Editorial Commentary

Pancreatic cancer screening in high-risk individuals with genetic susceptibility

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Pancreatic cancer is still associated with a dismal prognosis, sometimes with a 5-year survival reported up to 10%, but the true figure is probably about 5% (1). Major breakthroughs in outcomes are lacking. One avenue for improving is survival is by earlier tumor detection, thereby increasing the proportion of patients that can undergo curative-intent surgery and concomitant chemotherapy. In recent years, optimistic outcomes have been reported for localized-stage disease, with 5-year survival rates of up to 44% (2).

Screening for pancreatic cancer in the general population is not advised, mainly due to the low incidence of the disease (3). Surveillance programs are therefore restricted to selected individuals with an increased life-time risk of developing pancreatic cancer, especially those who carry specific genetic mutations or have a strong family history (4). However, screening recommendations for individuals with genetic susceptibility is highly variable and evidence levels are uncertain. It is, therefore, most welcome, that the American Society for Gastrointestinal Endoscopy (ASGE) has published evidence-based guidelines on screening for pancreatic cancer in these individuals (5). ASGE addressed carriers of a germline mutation in known pancreatic cancer susceptibility genes (e.g., *BRCA1*, *BRCA2*, *PALB2*, *CDKN2A*, *STK11*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *PRSS1*) and individuals with a family history of pancreatic cancer in at least two blood relatives [familial pancreatic cancer (FPC) kindreds]. The ASGE guidelines recommend screening, but the recommendations are based on low-quality evidence. Annual screening with magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) is suggested. The age to start screening depends on the underlying genetic condition, beginning at age 50 or 10 years earlier than the youngest relative with pancreatic cancer. For individuals with germline mutations in CDKN2A [familial atypical multiple mole melanoma (FAMMM) syndrome], STK11 (Peutz-Jeghers syndrome) or PRSS1 (hereditary pancreatitis), it is recommended to begin screening at age 35 to 40. CA 19-9 is not included in the screening algorithm, although it may have a role as an adjunct to imaging. Other biomarkers, such as circulating tumor cells and DNA are mentioned, but are not clinically available yet. A screening interval of 1 year may be suitable in general, but for some individuals this interval may be too long, as just 1 year might mean a non-visible tumor to a 2 cm mass in the pancreas in an asymptomatic patient (6). The timeline for pancreatic cancer progression is controversial, with some tumors progressing slowly, while others present with early metastatic disease even when the primary tumor is very small (7-9).

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So, what can we learn from ASGE guidelines and what is new? Surveillance for mutation carriers is already recommended by several previous guidelines, such as those published by the International Cancer of the Pancreas Screening (CAPS) Consortium (10). The ASGE guidelines suggest that all BRCA1/2 mutational carriers should undergo screening for pancreatic cancer, while previous guidelines limited screening to those with a family history.

One aspect that is seldom discussed in pancreatic cancer screening guidelines is the resources spent and health economical aspects (11,12). Furthermore, the diagnostic yield and effect on stage and survival remain uncertain. Results from the multicenter Cancer of Pancreas Screening-5 (CAPS5) study and updated outcomes of patients enrolled in prior CAPS studies suggest a low yield of detection of pancreatic cancer, but a high incidence of resectable, early-stage disease (stage I) and superior survival (13). The 5-year survival among screening-detected pancreatic cancer was 73.3%, with a median overall survival of 9.8 years, compared to 1.5 years for patients diagnosed with pancreatic cancer outside surveillance. On the other hand, the Dutch Familial Pancreatic Cancer Surveillance Study Group (14) reported a pancreatic cancer resectability rate of only 60%, likely due to an overrepresentation of CDKN2A mutation carriers, which may have a more aggressive clinical course compared to other genetic syndromes. Therefore, it has been suggested that CDKN2A carriers should undergo more frequent surveillance, e.g., every 6 months.

The timely identification of resectable lesions during surveillance programs remains a challenge, despite the use of MRI and EUS. There is a need for complementary diagnostic methods, such as biomarkers, in order to improve diagnostic yield. Importantly, levels of biomarkers in the circulation may be increased up to 4 months before radiologic evidence of a pancreatic tumor (15). A high-performing blood test may be taken with increased frequency (e.g., every 3–6 months) and thereby replace costly imaging during routine surveillance. A positive biomarker test may then select patients that need further diagnostic work up, including MRI or EUS, in order to detect early-stage tumors.

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