Pancreatic cancer (pancreatic ductal adenocarcinoma) is one of the most lethal malignancies. In the United States, it ranks tenth in newly diagnosed cancer and fourth in estimated annual death in both sexes. Moreover, it’s still challenging to detect it at an early stage, and patients with potentially resectable disease are only 10–20%. As a result, the mortality from this cancer is almost equal to incidence, with a 5-year survival rate of less than 10%. In those cases in which resection can be performed, the average survival rate is up to 18–20 months, and 5-year survival can rise as high as 20–25%. Therefore, emphasis has been placed on intensifying efforts for early detection and management of this otherwise fatal disease. Early detection entails an effective screening program, which is biologically feasible, as pancreatic cancer is known to evolve from precursor lesions.

High-risk Population
Since pancreatic cancer rarely shows specific symptoms at an early stage, screening should target asymptomatic individuals. However, considering low incidence and prevalence of this cancer, it’s not effective to screen the general population. For screening, a recent study estimated that the probability of detecting dysplasia, a precursor lesion of pancreatic cancer, needs to be greater than 16%. Therefore, it is more effective to target a high-risk population with higher prevalence of cancer for screening.

There are many risk factors for pancreatic cancer that can be divided into three categories. Low risk (<5-fold) factors include male, black, Ashkenazi Jewish descent, obesity, smoking, diabetes mellitus, Helicobacter pylori infection, familial adenomatous polyposis, HNPCC, pancreatic cancer in one first-degree relative, and BRCA1 mutation carrier. Moderately increased risk (5–10-fold) includes history of pancreatic cancer in two first-degree relatives, cystic fibrosis, chronic pancreatitis, BRCA2 mutation carrier. High risk (>10-fold) factors include FAMMM kindreds with p16 germline mutation and at least one case of pancreatic cancer in a first-degree or second-degree relative, Peutz-Jeghers Syndrome, hereditary pancreatitis, and 3 or more first-degree, second-degree, or third-degree relatives with pancreatic cancer.

Familial Pancreatic Cancer
According to a consensus conference, the term of familial pancreatic cancer (FPC) is defined as clinical setting in which a family has two or more first-degree relatives affected with pancreatic cancer without accumulation of other cancers or familial diseases. The comprehensive clinical and genetic analysis of FPC from registries revealed following characteristics: 1) a pattern is indictable of an autosomal dominant trait of inheritance in 58–80% of FPC families, 2) the phenomenon of anticipation that patients in younger generations develop the disease about 10 years earlier than their affected parent, 3) the risk of developing pancreatic cancer in relatives of families with at least two affected first-degree relatives was 18-fold higher than that of sporadic cases. Additionally, kindreds with three affected first-degree relatives had a 57-fold risk increase of developing pancreatic cancer. The genetic basis of the majority of FPC cases has not been uncovered yet. On the basis of current knowledge, BRCA 2, PALB2, and ATM germline mutations are the most frequent genetic defects identified in FPC. A computer-based risk assessment tool, PancPro, has been shown to provide an approximate risk of developing a future pancreatic cancer for FPC families.

Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)
Familial atypical multiple mole melanoma (FAMMM) is an autosomal dominant inherited syndrome characterized by multiple nevi, atypical nevi, and multiple melanomas. A study of the one of the largest familial melanoma database documented an association between pancreatic cancer and CDKN2A mutations in melanoma multiplex families. One study estimated penetrance for pancreatic cancer to be 17% in CDKN2A mutation carriers by 75 years of age.

Peutz-Jeghers Syndrome
Peutz-Jeghers Syndrome is an autosomal dominant syndrome characterized by hamartomatous gastrointestinal polyps and mucocutaneous pigmentation. The germline mutation that accounts for this syndrome is the STK11/LKB1 gene. Patients with known Peutz-Jeghers Syndrome have a relative risk of 132 and a cumulative lifetime risk of 36% for ages 15–64 years for the development of pancreatic cancer.

Hereditary Pancreatitis
Hereditary pancreatitis is an autosomal dominant disorder, with 60% of cases attributed to the serine protease gene (PRSS1) mutation on the long arm of chromosome 7, encoding cationic trypsinogen. The cumulative risks of pancreatic cancer at 50, 60, and 75 years are 10%, 18.7%, and 53.5%, respectively. The risk is double in patients with hereditary pancreatitis who smoke, and it is diagnosed 20 years earlier in patients who smoke than in those who do not.
Non-hereditary Factors

Cigarette Smoking

Cigarette smoking is associated with 25% of pancreatic cancers. In those with a family history of pancreatic cancer, smoking has even a greater effect; they have up to a 3.7-fold increase of developing pancreatic cancer and may present with the disease one to two decades earlier. Smoking also increases the risk for pancreatic cancer in individuals with hereditary pancreatitis by 2-fold, as noted above. After smoking cessation, excess risk may decrease. In one prospective study, the risk fell by 48% by 2 years after smoking cessation and leveled off 10–15 years after discontinuation.

Long-standing Diabetes

The proportion of pancreatic cancer patients who also have hyperglycemia or diabetes has previously been under appreciated. Recognition of new-onset diabetes as an early manifestation of pancreatic cancer could lead to the diagnosis of early pancreatic cancer. However, primary type 2 diabetes is common and pancreatic cancer is uncommon in the general population. The success of the strategy to use new-onset hyperglycemia and diabetes as a screening tool to identify subjects with a high likelihood of having asymptomatic pancreatic cancer will depend largely on the ability to differentiate pancreatic cancer–associated diabetes from the more common type 2 diabetes by a biomarker or other method. Recently, Huang, et al. reported vanin-1 and matrix metalloproteinase 9 as useful blood biomarkers for the discrimination of pancreatic cancer–associated diabetes from type 2 diabetes, but it still requires validation in large clinical trials. Therefore, currently such differentiation is not possible in clinical practice and there is no recommendation to have new-onset type 2 diabetics undergo pancreatic cancer screening if they have no signs, symptoms, or risk factors for pancreatic cancer.

Biomarkers

Once a high-risk group is identified, next step is selection of an appropriate screening tool. Unfortunately, none of the current diagnostic modalities have all the attributes of an effective screening tool with acceptable sensitivity, specificity, invasiveness (or lack thereof), and cost effectiveness. These screening modalities, which range from noninvasive serum markers to invasive pancreatic imaging and tissue biopsies, have varied performance characteristics and limitations thus often necessitating combination of these tools for optimal PC screening. Measurement of the blood levels of serum markers specific for the presence of PC represents a potentially ideal noninvasive screening method. To date, studies using this strategy have measured levels of tumor-associated glycoproteins such as carbohydrate antigen (CA 19-9) or tumor isoenzymes such as tumor-M2-pyruvate kinase and oncofetal antigens. Of these, CA 19-9 has been most extensively examined. Unfortunately, the role of CA19-9 as a screening tool for PC in general population has not been encouraging with poor yield with low cost-effectiveness except in symptomatic patients. With sensitivity and specificity ranging from 70–90% with corresponding positive and negative predictive values of 60–90%, it lacks the diagnostic performance needed for an effective serologic screening test. Almost 15% of PC patients do not have elevated CA 19-9 levels, and it can be elevated in other gastrointestinal malignancies and benign disease such as obstructive jaundice. In summary, serum measures of tumor-associated glycoproteins lacks sufficient sensitivity and specificity for use in PC screening. Analysis of molecular abnormalities, such as genetic mutation and/or epigenetic alterations, provides another noninvasive means for identifying patients with early PC or high-grade lesions. Markers obtained from serum, stool, or pancreatic tissue such as p53 mutation, K-ras status, p16 (INK 4a) promoter methylation individually or in combination have been used to stratify the risk of PC in high risk patients. Macrophage inhibitor cytokine-1 (MIC-1) had a better accuracy to distinguish pancreatic cancer from normal patients than CA 19-9 (99% vs. 78%, respectively). Several microRNAs—relatively short, stable, non-coding RNA sequences that bind to target RNA and prevent translation into protein—play an important role in oncogenesis to negatively regulate tumor-suppressor genes. They have been demonstrated in precursor lesions of pancreatic cancer and considered to be candidate markers for pancreatic cancer detection. However, these tests are not yet ready to be used as a screening modality even in a high-risk population.

Screening in the High-risk Population

The results of several screening studies for high risk individuals in United States and Europe have been published. Diagnostic yield based on imaging demonstrating some pancreatic abnormalities was between 8.3% and 42.6%. Recently, the result of largest prospective study of American Cancer of the Pancreas Screening consortium study (CAPS 3 study) has been published. They screened asymptomatic adult high-risk patients (Peutz-Jeghers Syndrome patients, familial breast–ovarian cancer patients with at least one affected first- or second-degree relative with pancreatic cancer, and relatives of patients with familial pancreatic cancer with at least one affected first-degree relative) at five academic U.S. medical centers using computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). Ninety-two of 216 high risk individuals (42%) were found to have at least 1 pancreatic mass (84 cystic, 3 solid) or a dilated pancreatic duct (n=5) by any of the imaging modalities. The prevalence of pancreatic lesions increased with age. CT, MRI, and EUS detected a pancreatic abnormality in 11%, 33.3%, and 42.6% of the high-risk individuals, respectively. Among these abnormalities, proven or suspected neoplasms were identified in 85 (82 intraductal papillary mu-
cinous neoplasms and 3 pancreatic endocrine tumors). Among such patients with imaging abnormalities, five patients underwent pancreatectomy and three of them showed high-grade dysplasia in intraductal papillary mucinous neoplasms and in multiple intraepithelial neoplasias (3/216). The authors concluded that screening of asymptomatic high-risk individuals frequently detects small pancreatic cystic lesions, including curable, noninvasive high-grade neoplasms. EUS and MRI detect pancreatic lesions better than CT in this population.

**Conclusion**

Screening strategies should include identification of the population at risk for developing pancreatic cancer, and an intense application of screening tools with adequate sensitivity to detect early pancreatic cancer. Recent studies show EUS as well as cross-sectional imaging studies (e.g., MRI) may play an important role in screening population at increased risk for pancreatic cancer. On the other hand, there is currently no effective yet cost-effective screening program for the general population. Hopefully, further studies, including molecular makers, will lead to the development of less invasive and effective mass screening in the future.

**REFERENCES**


