



## Review

# Screening of pancreatic cancer: Target population, optimal timing and how?



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## ABSTRACT

Pancreatic cancer patients usually present at a late stage due to subtle clinical manifestations. One of the most predictive prognostic factors in pancreatic cancer is the pancreatic cancer stage at diagnosis; therefore, early diagnosis is essential. Until now, pancreatic cancer screening has not become a standard practice for the general population due to the low incidence. In current circumstances, targeting individuals with a high risk of pancreatic cancer may be more rational. Several screening modalities for pancreatic cancer have also become debatable topics. Therefore, this article will review current evidence and recommendations regarding pancreatic screening cancer protocol in general and in high-risk populations.

## 1. Introduction

Pancreatic cancer is still a worldwide problem, even after improvements in diagnosis and management. World Health Organization (WHO) GLOBOCAN 2020 showed that pancreatic cancer was ranked fifth in terms of the most common gastrointestinal cancer and seventh among all cancer death cases [1,2]. Pancreatic cancer was associated with a low survival rate. American Cancer Society (ACS) showed that the combined 5-year relative survival rate among all pancreatic cancer stages was 11% [3]. Several factors may be attributed to the low survival rate among pancreatic cancer patients. One of the most predictive prognostic factors in pancreatic cancer is the pancreatic cancer stage at diagnosis. Pancreatic cancer patients usually present at a late stage due to subtle clinical manifestations. Data showed that approximately 10–20% of patients were found in resectable or localized stages [4]. Data from ACS showed a significant difference in the 5-year relative survival rate

between the pancreatic stages, which stated as 42% for the localized stage, 14% for the regional stage, and 3% for the distant stage [3,4]. Therefore, it is crucial to detect pancreatic cancer at an early or localized stage.

Finding pancreatic cancer at an early stage is not easy because, as stated before, pancreatic cancer commonly shows significant symptoms only at a later stage. Therefore, relying solely on clinical manifestations as a screening method may not be sufficient. Until now, pancreatic cancer screening has not become a standard of practice for the general population, in contrast with the general recommendation of colorectal screening as a standard of care [5,6]. Appropriate screening protocols are needed for pancreatic cancer as the incidence of pancreatic cancer is not as high as colorectal cancer; therefore, targeting high-risk populations may be more rational. The efficacy of several screening modalities for pancreatic cancer has also become a topic of debate [5]. Therefore, in this review, we will discuss the current approach to

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pancreatic cancer, focusing on who should be screened, when to screen, which modalities should be used, and what are the current pancreatic cancer screening recommendations.

## 2. Risk factors of pancreatic cancer

In order to answer which population will benefit the most from pancreatic cancer screening, we need to understand the risk factors of pancreatic cancer. Several risk factors have been linked with pancreatic cancer [5].

### 2.1. Genetic syndrome and familial predisposition as risk factors of pancreatic cancer

Most pancreatic cancer cases were reported as sporadic cases, while around 10% of cases were attributed to familial or genetic predispositions [7]. Several genetic syndromes have been linked with the occurrence of pancreatic cancer. Peutz-Jegher syndrome, which is associated with *STK11* gene mutation, was reported to have a relative risk for pancreatic cancer up to 139.7, and the cumulative risk for pancreatic cancer development was 2–55%. The risk was increasing proportionally according to increasing age [8]. Hereditary pancreatitis was another genetic syndrome with a significantly increased risk of developing pancreatic cancer (RR: 53–87 and cumulative risk of 40–55%). Hereditary pancreatitis was characterized by pancreatitis that occurred in 2 or more individuals in the family for 2 or more generations and was associated with the mutation of the *PRSS1* gene [9,10]. Familial atypical multiple mole-melanoma (FAMMM), caused by mutation of the *CDKN2A* gene, was associated with pancreatic cancer occurrence. A study by Lynch et al. showed that FAMMM patients had up to 22 times increased risk of having pancreatic cancer [11]. Lynch syndrome or hereditary non-polyposis colorectal cancer, which is associated with *MLH1*, *MSH2*, and *MSH6* mutations, was reported by Bujanda et al. for increasing the risk of pancreatic cancer occurrence by 8.6 times; therefore should be considered as a high-risk group [12]. Patients with Li-Fraumeni syndrome, which is characterized by the lack of *TP53* suppressor gene, were 7.3 times more likely to have pancreatic cancer [13]. Ataxia telangiectasia, an autosomal recessive disease, was associated with an increased risk for developing pancreatic cancer by 4.2 times. The mutation of *ATM* gene was the underlying mechanism [14]. The mutation of *BRCA1* and *BRCA2* was commonly associated with breast and ovarian cancer, therefore commonly referred to as hereditary breast and ovarian cancer (HBOC). However, a study showed that pancreatic cancer is the third most common cancer to develop among HBOC patients [7]. Patients with HBOC had 4–13 times for developing pancreatic cancer [10]. Familial adenomatous polyposis (FAP), which is associated with *APC* gene mutation and characterized by multiple adenomatous colon polyps, was also associated with 4.46 times increased risk of having pancreatic cancer [15]. The summary of various genetic syndromes associated with pancreatic cancer can be seen in Table 1. The International Cancer of the Pancreas Screening Consortium released recommendations in 2020 regarding managing patients with increased risk for familial pancreatic cancer, stating that individuals with *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *CDKN2A*, *STK11*, *MLH1*, and *MSH2* should be put on pancreatic cancer surveillance [16].

American Gastroenterological Association (AGA) defined familial pancreatic cancer (FPC) as pancreatic cancer occurring in 2 or more first-degree relatives that do not meet the criteria for other hereditary cancer syndromes [17]. Several familial pancreatic cancer registries have been made to address the issue regarding increased pancreatic cancer risk in individuals with relatives having pancreatic cancer, such as the European Registry of Familial Pancreatic Cancer and Hereditary Pancreatitis (EUROPAC), National Familial Pancreas Tumor Registry (NFPTR), and many others [18,19]. From those registries, we can conclude that FPC was developed at a younger onset compared to sporadic cases (58–68 vs. 61–74 years old), the risk was raised

**Table 1**  
Genetic syndromes associated with pancreatic cancer [5,16,23].

Genetic Syndrome	Gene Mutation	Relative Risk of Pancreatic Cancer
Peutz-Jeghers syndrome	<i>STK11</i>	132
Hereditary Pancreatitis	<i>PRSS1</i>	69
	<i>SPINK1</i>	
	<i>CTRC</i>	
	<i>CFTR</i>	
Familia atypical multiple mole melanoma	<i>CDKN2A</i>	13–39
Li – Fraumani syndrome	<i>TP53</i>	7.3
Hereditary breast ovarian cancer syndrome	<i>BRCA1</i> ,	2.26
	<i>BRCA2</i>	3.5–6.2
Lynch Syndrome	<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i>	5–9
Familia adenomatous polyposis	<i>APC</i> , <i>MUTYH</i>	4.46
Ataxia telangiectasia	<i>ATM</i>	2.7

proportionately to the collective number of affected relatives, the closer degree of relationship and decreasing age of pancreatic cancer onset among relatives [17,20–23].

### 2.2. Non-genetic risk factors

Several non-genetic risk factors of pancreatic cancer have been studied, and some of the risk factors were modifiable; therefore, early intervention on modifiable risk factors may lead to decreased risk. Tobacco smoking was correlated with pancreatic cancer risk. Compounds in tobacco smoke may induce inflammatory cells, generating fibrosis, inhibiting apoptosis, and increasing the proliferation of pancreatic cancer cells. Studies have shown that the risks of pancreatic cancer are different among different types of tobacco. The predicted increased risk ranged from 1.7 to 2.6 [24,25]. Alcohol consumption was associated with pancreatic cancer. A meta-analysis by Wang et al. showed that heavy alcohol intake ( $\geq 24$  gr/dl) was associated 15% increased risk of getting pancreatic cancer [26]. Diabetes is another established pancreatic cancer risk factor. A study showed that patients with chronic type 2 diabetes mellitus were 1.5–2.0 more likely to develop pancreatic cancer [27]. Chronic pancreatitis is strongly related to pancreatic cancer. A meta-analysis showed that within 2 years after chronic pancreatitis, the pancreatic cancer risk was as high as 16 times more likely. The risk decreased after the period passed; however, patients were still 8 times more likely to develop cancer even 5 years after chronic pancreatitis [28]. Three lesions were identified as precursors lesions of pancreatic cancer, including pancreatic intraepithelial neoplasms (PanINs), intra-ductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs). Those precursors lesions were associated with malignant transformation and can be managed at an early stage; therefore, becoming the target of screening [26,29,30].

## 3. Which patients should be screened?

United States Preventive Services Task Force (USPSTF) in 2019 stated against screening for pancreatic cancer in asymptomatic adults. This recommendation was an update on the 2004 USPSTF recommendation, which was also against pancreatic cancer screening in asymptomatic adults. It must be noted that this recommendation does not evaluate high-risk pancreatic cancer groups which were termed as having familial pancreatic cancer or individuals with specific genetic syndromes. However, individuals with other pancreatic risk factors, such as new-onset diabetes, preexisting diabetes, older age, cigarette smoking, obesity, or a history of chronic pancreatitis, were included as a consideration in this recommendation. A review of evidence by USPSTF showed no benefit of pancreatic cancer screening, and screening of the general population may lead to overdiagnosis and overtreatment. They also

found potential harm in terms of screening for pancreatic cancer and treatment of screen-detected pancreatic cancer [31].

Several societies have published guidelines regarding pancreatic cancer screening protocol for high-risk individuals, such as the American College of Gastroenterology in 2015, the International Cancer of the Pancreas Screening Consortium in 2020, and the American Gastroenterology Association in 2020 [16,17,32]. All these guidelines had similarly recommended pancreatic cancer screening for patients with Peutz-Jeghers syndrome, *CDKN2A* gene mutation, hereditary pancreatitis, patients with 1 or more first-degree relatives with pancreas cancer, Lynch syndrome, mutations in *BRCA1*, *BRCA2*, *PALB2*, and *ATM* genes. International Cancer of the Pancreas Screening Consortium also recommends screening any individual: (1) If at least three affected relatives on the same side of the family, of whom at least one is a first-degree relative (FDR) to the individual considered for surveillance, (2) If at least two affected relatives who are FDR to each other, of whom at least one is an FDR to the individual considered for surveillance, (3) If at least two affected relatives on the same side of the family, of whom at least one is an FDR to the individual considered for surveillance [16,17].

#### 4. When should screening begin and stop for high-risk individuals?

American Gastroenterology Association recommends that screening in high-risk individuals should begin at 50 years old or 10 years younger than the initial age of familial onset. As stated before, pancreatic cancer associated with genetic syndromes can occur at a younger onset, and therefore screening should be conducted earlier. The AGA recommends that screening should be initiated at 40 years of age in *CKDN2A* and *PRSS1* mutation carriers with hereditary pancreatitis and at 35 years in the setting of Peutz-Jeghers syndrome [17]. The International Cancer of the Pancreas Screening Consortium also recommends starting screening at age 50 for patients with familial risk and without genetic syndromes [16]. The AGA advised that pancreatic cancer screening in high-risk individuals can be stopped if the individuals are more likely to die of non-pancreatic related causes or due to other comorbidities and/or are ineligible for pancreatic resection [17].

#### 5. Which screening modalities should be used for screening?

The AGA recommends a combination of Magnetic Resonance Imaging (MRI) and Endoscopic Ultrasound (EUS) as the choice for pancreatic screening modalities [17]. In contrast, the International Cancer of the Pancreas Screening Consortium recommends MRI and Magnetic Resonance Cholangiopancreatography (MRCP) and/or EUS combination as the preferred screening modalities [16].

Nowadays, EUS has become the most sensitive imaging modality to evaluate pancreatic lesions. Studies have shown that EUS has a 93% sensitivity in detecting pancreatic tumors with sizes less than 30 mm, and this number is significantly higher compared to sensitivity is shown by MRI (63%) and Computed Tomography (CT) scans (53%). Data also showed that EUS might detect pancreatic lesions missed by other imaging modalities [33,34]. Therefore, the high sensitivity and negative predictive value of EUS in excluding pancreatic tumors make it valuable as a screening tool. EUS can also be used to guide a fine needle aspiration (FNA) biopsy, in order to obtain tissue samples whenever needed [34, 35]. EUS is not only accurate in detecting solid pancreatic lesions, but can also assess chronic pancreatitis-like parenchymal changes and PanINs, which may become pancreatic cancer [36]. Magnetic resonance imaging is more accurate in detecting pancreatic cysts compared to EUS and has a high sensitivity for pancreatic cancer screening. The MRI can also detect other abdominal tumors besides pancreatic tumors, which may occur in high-risk individuals [17,37]. The use of MRCP may be useful in evaluating pancreatic ductal abnormalities, and in some cases, secretin can be injected to improve diagnostic accuracy [38]. Nowadays, EUS and MRI are preferred compared to CT scans due to the lack of

radiation exposure for patients and higher sensitivity in detecting small pancreatic lesions [18,39]. Transabdominal ultrasound is generally not recommended as a pancreatic cancer screening modality due to its low sensitivity in detecting small lesions. The endoscopic ERCP is also not recommended as a routine screening method due to the risk of post-ERCP pancreatitis [39].

The use of the tumor marker CA 19-9 as a pancreatic cancer screening modality has not been recommended by AGA [17]. The International Cancer of the Pancreas Screening Consortium stated that CA 19-9 should be checked if worrisome features were found during imaging [16]. Results from studies have shown the low positive predictive value of CA 19-9 as a screening method for asymptomatic cancer patients. Several conditions may be linked to increased CA 19-9 levels, such as bile duct obstruction, infection, ovarian cysts, and many other inflammatory states or benign diseases [40]. Several biomarkers have been evaluated as pancreatic screening modalities, such as microRNAs, but further study is needed to confirm the efficacy [41].

National Comprehensive Cancer Network (NCCN) in 2022 recommended genetic testing for every confirmed pancreatic cancer patient in order to find inherited mutations. Genetic testing was also recommended for patients with a family history of cancer, especially pancreatic cancer [42]. The NCCN in, September 2022 also released clinical practice guidelines regarding genetic/familial high-risk assessment of breast, ovarian, and pancreatic cancer [43]. High-risk individuals may benefit from multiple germline genetic testing, not only for stratifying their risk but also for identifying the potential use of PARP inhibitors in selected pancreatic cancer patients [44]. Previous recommendations by the American Society of Clinical Oncology (ASCO) in 2018 also stated that all pancreatic carcinoma patients should be assessed for hereditary syndromes. The ASCO also recommends genetic testing for patients with a history of pancreatic cancer [45].

#### 6. Screening interval

The previous findings influence the determination of screening intervals during screening. International Cancer of the Pancreas Screening Consortium recommends a 12-month screening interval in high-risk patients if no abnormalities or non-concerning abnormalities are found. Screening every 3–6 months was recommended for high-risk individuals with newly detected pancreatic cancer, but this did not lead to a surgical indication [16]. The AGA also supported this recommendation; 12 months was the recommended screening interval. Screening every 6–12 months was suggested for low-risk lesions, every 3–6 months for indeterminate lesions, and within 3 months for high-risk lesions [17].

#### 7. Goals of pancreatic cancer screening

The goal of pancreatic cancer screening in high-risk patients is to find precursor lesions of pancreatic cancer or resectable stage I pancreatic cancer, which can be followed up or managed early. As stated above, the 5-year survival rate of pancreatic cancer patients was significantly reduced if the stage at diagnosis was beyond resectable. As a result, finding early lesions is suggested to reduce mortality, avoid complications and improve patients' quality of life [22,23,46].

#### 8. The value of pancreatic cancer screening

Ideal cancer screening protocols should be simple, affordable, and applicable for every population and should aim to avoid overdiagnosis. Various studies have been conducted to evaluate the effectiveness of pancreatic cancer screening protocol in terms of reducing morbidity and mortality. Dbouk et al., in 2022 reported on the surveillance outcomes of high-risk pancreatic cancer individuals enrolled in the Cancer of Pancreas Screening-5 (CAPS5) multicenter study. This multicenter study included 1461 high-risk individuals, with almost half having a

pancreatic cancer susceptibility gene. On surveillance, they found nine patients who had developed pancreatic cancer, with seven patients at stage I, one at stage II, and one at stage III. Eight patients underwent surgery for worrisome lesions, and 62.5% of them showed low-grade dysplasia. Reviewing all data from CAPS1-5 (including 1731 patients) showed that 26 individuals developed pancreatic cancer, and 57.9% of them were at stage I. Five-year survival data showed a 73.3% survival rate in screen-detected pancreatic cancer and a median overall survival of 9.8 years. This finding is in contrast with pancreatic cancer patients outside the surveillance study, which had an average survival of 1.5 years due to late-stage presentation. Therefore, Dbouk et al. concluded that the current screening protocol might detect a higher number of stage I pancreatic cancer and was associated with long-term survival [47].

Another new evidence supporting the current pancreatic cancer protocol was demonstrated by Klatte et al., in 2022. Klatte et al. conducted a 20-year prospective cohort surveillance study in 347 patients with CDKN2A mutation; they found that 83.3% of 36 individuals that developed pancreatic cancer were diagnosed at a resectable stage, 33.3% were in stage I, and the median survival was 26.8 months, and 5-year survival rate was 32.4%. This finding showed the benefit of pancreatic cancer screening in high-risk individuals, which may detect a high number of resectable-early stage pancreatic cancer, therefore improving survivability [48]. A further benefit of pancreatic cancer screening in familial high-risk individuals was shown in a systematic review by Lu et al. This review included 16 studies and demonstrated a higher curative resection rate, longer median survival time, higher 3-year survival rate, higher diagnostic rate, and higher detection rate at earlier pancreatic cancer stages [49].

## 9. Conclusion

Advanced pancreatic cancer is associated with low survival rates, and therefore early management of precursor lesions and early stages of pancreatic cancer is essential. Current recommendations do not recommend screening for asymptomatic individuals. However, identifying high-risk pancreatic cancer individuals and following up with appropriate screening protocols are recommended.

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All authors are equally contributed in study concept and design, along with manuscript writing, reviewing, and approving.

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The authors declare that there is no conflict of interest.

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