated that patients with (non-genetic) chronic pancreatitis had a higher incidence of pancreatic cancer over the general population (odds ratio: 2.23)[10-12].

HIGH RISK POPULATIONS

Screening is suggested in high risk populations, including individuals with lifetime risk of pancreatic cancer over 5% or/and increased relative risk over 5 times proposed by CAPS[8]. Table 1 listed the proposed high risk population to screen and their relatively risk and/or lifetime risk of pancreatic cancer.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers (PJ) syndrome is an autosomal dominantly inherited syndrome caused germline STK11 gene mutations with high penetrance[13,14]. It is characterized by mucocutaneous pigmentation and hamartomatous polyps of the gastrointestinal (GI) tract. Patient with PJ syndrome have a risk of multiple GI and non-GI cancers. The cumulative lifetime risk of pancreatic cancer is 36%, with a relatively risk (RR) of 132[14,15]. Patients with PJ syndrome whatever with family history of pancreatic cancer are suggested to be candidates for pancreatic cancer screening[8].

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

Familial atypical multiple mole melanoma syndrome is an autosomal dominantly inherited disease with variable penetrance caused by p16/CDKN2A gene mutation[16]. It is characterized by familial occurrence of multiple benign melanocytic nevi, dysplastic nevi, and melanoma[17,18]. Familial Atypical Mole Melanoma (FAMMM) syndrome is associated with extrapancreatic (sarcomas, endometrial, breast and lung cancers) and pancreatic cancers. The risk of developing pancreatic cancer risk is about 13-22 folds[18,20]. p16 mutation carriers with one or more affected first degree relative (FDR) with pancreatic cancer should be considered for screening[19,20].

FAMILIAL BREAST AND OVARIAN CANCER

Familial breast and ovarian cancer syndrome is an autosomal dominantly inherited syndrome associated
HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME

The Lynch syndrome is associated with mismatch repair genes (MLH1, MSH2, MSH6, and PMS2). Hereditary non-polyposis colorectal cancer (HNPCC) is characterized by early-onset colorectal cancers and extra-colonic cancers including pancreas. The lifetime risk of pancreatic cancer is 3.7% by age of 70, an 8.6-fold increased risk compared to general population. Patients with Lynch syndrome and one affected FDR with PC should be considered for screening.

HEREDITARY PANCREATITIS

Hereditary pancreatitis is a rare inherited disorder. It is transmitted as an autosomal dominant disorder with incomplete penetrance. Hereditary pancreatitis is associated with a high risk of pancreatic cancer with a lifetime risk about 40%. In those individuals with a paternal inheritance pattern, the cumulative risk is even approaching 75%. This risk of pancreatic cancer is related to the duration of inflammation. Screening of PRSS1 (Cationic trypsinogen) mutation carriers with longstanding chronic pancreatitis is being performed within established programs.

FAMILIAL PANCREATIC CANCER

Familial pancreatic cancer (FPC) describes families with at least two first-degree relatives with confirmed exocrine pancreatic cancer that do not fulfill the criteria of other inherited tumor syndromes. FPC is also used to describe families with exocrine pancreatic cancer in two or three or more relatives of any degree of relatedness. An indicative pattern of an autosomal dominant trait of inheritance has been identified in 58%-80% of FPC families. Previous studies have described an increased risk of developing pancreatic cancer in unaffected FDRs that depends on the number of relatives with pancreatic cancer. Studies of the European Registry of Hereditary Pancreatitis and FPC (EUROPAC) and German national case collection for FPC (FaPaCa) described the phenomenon that patients in younger generations develop the disease about 10 years earlier than their affected parents. The proportion of patients younger than 50-year-old appeared to be higher (16%) in FPC families compared to the general population. For individuals with two affected first-degree relatives and individuals with three affected first-degree relatives, the relative risk are 3.9. The risk of pancreatic cancer seemed to be higher among members of FPC kindred with a young age of onset (younger than 50 years of age) compared with kindred with an age of onset older than 50 years of age. The life-time risk rose to 38% for individuals with three affected first-degree relatives, if one of the affected was diagnosed under the age of 50 years.

PALB2 gene was identified as a PC susceptibility gene recently. It is a partner and localizer of BRCA2. PALB2 germline mutations have been detected in up to 3% of patients with familial PC. The risk of PC among PALB2 gene mutation carriers is estimated to be similar to that found for BRCA2 gene mutation carriers. PALB2 mutation carriers with one or more affected FDR with PC should be screened.

WHEN TO SCREEN?

Patients with hereditary pancreatitis has a higher risk of early onset pancreatic cancer. Screening typically begins at age 40 in PRSS1 mutation carriers. In other high risk populations, there is no consensus as to whether to recommend initiating screening and the end of screening.

SCREEN TECHNIQUES

Up to now, there is no ideal single screening method or screening program for detection of early pancreatic cancer. Serum CA19-9 levels is the most commonly used serum marker in pancreatic cancer. However, the sensitivity and specificity of serum CA19-9 as a diagnostic marker are not good for screening pancreatic cancer.

Table 1 High risk population and the estimated risk for pancreatic cancer

| Syndrome                        | Gene          | RR  | Lifetime risk |
|---------------------------------|---------------|-----|---------------|
| Peutz-Jeghers syndrome          | STK11/LKB1    | 132 | 36% by age 65 yr |
| Hereditary pancreatitis         | PRSS1         | 53  | Male: 11% and 49% by age 50 and 75 yr  |
|                                 |               |     | Female: 8% and 55% by age 50 and 75 yr  |
| FAMMM                           | p16           | 13-22 | 16% lifetime risk |
| Familial breast and ovarian     | BRCA1/2       | 3-10 | 5% lifetime risk |
| HNPPC                           | MLH1, MSH6, MSH2, PMS2 | 1.5-9 | 8.6% lifetime risk |
| Familial pancreatic cancer      | 2 FDR         | Unknown | 6.4 | 8%-12% lifetime risk |
|                                 | 3 FDR         | Unknown | 32  | 40% lifetime risk |

FDR: First degree relative; HNPPC: Hereditary non-polyposis colorectal cancer; PRSS1: Cationic trypsinogen gene; FAMMM: Familial atypical multiple mole melanoma syndrome.

with germline mutations of BRCA1 and BRCA2 genes. Mutation carriers are at high risk for breast, ovarian, GI cancers (bile duct, gallbladder, stomach, pancreas) and prostate cancers. BRCA2 carriers are associated with higher risk of pancreatic cancer (3-10 folds) than BRCA1 carriers (2.3-3.6 folds). BRCA2 mutation carriers with one or more affected FDR with pancreatic cancer and those with two or more affected family members (even without a FDR) should be considered for screening.

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Table 2  Reported pancreatic cancer screening programs and diagnostic yield

| Study            | Screening modalities | Case (n) | Study population | Diagnostic yield upon imaging |
|------------------|----------------------|----------|------------------|-------------------------------|
| Ruliyak et al.   | EUS                  | 35       | FPC              | 34.3%                         |
| et al., 2001     |                      |          |                  |                               |
| Canto et al.     | EUS                  | 38       | FPC, PJS         | 76%                           |
| et al., 2004     |                      |          |                  |                               |
| Canto et al.     | EUS                  | 78       | FPC, PJS         | 22%                           |
| et al., 2006     |                      |          |                  |                               |
| Foley et al.     | EUS                  | 44       | FPC              | 23%                           |
| et al., 2009     |                      |          |                  |                               |
| Langer et al.    | EUS + MRCP           | 76       | FPC, PCMS        | 36%                           |
| et al., 2009     |                      |          |                  |                               |
| Verna et al.     | EUS and/or MRCP      | 51       | FPC, FAMMM, HPNPC | EUS: 65% MRI: 33%            |
| et al., 2010     |                      |          |                  |                               |
| Ludwig et al.    | MRCP                 | 109      | FPC              | 8.3%                          |
| et al., 2011     |                      |          |                  |                               |
| Vassen et al.    | MRCP                 | 79       | FAMMM            | 20%                           |
| et al., 2012     |                      |          |                  |                               |
| Canto et al.     | MRCP                 | 216      | FPC, HBOC, PJS   | 42.6%                         |
| et al., 2012     |                      |          |                  |                               |
| Al-Sukhni et al. | MRCP                 | 262      | FPC, FAMMM, HPNPC | 32%                          |
| et al., 2012     |                      |          | hereditary pancreatic cancer |                   |

EUS: Endoscopic ultrasonography; MRI: Magnetic resonance imaging; CT: Computed tomography; FAMMM: Familial atypical multiple mole melanoma syndrome; FPC: Familial pancreatic cancer; HBOC: Hereditary breast-ovarian cancer; HPNPC: Hereditary nonpolyposis associated colorectal cancer; IPMN: Intraductal papillary mucinous neoplasia; MRCP: Magnetic resonance cholangiopancreatography; PCMS: Pancreatic carcinoma-melanoma syndrome; PJS: Peutz-Jeghers syndrome.

The most common screening imaging used for the detection of pancreatic cancer are endoscopic ultrasonography (EUS), computed tomography (CT) and magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP). EUS is an invasive procedure which might detect lesions smaller than 1 cm. However, the major problem of EUS is its operator dependent. CT scanning demonstrated a low sensitivity to detection pancreatic dysplasia. MRI with MRCP is a non-invasive procedure which could detect earlier ad minor changes in pancreatic parenchymal and (main) pancreatic duct compared to CT scan. Table 2 summarized the reported pancreatic cancer screening programs with the reported diagnostic yield. MRI with MRCP and EUS are considered the most accurate tools for pancreatic imaging as promising recommended tool for screening. MRI with MRCP is less invasive and more objective compared to EUS. It still lacks randomized controlled studies to compare EUS and MRI with MRCP in pancreatic cancer screening in high risk individuals. Regarding to the imaging study as a screening tool, over diagnosis is a major problem which might cause over treatment of a benign lesion. The risk of incorrect diagnosis is particularly high for EUS because of it is an operator-dependent examination with only modest interobserver agreement. Abdominal ultrasound and endoscopic retrograde cholangiopancreatography are not recommended for screening, owing to their low diagnostic sensitivity and the risk of pancreatitis, respectively.

EMERGING PROBLEMS AND FUTURE PROSPECTIVE

There are still some unresolved problems in pancreatic cancer screening. First of all, the aim of screening is to find the earliest pancreatic cancer (T1N0M0) or high grade precursor lesions in PanIN, IPMN and MCN. In fact, the high grade PanINs are actually microscopic lesions which might cause some tiny or abnormal findings in imaging. Even with fine needle aspiration, the aspirated substance could not represent the worst condition or whole picture what it is. Secondly, we still have no imaging modality or accurate criteria to differentiate benign pancreatic cystic lesions from malignant cystic tumors with dysplasia or malignancy. There are some proposed “high risk stigmata and worrisome features” to help us for picking up true meaningful or suspected malignant pancreatic cystic lesions or IPMN to avoid unnecessary operations or overtreatment. However, there is still no reliable or good method to differentiate the nature of pancreatic cystic lesions. With the advancement and frequent use of abdominal imaging, more and more incidentally found pancreatic lesions and/or IPMNs are disclosed. How to follow up the increasing numbers of patients with optimal programs to avoid under detection of pancreatic cancer and also to avoid overtreatment will be a great challenge for the clinician.

CONCLUSION

Screening pancreatic cancer in high risk populations is suggested to enhance the potential early detection of curable early pancreatic cancer. It is a potential way to improve the outcome of pancreatic cancer. Although some consensus are proposed to be followed, there is still lack of ideal screening method and program at the present time. Further study and advancement for improving the sensitivity and specificity of screening methods to achieve the goal of early detection of pancreatic cancer is warranted in the near future.

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