Early Detection of Pancreatic Cancer: Risk Factors and the Current State of Screening Modalities

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Abstract: Pancreatic cancer (PC) is expected to become the second leading cause of cancer-related mortality in the United States within the next decade. Patients often present at late stages of the disease, when they become symptomatic; in many cases, these patients have unresectable disease that is associated with a poor prognosis. Considering the low incidence of PC in the general population, routine screening of average-risk individuals is not feasible and not recommended. Individuals with familial germline mutations or familial PC are at higher risk of developing PC. Improving detection of PC at an earlier stage entails the recognition of high-risk individuals who may benefit from a long-term screening program. This article identifies patients who may be at increased risk of developing PC, discusses PC screening recommendations, and compares imaging-based modalities and biomarkers for early detection of PC.

Pancreatic cancer (PC) is the fourth leading cause of cancer-related deaths in the United States.¹ The incidence of PC death has risen by almost 1.2% annually throughout the past decade.¹ According to data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, from 2010 to 2016, overall 5-year relative survival was 10% among patients with PC.² The 5-year survival rates were 39.4% for patients with localized disease and 2.9% for those with distant disease.² PC is projected to rise to the second leading cause of cancer deaths in the United States by 2030.³

PC is most frequently diagnosed among individuals ages 65 to 74 years old. Once PC becomes detectable, progression from stage I to stage IV is quite rapid, occurring at an average of 1.3 years.⁴ PC is more common in men than women (3:1) and more common in Black than White populations.² At diagnosis, PC is rarely confined locally (11%); regional and distant metastases are common (30% and 52%, respectively).² A higher stage of PC at diagnosis is inversely correlated with 5-year survival.
The challenges of early PC detection include identification of at-risk populations and selection of optimal serologic and radiologic modalities for a screening program. Almost 85% of patients with PC have adenocarcinoma; most of the remaining cases are neuroendocrine tumors. This article identifies patients who may be at increased risk of developing PC, discusses PC screening recommendations, and compares imaging-based modalities and biomarkers for early detection of PC.

**Risk Factors for Pancreatic Cancer**

Risk factors for PC can be divided into environmental exposures, patient-related factors, and hereditary factors. Environmental and patient-related risk factors are potentially modifiable. Patients carrying hereditary risk factors may benefit from a comprehensive, longitudinal screening program for early detection.

**Environmental Exposures**

**Tobacco Exposure** Tobacco exposure is a known and modifiable PC risk factor. Compared with never smokers, the odds of PC are 1.2 times higher in former smokers and 2.2 times higher in current smokers. After cessation of tobacco use, a person's risk of PC decreases exponentially, reaching that of nonsmokers in less than 20 years. Exposure to tobacco is associated with upregulation of Yes-associated protein 1 (YAP1), which leads to a more aggressive tumor. The combination of heavy smoking and a deletion polymorphism in glutathione S-transferase theta 1 (GSTT1) is associated with an increased risk of PC, with the association possibly stronger in females than males (odds ratio, 5 vs 3.2, respectively). It is estimated that 10% to 30% of PC cases are related to tobacco use. The risk of PC among people with substantial exposure to second-hand smoke currently remains unknown.

There are various proposed mechanisms to explain the worsened overall outcomes among patients with PC with tobacco exposure. A recent microbiome study demonstrated higher rates of Acinetobacter baumannii and Mycoplasma pneumoniae in PC patients with a history of smoking. These species correlate with the upregulation of oncogenic signatures, the downregulation of immune and tumor suppressive signatures, and significant methylation activity.

**Alcohol Consumption** According to the Centers for Disease Control and Prevention, a standard alcoholic drink contains 14 g of alcohol. Moderate alcohol intake is defined as 2 drinks or less per day for men and 1 drink or less per day for women. Heavy alcohol use refers to more than 4 drinks on any given day in men and more than 3 drinks on any given day for women, according to the National Institute on Alcohol Abuse and Alcoholism. There are conflicting data regarding the association between alcohol intake and PC. A study from Australia showed no association between alcohol intake and PC; however, patients with higher alcohol intake had lower overall survival following a diagnosis of PC (mortality hazard ratio, 1.09 per 10 g/day increment). Wang and colleagues demonstrated a positive association between alcohol consumption (>24 g/day, more than moderate alcohol consumption) and PC in a follow-up period lasting longer than 10 years. Despite the various published results in this regard, heavy alcohol use is strongly associated with chronic pancreatitis, which is a known risk factor for PC.

**Patient-Related Risk Factors**

**Obesity** An estimated 42.4% of the US population is obese. The risks of PC incidence and mortality increase by 10% for every 5-unit increase in body mass index (BMI). Chung and colleagues proposed that metabolic factors such as insulin resistance, hyperlipidemia, and hypertension in obese patients are associated with the development of PC. Hazard ratios for PC incidence in metabolically unhealthy normal-weight and obese individuals were 1.52 and 1.34, respectively. Perhaps it may be the comorbid conditions associated with obesity, rather than the obesity itself, driving the PC risk. In the study by Chung and colleagues, obese patients without metabolic abnormalities did not have an increased risk of PC compared with healthy, normal-weight adults.

Although obesity and its associated metabolic derangements are linked to a higher incidence of PC, the effect of obesity on survival remains controversial. A recent study by Téoule and colleagues demonstrated that despite increased risks of perineural invasion in obese patients, overall survival and postoperative complications were similar to those in patients with a normal BMI. In contrast, Shamali and colleagues demonstrated higher risks of intraoperative bleeding and postoperative fistula in patients with a BMI exceeding 30.

Fleming and colleagues showed a 12-fold increase in the risk of lymph node metastasis in patients with a BMI higher than 35; overall survival rates were lower in obese patients, with a 2-fold increase in recurrence and death after pancreatectomy. Obesity promotes desmoplasia and impairs delivery of chemotherapeutics through reduced perfusion, so obese patients may have a poor response to chemotherapeutic agents.

**Diabetes Mellitus** Diabetes mellitus and PC have a relationship that is bidirectional. Chronic diabetes mellitus increases the risk of PC by 1.5- to 2-fold, and conversely, new-onset diabetes mellitus may be an early manifestation of PC.
of PC, with multiple proposed mechanisms. Hyperglycemia may present as early as 30 to 36 months in advance of a PC diagnosis, with worsening hyperglycemia paralleling increased tumor volume.22

One of the main mechanisms involved in cell proliferation, survival, and growth is the phosphoinositide 3-kinase/protein kinase B/mammalian target of the rapamycin (PI3K/AKT/mTOR) pathway. This pathway can enhance PC tumor growth and aggressiveness.23 Metformin markedly decreased mTOR signaling and inhibited growth of PC xenografts.24 Metformin also has been shown to exert tumor progression inhibitory effects via the activating AMP-protein kinase (AMPK) pathway and by suppressing desmoplasia,25 and may prevent metastases by inhibiting epithelial-mesenchymal transition.26

In a study by Jang and colleagues of patients with type 2 diabetes mellitus and localized resectable PC, 5-year cancer-specific survival was 31.9% among those who received metformin vs 22.2% among those who did not.27 Cancer-specific mortality decreased as the metformin dose increased.27

Diabetes mellitus is associated with unfavorable tumor features. In a recent study of patients with resected PC, those with diabetes mellitus had a larger tumor size (30 vs 26 mm), higher lymph node involvement (69% vs 59%), and higher perineural invasion (88% vs 82%), leading to decreased overall survival (18 vs 34 months), compared with those without diabetes mellitus.28

**Chronic Pancreatitis** Chronic pancreatitis is an inflammatory condition of the pancreas leading to fibrosis and acinar cell destruction. Chronic pancreatitis is a known risk factor for PC. Lifetime risk increased by 16-fold just 2 years after a diagnosis of chronic pancreatitis.28 This risk decreased to 3-fold by 9 years after the diagnosis.29 Although chronic pancreatitis is linked to PC, only a small portion (~5%) of chronic pancreatitis patients developed PC over a 20-year follow-up period.30

A link between acute pancreatitis and PC has not been clearly established. A recent meta-analysis, however, identified an effect estimate of 23.47 in the first year after diagnosis of acute pancreatitis.31 This finding likely suggests that acute pancreatitis is the initial manifestation of PC, rather than a causative etiology. The effect estimate decreased gradually to 1.17 by 10 years after the diagnosis.31 Acute pancreatitis can be caused by duct obstruction by the tumor in the early stages of cancer.

**Pancreatic Cystic Lesions** The malignant potential of a pancreatic cyst is largely dependent on the type of cystic lesion. Pancreatic cysts can be divided into neoplastic and nonneoplastic types. The latter includes retention cysts and lymphoepithelial cysts.32 Pancreatic neoplastic cystic lesions can be categorized as nonmucinous and mucinous. Nonmucinous lesions include serous cystadenomas, which carry little malignant potential, and solid pseudopapillary neoplasms. Mucinous lesions include mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMNs), which may become malignant.32

IPMNs can be categorized as main duct, branch duct, and mixed type, depending on the location and extent of involvement.33 Almost 15% of PC cases are estimated to arise from mucinous cystic neoplasms or IPMNs.34 Main duct–IPMN, which accounts for 15% to 21% of the cases, is defined as dilation of the main pancreatic duct (≥5 mm).34 This type of tumor should be resected, given the malignant potential, in a surgically fit candidate. The most common IPMN type is branch duct–IPMN, which accounts for 41% to 64% of cases.35 Among patients with main duct–IPMN, the carcinoma is noninvasive in approximately 20% and invasive in approximately 10%.34 In branch duct–IPMN, these estimates are 40% and 13%, respectively.35

Among people at high risk for PC, the prevalence of pancreatic cysts is 20%, which is higher than that in the general population (2.5%).36,37 When evaluating pancreatic cysts, it is highly important to focus on worrisome features and high-risk stigmata, such as obstructive jaundice or acute pancreatitis secondary to the cyst, an enhancing mural nodule or solid component within the cyst or pancreatic parenchyma, main duct dilation exceeding 5 mm, focal dilation of the main pancreatic duct, lesions of 3 cm or more in diameter, lymphadenopathy, and a rate of cyst growth higher than 5 mm per 2 years.38,39 These features are associated with a higher chance of finding dysplasia in a pancreatic cyst. In guidelines from the American College of Gastroenterology, the cutoff for high neoplastic risk in pancreatic cystic lesions is a main pancreatic duct size of 5 mm.39 However, European, Asian, and international consensus guidelines consider a main duct size of 10 mm or more as high-risk stigmata.36,38,40 A size of 5 to 9 mm is considered a worrisome feature.38,40 In a prospective follow-up of 312 high-risk patients, a main pancreatic duct size of 9 mm or higher in the pancreatic head and of 7 mm or higher in the body or tail were independent predictors of malignancy, along with macroscopic solid components, positive cytology, and elevated carbohydrate antigen (CA) 19-9.41

**Hereditary Risk Factors**

**Blood Group** The ABO blood type has been linked with PC in large, prospective cohort studies. Patients with blood groups A, B, and AB had higher adjusted hazard ratios for PC incidence (1.32, 1.72, and 1.51, respectively) in comparison with blood group O.42 Similar results have been reported frequently in the literature.
showing higher frequency of PC in patients with blood group A compared with blood group O. The mechanism behind this association is yet to be elucidated.

**Genetic Predisposition**  Genetics play an important role in the development of PC. More than 80% of cases of PC are caused by sporadic genetic mutations. Mutations can be germline or somatic. Inherited germline mutations, found in 5% to 10% of all patients, are usually present in the setting of genetic syndromes.

Familial PC refers to disease that develops in patients who lack a specific associated gene and who have at least 2 family members with PC who are first-degree relatives. The risk of PC increases according to the number of first-degree relatives with the disease. Risk increases by 32-fold in patients with 3 or more first-degree relatives, by 6.4-fold in patients with 2 first-degree relatives, and by 4.6-fold in patients with 1 first-degree relative. However, there are conflicting data in terms of PC risk based on family history and the absence of known mutated genes. Another study found that the risk of PC can increase up to 57-fold in individuals with 3 affected first-degree family members. The most common mutation in familial PC is BRCA2. Other mutations include PALB2.

There are 4 main genes involved in sporadic PC:
- Kirsten rat sarcoma (\(KRAS\), found in 95% of tumors; cyclin dependent kinase inhibitor 2A (\(CDKN2A\) [p16]), found in more than 90%; tumor suppressor protein 53 (\(P53\)), found in 50% to 75%; and SMAD family member 4 (\(SMAD4\)), found in 55%.
- Multiple familial syndromes are known to predispose individuals to PC, and the most common of these syndromes are summarized in the Table.

**Who Needs to Be Screened?**

The annual incidence of PC is 12.9 cases per 100,000 person-years. A 2019 position statement from the US Preventive Services Task Force concluded that the risks of PC screening outweigh the benefits in the general population, and recommended against routine screening for PC. There is no clear consensus on the screening modalities.

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### Table. Inheritable Familial Syndromes With Associated Lifetime Risk of Pancreatic Cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Lifetime Risk of Pancreatic Cancer</th>
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<tbody>
<tr>
<td>Hereditary pancreatitis</td>
<td>(PRSS1) and (SPINK1)</td>
<td>SIR of pancreatic cancer 59-87&lt;sup&gt;47&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>Cumulative incidence of 7.2%,&lt;sup&gt;48&lt;/sup&gt; which reaches 40%-53% by age 70 years&lt;sup&gt;46&lt;/sup&gt;</td>
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<td></td>
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<td>Smoking is an additional risk factor and lowers the age of onset by 20 years&lt;sup&gt;51&lt;/sup&gt;</td>
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<tr>
<td>Peutz-Jeghers syndrome</td>
<td>(STK11/LKB1)</td>
<td>Risk of 5% at age 40 years, which increases to 8% at age 60 years&lt;sup&gt;52&lt;/sup&gt;; 132-fold increased risk compared with the general population&lt;sup&gt;53&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hereditary breast/ovarian cancer</td>
<td>(BRCA1) and (BRCA2)</td>
<td>SIR, 4.11-5.79&lt;sup&gt;56&lt;/sup&gt;</td>
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<tr>
<td>Familial atypical multiple mole melanoma syndrome</td>
<td>(CDKN2A)</td>
<td>13-47-fold increased risk&lt;sup&gt;57,58&lt;/sup&gt;; the risk is 14% by age 70 years&lt;sup&gt;59&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>SIR, 38 overall; SIR, 52 in patients with concurrent melanoma&lt;sup&gt;60&lt;/sup&gt;</td>
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<tr>
<td>Ataxia-telangiectasia</td>
<td>(ATM)</td>
<td>Estimated relative risk, 2.41 (95% CI, 0.34-17.1)&lt;sup&gt;61&lt;/sup&gt;</td>
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<tr>
<td>Lynch syndrome</td>
<td>DNA mismatch repair genes ((MLH1, MSH2, MSH6, and PMS2))</td>
<td>8.6-fold increased risk&lt;sup&gt;62&lt;/sup&gt;; 4% risk by the age of 70 years&lt;sup&gt;63&lt;/sup&gt;</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>(APC)</td>
<td>4.5-fold increased risk&lt;sup&gt;64&lt;/sup&gt;</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>(P53)</td>
<td>Relative risk, 7.3 (95% CI, 2-19)&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>(CFTR)</td>
<td>Relative risk, 5.3 (95% CI, 2.4-10.1)&lt;sup&gt;66&lt;/sup&gt;</td>
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SIR, standard incidence rate.
indications, and length of surveillance among different societies. The decision for screening should be made on an individual basis after extensive discussion between the patient and the practitioner regarding the rationale, risks, and benefits of long-term surveillance. The International Cancer of the Pancreas Surveillance consortium, the American Gastroenterological Association, and the American College of Gastroenterology have released almost similar statements in regard to PC screening in high-risk individuals. A long-term longitudinal PC screening program is recommended for the following groups: (1) all patients with a germline serine threonine kinase gene 11 (STK11; also known as LKB1) or CDKN2A gene mutation; (2) carriers of a germline BRCA2 DNA repair associated 2 (BRCA2), BRCA1 DNA repair associated 1 (BRCA1), partner and localizer of BRCA2 (PALB2), ataxia telangiectasia mutated (ATM), mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), or mutS homolog 6 (MSH6) gene mutation with at least 1 affected first-degree relative; and (3) patients with familial PC.

Although smoking, alcohol, obesity, diabetes mellitus, and chronic pancreatitis are well-known nongenetic risk factors for PC, current data are lacking to support the benefit of routine screening among these patients. However, individuals with alarming signs, such as obstructive jaundice, weight loss, or new-onset diabetes mellitus, would benefit from further evaluation and investigation for PC.

### When to Start Screening?

Screening for PC in high-risk individuals should begin when they are age 50 years or, in those with a family history, 10 years before the age of onset in the family member. Screening should be initiated at age 40 years in CDKN2A and serine protease 1 gene (PRSS1) mutation carriers with hereditary pancreatitis, and at age 35 years in the setting of Peutz-Jeghers syndrome. The long-term benefits of PC screening programs are debatable. In a prospective study of 354 high-risk individuals who underwent surveillance for 16 years, 7% had neoplastic progression, with a 1.6% per year progression rate. Detectable lesions with worrisome features were reported in 93%. The decision to discontinue PC screening should be made on an individual basis. Screening should be discontinued when the risks of death from non-PC causes are higher than those from PC.

### Radiographic and Endosonographic Screening

Most of the PC screening recommendations for high-risk individuals focus more on magnetic resonance imaging (MRI)/magnetic retrograde cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS), rather than computed tomography (CT). In a review of 1170 patients, the sensitivity of PC detection was highest with EUS, at 94%, compared with CT scans at 74% and MRIs at 79%. EUS has higher sensitivity than CT scans or MRI for detecting smaller pancreatic tumors. In tumors smaller than 30 mm, EUS has 93% sensitivity and 100% specificity. In comparison, sensitivity and specificity are 53% and 64%, respectively, for CT scans and 67% and 100%, respectively, for MRI. For detection of PC tumors smaller than 20 mm, EUS has significantly higher sensitivity (94.4%) compared with contrast-enhanced CT (50%). EUS has higher yields for differentiating among different subtypes as compared with contrast-enhanced CT, at 83.3% vs 50%. In a recent meta-analysis of 24 prospective studies of screening of high-risk individuals for PC, the weighted pooled proportion of focal pancreatic abnormalities detected by EUS was statistically higher than for MRI (0.34 vs 0.31; P=.006). According to this study, the number needed to screen for detection of 1 high-grade dysplasia or T1N0M0 adenocarcinoma was 111.

One advantage of EUS is the ability to obtain tissue for histopathologic evaluation from the lesion and from possible regional metastases via fine-needle biopsy (FNB), as well as cyst fluid aspirate for cytology and mutational analysis via fine-needle aspiration (FNA). Considering the higher sensitivity of MRI/MRCP and EUS compared with CT in detecting smaller lesions—and in order to limit ionizing radiation exposure—EUS and MRI/MRCP are recommended by most societies as the primary screening modalities.

In the presence of concerning cystic or solid lesions, FNA or FNB may be indicated for further investigation. For the diagnosis of pancreatic malignancy, EUS-FNA has accuracy of 85% to 92%, sensitivity of 80% to 95%, and specificity of 92% to 100%. FNB provides a core tissue sample with preserved architecture for establishing histologic evaluation and can provide tissue for molecular profiling and next-generation sequencing, as well as to guide therapy in the future if the diagnosis of malignancy is established. Pooled accuracy for the diagnosis of PC via FNB is 78% to 98.3%. In comparison with EUS-FNA, EUS-guided through-the-needle forceps biopsy (EUS-TTNB) provides additional diagnostic yield for mucinous pancreatic lesions, with a specificity of 74.6%. Needless to say, EUS-TTNB is a newer diagnostic platform that endoscopists find less generalizable, considering its associated higher adverse events, which range from abdominal pain and intracystic hemorrhage to acute pancreatitis. Although not commonly used in routine practice, concurrent EUS-FNA with KRAS-mutation testing among
patients with an inconclusive pathologic evaluation improved sensitivity from 73% to 88% and accuracy from 75% to 93% compared with cytopathologic evaluation alone.78

Obtaining tissue or fluid sampling for histologic evaluation increases the diagnostic accuracy, with the tradeoff of a low, but increased, adverse event rate due to the invasive nature of the procedure. The risk of mild pancreatitis, bleeding, and abdominal pain is reported in up to 3.4% of patients who undergo EUS-FNA for solid pancreatic lesions.79 A tumor size of 20 mm or less in diameter and a pancreatic neuroendocrine tumor are independent risk factors for adverse reactions associated with EUS-FNA.79 The overall risk of major complications, such as infection, peritonitis, pancreatitis, and malignant seeding, after EUS-FNB reaches 2.5%.80 The risk of peritoneal carcinomatosis in the setting of needle tract seeding after EUS-FNA is low (2.2%) and less than that for percutaneous FNA sampling (16.3%).81

Additional pancreatic parenchymal abnormalities may be detected in patients undergoing an imaging-based screening program. Compared with the general population, individuals at high risk for PC were 16 times more likely to have 3 or more chronic pancreatitis features on EUS, such as hyperechoic strands, lobularity, cysts, hyperechoic ducts, and hypoechoic foci.82 Chronic pancreatitis increases the risk for PC, and these parenchymal abnormalities may mask subtle, early findings of a mass lesion. In the setting of concerning features or when there is a need to differentiate between a pseudotumor mass or solid pancreatic lesions, FNB has higher diagnostic accuracy and sensitivity compared with FNA (accuracy, 93% vs 83%; sensitivity, 86.8% vs 69.5%).83

Although any initial screening modality might demonstrate lesions such as IPMN, it is crucial to utilize a subsequent test that can differentiate between low-risk IPMNs and those that may harbor high-grade dysplasia or PC. In a recent meta-analysis of 24 studies comparing CT, MRI/MRCP, positron emission tomography (PET)/CT, EUS, and MRI diffusion-weighted imaging (DWI) in distinguishing low-risk vs high-risk IPMNs, the highest pooled specificity was 97%, as demonstrated by MRI-DWI, whereas the highest sensitivity was 80% for PET/CT.84

There is no clear agreement among different societies on a single modality for optimal screening of high-risk individuals. In a prospective study of 253 individuals at risk for pancreatic adenocarcinoma, there was no statistically significant difference in the diagnostic yields of annual MRI/EUS compared with annual MRI with EUS performed every third year, although EUS should be performed earlier if any changes are noted on MRI.85

Most societies recommend that screening start with EUS/MRI, and then proceed with MRI or EUS annually, in an alternating fashion, unless concerning features arise.

Current Japanese guidelines recommend against the use of EUS-FNA for the diagnosis of pancreatic cystic lesions.86 In contrast, the most recent American Society for Gastrointestinal Endoscopy guidelines, from 2016, focus on the importance of EUS-FNA plus cyst fluid cytology and tumor markers to differentiate pancreatic neoplastic cystic lesions.86

Interventional endoscopy remains a dynamic field, with ongoing advances in the diagnostic application of EUS for the differentiation of pancreatic cysts. One of the newer techniques to improve the accuracy of EUS in the diagnosis of solid pancreatic neoplasm is EUS-elastography. With this technique, the diagnosis of a stiff lesion with main pancreatic duct dilation was associated with a sensitivity of 94%, a specificity of 23%, and a negative predictive value of 50%.86 In comparison, for a lesion without main pancreatic duct dilation, these rates were 100%, 60%, and 100%, respectively.87

Contrast-enhanced EUS (CE-EUS) is another new technique to improve the diagnostic accuracy of EUS for PC. In a meta-analysis of 18 studies, the pooled sensitivity and specificity of CE-EUS for the diagnosis of PC were 91% and 86%, respectively.88 In comparison with EUS-elastography, CE-EUS had higher specificity for the diagnosis of PC.88 CE-EUS provided a higher yield in differentiating benign and malignant pancreatic tumors and cystic lesions, as enhancement of intracystic septation is diagnostic for serous cystadenoma, whereas irregular enhancement of the intraleseional septum and nodule is diagnostic for mucinous cystic neoplasm.76,88 CE-EUS can differentiate malignant from benign IPMNs via invasive/papillary mural nodules, as well as polypoidal noninvasive papillary nodules from the appearance of cystic lesions.76,88

Other Markers

The most common and useful serum marker for PC is CA 19-9. The sensitivity and specificity of CA 19-9 for the diagnosis of PC are 77% to 80.8% and 89% to 100%, respectively.89,90 CA 19-9 elevations are not exclusive to PC, and high levels may also be seen in colorectal and gastric cancers, as well as in other conditions causing biliary obstruction.91 Furthermore, not all patients with PC will have elevated CA 19-9 levels. CA 19-9 has low diagnostic value in establishing the diagnosis of PC. It is most useful to follow treatment response in patients with PC and an elevated baseline CA 19-9 level undergoing chemotherapy, surgery, or radiation, and then for surveillance thereafter. Elevated CA 19-9 levels higher than 178 IU/mL are strongly associated with unresectable disease,
even in jaundiced patients. In a study of 546 patients at high risk for PC, elevated CA 19-9 levels in 27 patients led to the use of targeted EUS; neoplastic or malignant findings were diagnosed in 0.9%, and pancreatic adenocarcinoma was diagnosed in 0.2%. Most societies recommend against routine monitoring of CA 19-9 levels for PC screening, while emphasizing the role of CA 19-9 as an adjunctive tool in patients with potential concerning features on radiology.

New-onset diabetes mellitus or rapidly worsening preexisting diabetes mellitus is suspicious for PC and should prompt further investigation for an underlying malignancy. In high-risk individuals, all societies recommend baseline measurement of hemoglobin A1C levels and fasting blood sugar, followed by subsequent testing; however, controversy remains regarding the optimal interval for follow-up testing. Although it was not studied in high-risk patients, CA 19-9 was evaluated as a screening tool in 5111 patients with new-onset diabetes mellitus. Diagnostic accuracy of elevated CA 19-9 for the diagnosis of PC among patients with a total bilirubin higher than 1.7 mg/dL was 73.7%; accuracy decreased to 3.8% when the bilirubin level was normal. Further studies are needed to confirm the generalizability of CA 19-9 for screening individuals with new-onset diabetes mellitus for PC.

Measurement of carcinoembryonic antigen (CEA) in serum has low sensitivity and specificity for the diagnosis of PC. However, assessment of the CEA level in the pancreatic cyst fluid has value in differentiating pancreatic cystic lesions. Most recently, a cutoff CEA level of higher than 100 ng/mL was associated with a 100% negative predictive value in differentiating low-risk IPMN from low-risk mucinous cystic lesions and high-risk IPMN. (Low risk was defined as low-grade and intermediate-grade dysplasia.)

Serum microRNA-25 (miR-25) has been proposed as a diagnostic biomarker for PC. The combination of miR-25 and CA 19-9 had a sensitivity of 97.5% and a specificity of 90.11% for the detection of stage I and II PC.

The methylation status of a disintegrin and metalloproteinase with thrombospondin motifs 1 (ADAMTS1) and basonuclin 1 (BNC1) in cell-free DNA has been proposed as a diagnostic tool for early-stage PC in high-risk individuals, with further study needed to assess its real-world value. Other biomarkers and enzymes that have shown promising prognostic value for PC include hematopoietic growth factors, such as macrophage-colony stimulating factor and granulocyte-colony stimulating factor; interleukin-3; macrophage inhibitory cytokine; alcohol dehydrogenase; aldehyde dehydrogenase; and lysosomal exoglycosidases.

Traditional pancreatic juice analysis for enzymes and biomarkers has been an interesting field for differentiating PC precursor lesions. DNA and genetic testing of the pancreatic juice are additional diagnostic tools to improve accuracy. P53 and KRAS mutations in the pancreatic juice are genetic markers for concurrent IPMN and PC, and could be used as a screening tool. Methylated DNA markers (at C13orf18, FER1L4, and BMP3) in pancreatic juice also have been shown to identify early-stage PC. There are a variety of methods to collect pancreatic juice. Most recently, Simpson and colleagues studied the difference in mutated genes present in pancreatic juice collected via secretin-induced duodenal aspirate (SIDA) and fluid collected via EUS-FNA. They found that the SIDA mutation yield was low compared with the pancreatic fluid collected via EUS-FNA: for KRAS, these rates were 2.5% vs 40.0%, respectively, and for GNAS, they were 2.6% vs 11.1%. In contrast, Levink and colleagues showed that pancreatic fluid sampling through the endoscope suction channel was superior to collection with a catheter, with improved yield in those with suction timing of up to 8 minutes.

**Conclusion**

PC is expected to be the second leading cause of cancer death in the United States by 2030. Early detection of PC is a crucial step toward improving long-term survival. Among the various risk factors associated with PC, genetic predisposition plays an important role, and these patients require a more programmatic surveillance program. Among individuals with familial PC, the recommendation is to start screening with EUS/MRI at age 50 years or 10 years before the family member’s initial age of onset. However, screening at a younger age is indicated in carriers of PRSSI, SPINK1, and STK11/LKB1 genetic mutations. Biomarkers and circulating tumor cells and genes have been the focus of interest in the past few years, although their sensitivity and specificity have been varied in the published literature.

**Disclosures**

The authors have no relevant conflicts of interest to disclose.

**References**

4. Yu J, Blackford AL, Dal Molin M, Wolfgang CL, Goggins M. Time to progres-