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Surveillance for neoplasia in the pancreas

Kasper A. Overbeek, MD^{a,*} [Research fellow], Djuna L. Cahen, MD, PhD^{a,1} [Assistant professor], Marcia Irene Canto, MD, MHS^b [Professor of Medicine and Oncology], and Marco J. Bruno, MD, PhD^{a,1} [Professor]

^aDepartment of Gastroenterology and Hepatology, Erasmus University Medical Center, 's Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands ^bDivision of Gastroenterology and Hepatology, The Johns Hopkins Medical Institutions, 1800 Orleans St., Blalock 407, Baltimore, MD, 21287, USA

Abstract

Despite its low incidence in the general population, pancreatic cancer is one of the leading causes of cancer-related mortality. Survival greatly depends on operability, but most patients present with unresectable disease. Therefore, there is great interest in the early detection of pancreatic cancer and its precursor lesions by surveillance. Worldwide, several programs have been initiated for individuals at high risk for pancreatic cancer. Their first results suggest that surveillance in high-risk individuals is feasible, but their effectiveness in decreasing mortality remains to be proven. This review will discuss which individuals are eligible for surveillance, which lesions are aimed to be detected, and which surveillance modalities are being used in current clinical practice. Furthermore, it addresses the management of abnormalities found during surveillance and topics for future research.

Keywords

Pancreatic neoplasms; Early detection of cancer; Pancreatic cyst; Neoplastic syndromes; Hereditary; Genetic predisposition to disease

Introduction

Pancreatic cancer (PC) has a low age-adjusted incidence of 13.5 per 100,000 per year [1], yet is the fourth leading cause of cancer-related death in the United States, with an estimated 50,000 deaths in 2016. Mortality has been increasing by 0.4% each year, and in 2030, it is projected to be the second leading cause of cancer-related death [2,3]. PC has a dismal prognosis, with a 5-year survival rate of 7%. Because surgery provides the only cure, survival greatly depends on operability at diagnosis. After surgery, the 5-year survival rate increases to 27%. However, only 15–20% of patients present with resectable disease and

*Corresponding author. Fax: +31 10 703 03 31.

¹Fax: +31 10 703 03 52.

Conflict of interest

None.

even in resected cases, 24% experience recurrence [4]. Earlier detection of PC would increase the chances of survival. It is estimated that precursor lesions require an average of 11.7 years to evolve into a malignant clone, and that metastatic subclones occur 6.8 years later [5]. This creates a window for early detection of PC cases through a surveillance program for high-risk individuals (HRIs).

Who is at risk for pancreatic cancer?

The lifetime risk of PC in the United States' general population is estimated at 1.5% [6]. Most PC cases are sporadic. Hereditary PC makes up for 10% of cases, but only in 3%, this can be related to known genetic cancer susceptibility syndromes or inherited disease (described below). In the remainder 7%, no underlying cause is found to explain the familial aggregation. This group is commonly referred to as familial PC (FPC) [7–9]. FPC family members and carriers of known hereditary cancer syndromes are at a higher risk than the general population to develop PC. Therefore, they are designated candidates for surveillance.

Modifiable risk factors

Smoking is the most important modifiable risk factor for PC and doubles the risk (ORs range 1.74–2.2) [10,11]. This effect is dose-dependent, but even second-hand tobacco exposure increases the risk to develop PC (OR 1.2) [12]. After cessation, the risk decreases, but it remains elevated for 10–20 years (OR 1.2) [10,11]. Alcohol use has long been associated with PC [13,14]. A recent meta-analysis of 19 prospective studies showed that low-to-moderate alcohol intake has little effect on PC risk, but high alcohol intake increases the risk (RR 1.15) [15]. As this analysis showed the highest risk in the subgroup with a follow-up greater than 10 years, the long-term impact of alcohol use may have even been underestimated. Also, overweight or obesity at any age increases the risk of PC (HRs range 1.12–1.25 for different age cohorts at the time of BMI measurement) [16]. A pooled analysis of 14 cohort studies showed a 47% increased risk in obese persons (BMI ≥ 30 kg/m²) [17]. Another meta-analysis showed a higher PC-related mortality for overweight (BMI 25–29.9 kg/m², adjusted HR 1.06) and obese (BMI ≥ 30 kg/m², adjusted HR 1.31) patients [18]. Many dietary factors have been suggested to influence PC risk, but evidence is inconclusive on this matter, partly due to confounding factors and the lack of randomized trials [19,20]. Fruits, vegetables, and whole grain intake are thought to have a protective effect [21–23] whereas the consumption of red meat in men, unsaturated fatty acids, and some saturated fatty acids were found to increase PC risk [24–26]. It has been suggested high serum Vitamin D levels have a protective effect, but case-control studies have not been able to support this [27,28].

Non-modifiable risk factors

Men are more often affected than women, but this difference is minimal [2]. African-Americans and persons of Ashkenazi Jewish descent are found to be at higher risk [29,30]. Furthermore, the incidence of PC increases with age. Most diagnoses are made between 60 and 80 years [31,32]. Blood types A, B and AB are at modestly increased risk compared to type O (ORs 1.60, 1.09, and 1.14, respectively) [30,33]. Both recent diagnosis of chronic

pancreatitis and long-standing chronic pancreatitis of any origin are identified risk factors [30,34,35].

Diabetes mellitus

There is a strong association between diabetes mellitus and PC. Long-term type 2 diabetes is associated with a 1.5–2-fold increased risk of PC and the prevalence of diabetes is much higher in patients with PC (68%) than in patients with other cancer types [36,37]. This may be due to the associated hyperglycemia and hyperinsulinemia. A recent systematic review and dose–response meta-analysis found a strong linear association between elevated fasting blood glucose levels and risk of PC [38].

Additionally, new-onset diabetes and high HbA1c levels in diabetic patients are regarded as a possible early symptom of PC. Aggarwal et al. demonstrated that 40% of PC patients developed diabetes mellitus in the 36 months prior to PC diagnosis [36]. Liao et al. showed increments in pre-diabetic glucose levels to be associated with an increased PC risk (rate ratio 1.15 per 0.56 mmol/L increase) [38]. In diabetic patients, a pattern of increasing HbA1c levels preceding the clinical detection of PC has been observed, further affirming the possibility of rising glucose levels as an indicator of subclinical PC [39]. Its use in surveillance of PC remains to be proven, however.

In line of this rationale, an effect of antidiabetic drugs on PC carcinogenesis can be expected, but this seems to vary according to drug class. Sulfonylureas and glinides do not seem to affect PC risk, but incretin-based drugs are currently not recommended in patients with (a history of) acute pancreatitis, because of conflicting results [40]. Diabetes patients using insulin are at higher risk than non-insulin using diabetes patients [41]. Metformin has been found to decrease PC risk, and increase short-term survival in non-metastatic PC [40].

Familial pancreatic cancer

The familial aggregation of PC has been demonstrated by both case-control and cohort studies [7]. Individuals with at least one first-degree-relative (FDR) with PC are at higher risk (OR 1.76). This risk further increases in case of two or more FDR cases (OR 4.26). If a family contains two affected FDRs, the members of this family are defined as FPC kindreds. Prospective registries have shown that within FPC kindreds, risk increases rapidly according to the number of affected family members; 4.6-fold with one, 6.4-fold with two, and 32-fold with three affected FDRs [42]. A minority of this familial aggregation is explained by well-defined genetic cancer susceptibility syndromes and inherited diseases, associated with PC, as shown in Table 1.

Who should be screened?

Because the incidence of PC is low, and a non-invasive reliable screening tool is unavailable, screening is not recommended in the general population. However, in selected HRIs, a surveillance program may be effective. In 2011, the International Cancer of the Pancreas Screening (CAPS) Consortium held a summit to develop recommendations on screening, surveillance and management of HRIs [60]. They appointed the following candidates for surveillance: FPC kindreds with a first-degree-relative with PC, patients with Peutz-Jeghers

syndrome, and *p16*, *BRCA2*, *PALB2* and Lynch syndrome mutation carriers with 1 PC affected first-degree-relative. Since the relative risk of PC is lower or not well-defined in the other susceptibility syndromes, there are no guidelines on surveillance in these families. Some experts suggest surveillance in *BRCA1*, *ATM* and *TP53* mutation carriers should be limited to those with a first- or second-degree relative with PC [61].

Despite their high risk of PC, patients with chronic pancreatitis, including hereditary pancreatitis, are currently not included in surveillance programs. The diagnostic accuracy of imaging modalities for detecting precursor lesions in this group is much lower, because of the morphological changes associated with chronic inflammation. Annual surveillance with computed tomography (CT) or magnetic resonance imaging (MRI) may be considered for patients 40 years, but this is not evidence-based [34,46].

What is the age to begin and end surveillance?

The CAPS consortium did not reach consensus on the age to begin and end surveillance [60]. The average age at diagnosis of FPC is 68 years [62], but a trend of earlier age of onset is seen in successive generations, a phenomenon known as genetic anticipation [63]. In a study of 1223 FPC kindreds, the median age of death from PC was 70 for the first, 64 for the second, and 49 for the third generation [63]. Furthermore, Brune and colleagues [62] demonstrated an increased risk of PC associated with the presence of a young-onset PC case (<50 years) in FPC families (SIR 6.34). This relation was not found in sporadic pancreatic cancer families. Based on these findings, current programs mostly use the screening principles of colorectal cancer and start surveillance at the age of 50 or 10 years earlier than the youngest PC case in the family, whichever comes first.

Since the consensus is that surveillance should only be offered to individuals who are candidates for surgery [60], and it takes an estimated average of 18.5 years for precursor lesions to develop into distant metastases [5], surveillance programs currently stop at the age of 75.

What should be detected during surveillance?

Since surgery is the only curative treatment, surveillance is aimed to detect advanced precursor lesions or PC in an early, operable stage. Several precursor lesions have been identified: pancreatic intra-epithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs).

PanIN

Most invasive pancreatic ductal adenocarcinomas develop from PanINs. PanINs are non-invasive microscopic epithelial neoplasms and arise in the smaller pancreatic ducts. They are defined by cytologic architectural atypia, by which they are divided in three categories: minimal atypia (PanIN1a: flat type, PanIN1b: papillary type), mild-moderate atypia (PanIN2), and marked atypia (PanIN3). PanINs are common lesions and their incidence increases with age. They occur far more often in the head than in the corpus/tail area. PanIN is strongly associated with diseases of the pancreas, occurring in 82% of pancreata with

pancreatic cancer and in 60% with chronic pancreatitis. However, 16% of healthy pancreata also contain PanIN1 or PanIN2 lesions. PanIN2 lesions are three times more common in pancreata with cancer. PanIN3 lesions are exclusively observed in pancreata with cancer and are classified as carcinoma in situ. The ideal aim of surveillance is to detect all PanIN lesions and specifically to identify those lesions with high-grade dysplasia and at high risk of malignant transformation [64].

MCN

MCNs make up for 2–5% of pancreatic tumors. As they originate from ovarian-type stroma, they occur almost exclusively in women at childbearing age [65]. Over 90% is located in the body or tail, most are unifocal, and 7–18% has ductal communication [65,66]. A variable mean size is reported, ranging from 1 to 12.5 cm [64–67]. Roughly 30% is associated with invasive carcinoma [64,65,67], making surgery compulsory. In resected MCN without invasive carcinoma, 5-year survival is close to 100%. In case of invasive carcinoma, 5-year survival is 50–60% [67].

IPMN

Three to five percent of pancreatic neoplasms are IPMNs. Like MCNs, IPMNs are mucin-producing cystic neoplasms, originating from pancreatic duct cells. The mean age of patients is 65 years, the male to female ratio is 3:2. IPMNs occur predominantly in the head (70%), 20–30% are multifocal, and they involve the ductal system by definition. The mean size of IPMNs is 1 cm [64]. They are classified based on their grade of dysplasia (low, moderate, and high-grade dysplasia) or on the extent of ductal involvement (side branch (SB), main duct (MD), or mixed type). Main duct involvement contains a high risk for malignant transformation (5-year risk for high-grade dysplasia of 63% compared with 15–24% for SB-IPMN) [68,69]. Other high-risk stigmata include an enhanced solid component and a main duct larger than 10 mm [70]. Worrisome features include a thickened cyst wall, mural nodules, size ≥ 3 cm, main duct >5 mm, abrupt main duct caliber change with distal pancreatic atrophy, lymphadenopathy and cyst growth. Growth is defined as an increase in size of 2–5 mm/year (HR 11.4 for risk of malignancy) or ≥ 5 mm/year (HR 19.5), or a total increase ≥ 10 mm during follow-up [64,69,70].

What is the best test for surveillance?

Imaging

Different imaging modalities are used to diagnose PC (Table 2). CT is able to visualize the entire upper abdomen and has a high accuracy in evaluating resectability [71], making it the modality of choice for staging. In the light of surveillance for PC, however, CT has some limitations. Both CT and multi-detector row CT (MDCT) have a low diagnostic accuracy for the detection of small PC. Also, repeated exposure to radiation increases the risk of developing radiation-related cancers.

¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) and PET/CT are also used to confirm suspected PC, and some studies report higher sensitivities for the differentiation of PC compared to other modalities. Other advantages of FDG-PET are its

ability to differentiate between PC and (mass-forming) chronic pancreatitis [72,73] and its accuracy in detecting distant metastases. However, the role in detecting small tumors is still debated [74,75]. FDG-PET and PET/CT are currently not used as surveillance modality due to the high cost, doubtful specificity and ionizing radiation. It is mainly reserved for diagnosing PC when CT fails to identify a tumor or fine-needle aspiration (FNA) is non-diagnostic.

MRI does not share the radiation exposure of CT and PET/CT and is better at characterizing cystic lesions. Combined with cholangiopancreatography (MRCP) it reaches a sensitivity and specificity of 84% and 97% respectively, to diagnose PC in patients with a strong suspicion of a pancreatic tumor [76]. Additionally, it is possible to use intravenous secretin stimulation. A recent prospective study of 202 HRIs showed secretin-enhanced MRCP improved visualization of ductal communication of cystic pancreatic lesions, compared to normal MRCP (OR 1.28) [77]. This allows to more accurately distinguish IPMN from benign cystic lesions which do not have ductal communication. Another promising modality is diffusion weighted MRI. By analysis of the diffusion of water molecules, this technique provides additional information on cell size and density, presence of fibrosis, edema and intratumoral blood vessels [78]. A recent meta-analysis found a sensitivity and specificity of 91% and 86%, respectively, to differentiate benign and malignant pancreatic tumors [79].

The sensitivity of ultrasonography (US) for the detection of small pancreatic tumors is low, making it unsuitable for PC surveillance [80]. Endoscopic ultrasonography (EUS), on the other hand, can visualize the pancreas from close proximity, enabling the depiction of small focal lesions. In a blinded comparison of surveillance modalities in 216 HRIs, EUS detected 79% of all detected pancreatic lesions. The yield of CT and secretin-enhanced MRI/MRCP was 13.8% and 77%, respectively, making EUS one of the main surveillance modalities [81]. Some studies have reported sensitivities ranging up to 100%, but a meta-analysis showed a pooled sensitivity of 81% for the differentiation of PC [82]. The variable results could be explained by operator-dependent differences, one of the greatest downsides of EUS [83].

A great advantage of EUS is the possibility of targeted lesion sampling through fine-needle aspiration (FNA). A meta-analysis of studies performing EUS-FNA on pancreatic lesions showed a good sensitivity (89%) and specificity (96%) for diagnosing PC [84]. Unfortunately, the diagnostic accuracy of EUS-FNA is much lower within the subgroup of patients with cystic lesions (sensitivity 51–52% and specificity of 94–97%) [85].

Biomarkers

The low sensitivity of imaging studies to detect small pancreatic lesions and establish their grade of dysplasia provides a strong need for non-invasive biomarkers. Currently, carbohydrate antigen 19-9 (CA19-9) is the only approved biomarker for PC, but because of a low diagnostic accuracy, with both a sensitivity and specificity of 80% [88], it is unsuitable for surveillance. Combining CA19-9 with other biomarkers into panels has been shown to increase sensitivity and specificity [89], but these have not been validated for clinical use.

Several novel biomarkers are under investigation, of which molecular biomarkers seem the most promising. The evolution from normal pancreas to high-grade dysplasia to cancer is

accompanied with molecular and genetic alterations [90]. Detecting these alterations can possibly lead to a diagnosis before disease shows on imaging modalities.

Micro-RNAs are small non-coding RNAs that are either up- or down regulated in PC [91–93]. In an array analysis of 735 micro-RNAs in serum, several micro-RNAs were able to distinguish PC from healthy controls. Micro-RNA-1290 performed better than CA19-9 [94]. Panels of several validated messenger RNA biomarkers were able to distinguish PC from chronic pancreatitis with a sensitivity and specificity of 96.7%, and could differentiate PC from non-PC subjects with a sensitivity of 90% and specificity of 95% [95]. Because salivary glands take up many circulatory molecules from the blood-stream, RNA can be found in saliva, which could provide a non-invasive, simple and low-cost test [92].

Genetic alterations can also be analyzed in pancreatic juice (collected during EUS) and in stool. For instance, specific cancer-related methylated DNA markers have been identified in PC and precursor lesions [96–98]. A recent clinical pilot study with six selected methylation markers in pancreatic juice yielded area under the curve values of up to 0.92 for the distinction of PC compared with normal pancreas and chronic pancreatitis [98]. Another possibility is the detection of mutant DNA in duodenal collected pancreatic juice after secretin stimulation. Studies have shown *TP53* and *KRAS* mutations in pancreatic juice are associated with the presence of high-grade dysplasia and PC [99,100]. *GNAS* mutations were present in the pancreatic juice samples of 64.1% of IPMN cases, and *GNAS* mutations detected at baseline predicted emergence or increase in cyst size [101].

Another field of research is the detection of cancer-related mutations in circulating tumor DNA (ctDNA) and circulating tumor cells (CTC) in serum, also called “liquid biopsy” [102]. Unfortunately, detection rates have been insufficient and not enough data have been accumulated so far, leaving them far from current clinical practice [103].

Recommendations on surveillance modalities

The 2011 CAPS consortium summit reached consensus that initial surveillance examination should include EUS. Most participants deemed that MRI/MRCP should also be performed, but consensus was not reached. For follow-up visits, EUS was regarded as the best modality, followed by MRI/MRCP [60]. Since then, more studies have been performed to compare these modalities. Harinck et al. [104] compared the efficacy of EUS and MRI to detect clinically relevant lesions in HRIs. They concluded EUS is particularly sensitive for the detection of small solid lesions, while MRI is more sensitive for the detection of cystic lesions. Therefore EUS and MRI may be considered complementary rather than interchangeable. Recent results from a surveillance program in 253 HRIs by Bartsch et al. [105] showed no difference in diagnostic yield between annual surveillance with MRI and EUS or annual MRI with EUS every 3rd year. This suggests it may be sufficient to perform EUS at baseline and every 3rd year, or when changes on the yearly MRI occur.

How should patients be managed?

No abnormalities

The CAPS consortium summit did not reach consensus on the ideal surveillance interval in case no abnormalities are found at initial surveillance [60]. A majority of participants suggested a 12-month interval, but this was not based on solid evidence. Bartsch et al. [105] recently suggested an interval of 24 months in HRIs with a normal pancreas at baseline, because a 12-months surveillance interval did not detect more relevant lesions.

Solid lesions

If a solid lesion is identified by EUS or MRI/MRCP, a MDCT should be performed for further evaluation [60]. Subsequently, management should be individually assessed in a multidisciplinary setting [60]. Solid lesions ≥ 1 cm or lesions which are seen by multiple imaging modalities are suspect of malignancy and should be considered for resection, especially in HRIs. Also, for an indefinable newly detected solid lesion or main pancreatic duct stricture, surgery may be imminent. If not operated, these patients should be followed-up within 3 months [60].

Cystic lesions

In 2012, the Sendai international consensus guidelines for management of IPMN and MCN in the general population were updated [70]. These guidelines recommend resection for all MCNs, MD-IPMNs, and SB-IPMNs with high-risk stigmata, such as an enhanced solid component or a main duct ≥ 10 mm. These recommendations obviously also apply for HRIs [60]. However, these guidelines cannot be conveyed to HRIs where SB-IPMNs without high-risk stigmata are concerned. Guidelines suggest surgery should be considered in case of worrisome features such as symptoms attributable to the cyst, cyst size ≥ 2 –3 cm or the presence of mural nodules. If a cyst without worrisome features is found, surveillance can be repeated after 3–12 months [60,70]. In the general population, the incidence of malignant transformation of a low-risk SB-IPMN was found to be 2.4% in a recent systematic review (pooled estimate 0.004/pyrs), justifying close observation rather than resection [106]. Unfortunately, for HRIs, data are lacking to provide adapted recommendations. Because of the higher risk in this population, it seems justified to lower thresholds for resection, but it is unclear to what extent.

In patients with IPMN, a higher incidence of extra-pancreatic neoplasia (EPN) has been suggested. Most often reported are colorectal and gastric cancers [64,107]. However, studies report conflicting results [107]. A recent observational study investigated the incidence of EPN in SB-IPMN among patients enrolled in a surveillance protocol. The 5-year cumulative incidence of malignancies was 5.7% (SIR 1.40 for males and 1.37 for females) [108]. Based on these results, there is no justification for a stricter than usual surveillance of EPN in patients with IPMN.

What is the surgical and post-surgical management?

Surgery of pancreatic lesions should only be performed in high-volume centers [60]. The type of surgery is based on size and location of the lesion and is aimed to achieve negative margins. The CAPS consortium agreed that in HRIs, minimal surgery is recommended initially and should be extended intra-operatively, to achieve negative margins [60]. No further resection is recommended in case of PanIN2 or low- or intermediate-grade IPMN at the margins (either intra- or post-operatively). No consensus could be reached regarding further pancreatectomy when margins contain PanIN3 [60].

Findings suggest that HRIs who have undergone partial pancreatectomy are still at higher risk of developing PC and/or recurrent IPMN in the remnant pancreas. There have been cases who developed a second primary tumor after partial pancreatectomy of PC [109]. In addition, cases of PC in regions remote of radiographically identified and/or resected IPMN have been reported. This suggests IPMN represents a 'field defect' in which all ductal epithelial cells are at risk of dysplastic change [110]. In 356 prospectively followed patients with IPMN, 10 invasive lesions developed in regions remote of the identified cyst, making up 11% of all invasive disease in this cohort. Therefore, some suggest to perform a total pancreatectomy for HRIs, instead of close surveillance of a remnant pancreas [109].

It is not clear what follow-up interval should be used for resected IPMN. Recurrence rates in the general population range from 0 to 25% (34–60 months follow-up) [111–114] or even 62% (10 years follow-up) [114] for non-invasive IPMN, and 38–58% for invasive IPMN (34 months–10 years follow-up) [111,112,114]. Because positive margins and higher grades of dysplasia have been related to recurrence [113], follow-up should be based on resection status. For the general population, yearly surveillance has been suggested for non-invasive IPMN with positive margins, every 2 years for non-invasive IPMN with moderate to high-grade dysplasia margins, and less strict for non-invasive IPMN with low-grade or negative margins [113]. For HRIs, follow-up intervals may have to be shorter, as is the case for invasive IPMN. Resected MCN has a much lower recurrence rate than IPMN, and therefore does not require surveillance in the general population [113]. In HRIs, because the remnant pancreas is still at elevated risk, logic dictates continued surveillance is advisable.

What is the psychological burden of a surveillance program?

It has been suggested that PC surveillance imposes too great a psychological burden on patients, but recent studies report otherwise. Breitkopf et al. investigated the attitude of FPC kindreds and controls toward surveillance. Both groups had a high receptivity to surveillance, but FPC kindreds had greater receptivity for EUS, reported a greater perceived risk of PC and a higher level of PC worries. This illustrates the specific motivation of HRIs to participate in a surveillance program. Konings et al. evaluated the psychological burden of annual surveillance using MRI and EUS amongst 140 HRIs and showed cancer worries decreased significantly over time [115]. Anxiety and depression scores were low and comparable to the general population. Furthermore, only 11% experienced EUS as uncomfortable, and respondents dreaded EUS less as surveillance progressed. A surveillance program therefore seems to be feasible from a psychological point of view. However, some

individuals are prone to experience more distress than others [116,117]. Identifying these individuals and offering them additional psychological assessment and support could be helpful.

What is the cost-effectiveness?

The cost-effectiveness of surveillance programs for PC has not yet been established. Rulyak et al. reported that a one-time surveillance with EUS in a hypothetical cohort of 100 FPC kindreds appeared to be cost-effective [118]. In a recent Danish study, surveillance of 40 FPC kindreds with yearly EUS resulted in an incremental cost-effectiveness ratio of \$38,785 per QALY [119]. Although these studies are based on hypothetical models, one-time surveillance and a small number of patients [118–122], they raise hope that a surveillance program will be cost-effective.

What efforts have been made in pancreatic cancer surveillance?

Several centers have initiated and reported on PC surveillance programs for various high-risk groups, mainly using EUS and MRI/MRCP as surveillance modalities (Table 3). Inclusion criteria, population size, follow-up duration and definition of diagnostic yield vary greatly across study designs, resulting in a diagnostic yield ranging from 2 to 100%. Recently, results from the first multi-center cohort with a follow-up greater than ten years have been published. In CDKN2A mutation carriers surveillance was successful; PC was detected in 7.3%, with a resection rate of 75% and a 5-year survival of 24%. In FPC kindreds, the benefit of surveillance was smaller; one advanced PC case was found and 1.9% of patients underwent justified resection of a high-risk precursor lesion (high-grade IPMN or PanIN3). Thirteen patients underwent resection but did not have high-risk precursor lesions or PC.

Practice points regarding pancreatic cancer surveillance

- Surveillance for pancreatic neoplasia should be performed in designated high-risk individuals
- The aim of surveillance is to find advanced precursor lesions or early pancreatic cancer
- MRI/MRCP and EUS are the main surveillance modalities
- Currently, there is no validated biomarker available for surveillance
- The benefit of a surveillance program remains to be proven

Research agenda

- The role of yet unidentified pancreatic cancer susceptibility genes and the influence of other risk factors, such as diabetes, need to be defined, in order to improve risk stratification

- More prospective studies are necessary to identify which precursor lesions are at high risk of malignant transformation, and to reach consensus on the management of cystic and solid lesions, including post-operative management
- Multicenter, prospective studies with long-term follow-up are essential to determine the benefit and cost-effectiveness of a surveillance program

Several aspects should be taken into account when interpreting the results of PC surveillance programs. Longer survival of patients in surveillance cohorts may be attributable to a lead time bias. Since surveillance aims to detect PC before symptoms occur, survival may seem improved in surveillance cohorts compared to controls, while the total time from malignant transformation until death may actually remain unchanged. Furthermore, tumor progression rates may vary. A surveillance program favors the diagnosis of slow growing disease, thereby possibly overestimating survival time, also referred to as length time bias. Thirdly, given the non-ideal diagnostic accuracy of the currently available surveillance modalities, they may result in overtreatment of benign lesions and low-grade dysplasia. More multicenter prospective studies with long-term follow-up are needed to further prove the benefit of a PC surveillance program for HRIs. The founding of the CAPS consortium is an important step towards further collaboration.

Summary

Because of the relatively low incidence of PC in the general population and the lack of a low-cost, non-invasive test with sufficient diagnostic accuracy, surveillance is performed only in high-risk individuals. These include mutation carriers of genetic pancreatic cancer susceptibility syndromes and FPC kindreds. The ideal age to begin and end surveillance is unknown. Surveillance aims to detect early PC or advanced precursor lesions such as PanIN, IPMN and MCN. Currently, surveillance programs mainly use MRI/MRCP and endoscopic ultrasonography as surveillance modalities. It is open to debate if these tests should be used in conjunction or interchangeably, and at what interval. Multiple bio-markers show promise as novel surveillance tools, but as of yet, none of them have been validated for clinical use. In HRIs, all solid lesions ≥ 1 cm, MCNs, MD-IPMNs, and SB-IPMNs with high-risk stigmata should be evaluated for resection. The management of SB-IPMNs without high-risk stigmata in HRIs is less clear. Surgery is currently considered in case of worrisome features, but further research is warranted to enable the identification of those precursor lesions with high malignant potential. When performing surgery, a partial pancreatectomy is recommended initially, which can be extended intra-operatively to achieve negative margins. However, a total pancreatectomy has also been suggested for HRIs, because there have been cases with a second primary tumor after a partial pancreatectomy. So far, surveillance programs appear to be feasible, also from a psychological point of view. However, multicenter prospective studies with long-term follow-up are necessary to prove the benefit and cost-effectiveness of such a program.

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Table 1

Genetic cancer susceptibility syndromes and inherited diseases with associated risk of PC.

Syndrome	Gene(s)	Relative risk	Reference
Peutz-Jeghers syndrome (PJS)	<i>STK11</i>	132	[43,44]
Hereditary pancreatitis	<i>PRSS1</i>	69	[45,46]
	<i>SPINK1</i>	Unknown	
Familial atypical multiple melanoma and mole (FAMMM)	<i>CDKN2A</i>	46.6 ^a	[47,48]
Lynch syndrome	<i>MLH1/MSH2/MSH6</i>	8.6–10.7 ^c	[49–51]
Li Fraumeni syndrome	<i>TP53</i>	7.3 ^b	[52]
Familial adenomatous polyposis (FAP)	<i>APC</i>	4.46	[53,54]
Hereditary breast and ovarian cancer (HBOC)	<i>BRCA2</i>	3.5–22 ^{c,d}	[55–57]
	<i>BRCA1</i>	1–2.8 ^c	[56,58]
	<i>PALB2</i>	Unknown	
Ataxia telangiectasia	<i>ATM</i>	2.70	[59]

^aDoes not include other mutation variations than p16-Leiden.^bTested in *TP53* mutation carriers (tested or obligate) and their FDR with 50% chance on the mutation.^cRelative risk ranges between studies.^dUpper limit measured as standardized incidence ratio instead of relative risk.

Table 2

Imaging modalities and their sensitivity and specificity for the differentiation of PC.

Modality	Sensitivity	Specificity	Reference
US	76%	75%	[86]
EUS	81%	93%	[82]
EUS-FNA	89%	96%	[84]
CT	86%	79%	[86]
Helical CT	91%	85%	[86]
MDCT	85%	67%	[87]
FDG-PET/CT	85–93%	76–94%	[72,73,82,87]
FDG-PET	88–90%	76–83%	[72,82]
MRI	83–85%	72–82%	[86,87]
DW-MRI	91%	86%	[79]
MRCP	84%	97%	[76]

US, ultrasonography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; CT, computed tomography; MDCT, multi detector row computed tomography; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; DW-MRI, diffusion weighted magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography.

Table 3

Reported outcomes of pancreatic cancer surveillance programs in HRIs.

Study	City (Country)	N	High-risk group (n)	Imaging modalities (if abnormal surveillance)	Follow-up	Diagnostic yield (%) ^a	Definition of diagnostic yield ^b
Kimney 2002 ^c [123]	Seattle (United States)	46	FPC (46)	EUS (ERCP)	0–5y	26	Dysplasia
Canto 2004 [124]	Baltimore (United States)	38	FPC (37), PJS (1)	EUS (EUS-FNA, ERCP, MDCT)	11–51m	5.3	PDAC, IPMN
Canto 2006 [125]	Baltimore (United States)	78	FPC (72), PJS (6)	EUS (EUS-FNA, ERCP, MDCT)	3–12m	10.3	PDAC, IPMN, PanIN1–3
Kluijdt 2009 [126]	Amsterdam (The Netherlands)	3	CDKN2A (3)	EUS, MRI	NA	100	PDAC, SB-IPMN
Poley 2009 [127]	Rotterdam (The Netherlands)	44	FPC (21), CDKN2A (13), PJS (2), HP (3), BRCA1 (3), BRCA2 (2), p53 (1)	EUS (MRI, CT)	NA	23	PDAC, IPMN
Verna 2010 [128]	New York (United States)	51	FPC (44), BRCA1/2 (7)	EUS, MRI/MRCP (EUS-FNA, ERCP)	NA	11.7	PDAC, IPMN, PanIN-2
Ludwig 2011 [129]	New York (United States)	109	FPC (102), BRCA1/2 (7)	MRCP (EUS-FNA)	NA	7.3	PDAC, IPMN, PanIN2-3
Schneider 2011 ^d [130]	Marburg (Germany)	72	FPC, BRCA2, PALB2, CDKN2A (NR)	EUS, MRI/MRCP-S (EUS-FNA)	Median 44m	15.2	PDAC, IPMN PanIN1-3
Vasen 2011 [131]	Leiden (The Netherlands)	79	CDKN2A (79)	MRI/MRCP	0–10y	15.2	PDAC, IPMN
Al-Sukhni 2012 [132]	Toronto (Canada)	262	FPC (159), BRCA2 (68), BRCA1 (5), CDKN2A (11), PJS (7), HP (2), FDR of multiple primary cancers (10)	MRI/MRCP (EUS, MRI, CT, ERCP)	0–8y	7.3	PDAC, SB-IPMN, NET
Canto 2012 [81]	Baltimore (United States)	216	FPC (195), BRCA2 (19), PJS (2),	EUS, MRI/MRCP-S, CT (EUS-FNA)	NA	42.6	Dilated MPD, cystic lesion, solid lesion
Potjer 2013 [133]	Leiden (The Netherlands) Marburg (Germany)	241	FPC (116), CDKN2A (116), PALB2 (6), BRCA2 (3)	EUS, MRI/MRCP	0–127m	32.8	PDAC, cystic lesion
Sud 2014 [134]	Milwaukee (United States)	16 ^e	FPC (19), BRCA1/2 (7), PJS (2), CDKN2A (1), LS (1)	EUS (EUS-FNA)	0–3y	18.8	PDAC, IPMN
Del Chiaro 2015 [135]	Stockholm (Sweden)	40	FPC (32), CDKN2A (4), BRCA2 (3), BRCA1 (1)	MRI/MRCP-S (EUS-FNA)	Mean 13m	40	PDAC, IPMN
Mocci 2015 [136]	Madrid (Spain)	38 ^f	FPC (NR), BRCA1/2 (NR), early onset PC (5)	EUS, CT (MRI, EUS-FNA)	0–2y	10.5	Cystic lesion
Bartsch 2016 [105]	Marburg (Germany) Madrid (Spain) Leiden (The Netherlands)	253	236 (FPC), BRCA2 (8), BRCA1 (3), PALB2 (6)	EUS, MRI/MRCP-S	1–152m	5.9	PC, PanIN1–3, IPMN, NET
Joergensen 2016 [119]	Odense (Denmark)	71	FPC (40), HP (31)	EUS	Mean 60m	2.8 ^g	PDAC

Study	City (Country)	N	High-risk group (n)	Imaging modalities (if abnormal surveillance)	Follow-up	Diagnostic yield (%) ^a	Definition of diagnostic yield ^b
Vasen 2016 [137]	Leiden (The Netherlands) Marburg (Germany) Madrid (Spain)	411	FPC (214), CDKN2A (178) BRCA1/2/PALB2 (19)	EUS, MRI/MRCP (EUS-FNA, CT)	0–169m	4.4	PDAC, IPMN, PanIN3

NR, not reported; NA, not applicable, initial surveillance only; FPC, familial pancreatic cancer; PIS, Peutz-Jeghers syndrome; HP, hereditary pancreatitis; FDR, first-degree relative; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; CT, computed tomography; MDCT, multi detector row CT; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; MRCP-S, secretin-enhanced MRCP; ERCP, endoscopic retrograde cholangiopancreatography; PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; SB-IPMN, side-branch IPMN; PanIN, pancreatic intraepithelial neoplasm; SCA, serous cystadenoma; MPD, main pancreatic duct; NET, neuroendocrine tumor.

^aBased on per-patient analysis.

^bSerous cystadenomas were excluded.

^cContinuation of Brentnall 1999 [138] and Rulyak 2001 [139].

^dContinuation of Langer 2009 [140].

^e30 patients were included, 16 underwent EUS.

^f41 patients were included, 38 underwent EUS.

^gBoth lesions were found amongst the FPC population.