Pancreatic Cancer Surveillance in Individuals at High Risk: Clinical and psychosocial aspects

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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Pancreatic cancer remains one of the most fatal human malignancies. Incidence rates of pancreatic cancer have been stable since 1975 with 10-12 new cases per 100.000 persons per year [1-3]. Despite improvements in surgical techniques and (neo)adjuvant therapies, survival rates have not improved during the last decades [2, 4]. The median survival of patients diagnosed with pancreatic cancer is less than 6 months; the 5-year survival rate is approximately 6% [2, 4]. Survival rates are strongly dependent on stage of pancreatic cancer and therefore these poor survival rates are at least partly due to the late onset of symptoms, leading to only 8-27% of all patients to present with localized, curable disease [4]. The 5-year survival rate for stage IA disease after surgery is 31%, but this rate decreases dramatically with increasing stage [5].

Well recognized risk factors for the development of pancreatic cancer are tobacco smoking (including second-hand tobacco exposure), African American or Ashkenazi Jewish descent, chronic pancreatitis and familial predisposition (discussed below). Probable risk factors are obesity, heavy alcohol drinking, and dietary factors (saturated fats increase the risk of pancreatic cancer, fruit and vegetable consumption decreases the risk of pancreatic cancer) [6].

The only treatment for pancreatic cancer with a curative intention is surgery [4]. Despite advances in surgical techniques and supportive care, the median 5-year survival rate after surgical resection remains well below 20% [7, 8]. For this reason, both adjuvant and neoadjuvant therapies have been investigated. Widely used chemotherapeutic agents are 5-fluorouracil (5-FU) and gemcitabine. However, based on available data, adjuvant treatment with gemcitabine or 5-FU results in a gain of median survival of only a few months [9]. The role of adjuvant radiotherapy is subject of investigation. Recent data show a benefit of maximal 2 months of chemoradiation versus chemotherapy alone for locally advanced pancreatic cancer; however, other studies reported a decreased survival because of toxicity [10]. For metastatic pancreatic cancer, gemcitabine-based therapy is most commonly used. For patients in good clinical condition, a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) provides better survival benefits at the cost of increased toxicity [11].

Because of the poor prognosis once pancreatic cancer has become symptomatic, there is great interest in the prevention of this dreadful disease. Primary prevention strategies, such as lifestyle changes to reduce the number of risk factors (e.g. smoking, excessive alcohol consumption, obesity and dietary factors), are difficult for most people to implement and adhere to. People with many family members affected with pancreatic cancer might be better motivated to adhere to lifestyle changes, however, their risk of developing pancre-

atic cancer remains substantially increased. Secondary prevention strategies (the diagnosis and treatment of advanced precursor lesions or early stage of pancreatic cancer before it causes significant morbidity) might contribute to the prevention of pancreatic cancer in these patients. Currently, several studies are being performed to assess the feasibility of a pancreatic cancer surveillance program. This introduction provides an overview of these surveillance strategies.

Whom should we offer surveillance to?

The incidence of pancreatic cancer is relatively low with 10-12 new cases per 100.000 persons per year [1-3]. Pancreatic cancer is the tenth leading cancer type for new cancer cases in the United States, but, in contrast, it is the fourth leading cancer type for cancer deaths [4]. This underlines the burden of pancreatic cancer, from a patients' but also from a societal perspective. A non-invasive and reliable surveillance tool for pancreatic cancer is currently lacking. This is an important reason why it is not feasible to offer surveillance to the general population. However, there may be opportunities for secondary prevention by surveillance of selected individuals who are at high risk for the development of pancreatic cancer.

Well-known risk factors for pancreatic cancer are older age and cigarette smoking. Smoking doubles the risk and as many as one in four cases of pancreatic cancer might be attributable to smoking [12, 13]. Heavy alcohol consumption (i.e. 3 or more drinks per day) also increases the risk of pancreatic cancer by approximately 20% [14]. Furthermore, an increased risk was demonstrated for long-standing type-1 and 2 diabetes [15-17], as well as for obesity [18].

A family history of pancreatic cancer is a strong risk factor for developing pancreatic cancer. For decades, case reports have been suggesting that pancreatic cancer aggregates in families and multiple studies have shown inheritance in an autosomal dominant pattern [19-23]. Although most cases of pancreatic cancer are likely to be sporadic, it is estimated that in 5-10% of cases, genetic factors are involved [24, 25]. Several genes have been discovered that are responsible for the familial clustering of pancreatic cancer, which can also cause significant morbidity in other organs. At present, in less than 20% of the familial pancreatic cancers, a known genetic syndrome is identified [24, 25]. With new whole genome sequencing technologies, discovery of additional familial pancreatic cancer genes in the near future is likely.

Thus far, two groups of individuals with a hereditary risk of pancreatic cancer have been identified. First, individuals with a well-defined cancer susceptibility syndrome, of which the gene mutations are listed in Table 1. Germline mutations in the ***BRCA1*** or ***BRCA2*** gene increase the risk of pancreatic cancer, independently from the risk for breast and

ovarian cancer, the predominant cancer types in the Hereditary Breast and Ovarian Cancer (HBOC) susceptibility syndrome. The risk of pancreatic cancer in patients with a ***BRCA2*** mutation is 3-10 fold increased, as compared to the general population [26, 27]. Male ***BRCA2*** mutation carriers are at higher risk for pancreatic cancer than females, and the relative risk for pancreatic cancer increases with age [27]. It is important to realize that the absence of breast cancer in a family with aggregation of pancreatic cancer does not exclude a ***BRCA2*** mutation, since pancreatic cancer can run in ***BRCA2*** mutation-carrying families, without associated breast cancer [28, 29]. ***BRCA1*** mutation carriers have a slightly lower risk of pancreatic cancer than ***BRCA2*** mutation carriers (relative risk 2-4 [30]). More recently, ***PALB2*** gene mutations, a gene that codes for a protein that binds to the Brca2 protein, have also been proven to increase the risk for pancreatic cancer, albeit still unclear to what extent [31-33].

Patients with familial cutaneous malignant melanoma (familial CMM, formerly known as familial atypical multiple mole melanoma (FAMMM)), which is caused by mutations in the ***p16/CDKN2A*** gene, are at an 8 to 45-fold increased risk of developing pancreatic cancer [34, 35], which is independent from their increased risk of developing melanomas. Patients with hereditary chronic pancreatitis are also at high risk to develop pancreatic cancer (60 to 90-fold increased risk [36]). Hereditary pancreatitis is caused by germline mutations in the ***PRSS1*** and ***SPINK1*** genes, and is characterized by recurrent episodes of acute or chronic pancreatitis, starting at a young age.

Table 1. Cancer susceptibility syndromes or inherited disease with a known elevated risk of developing pancreatic cancer

Syndrome	Gene(s)	Risk of pancreatic cancer
Hereditary breast and ovarian cancer (HBOC)	BRCA 1 BRCA 2 PALB2	RR 2-3 RR 3-10 RR unknown
Familial cutaneous malignant melanoma (familial CMM)	CDKN2A (p16)	RR 8-45
Chronic (hereditary) pancreatitis	PRSS1 / SPINK 1	RR 60-90
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	MLH1 / MSH2 / MSH6	RR 9
Peutz-Jeghers syndrome	STK11 / LKB1	RR 75-135
Familial adenomatous polyposis (FAP)	APC	RR 4.5
Li-Fraumeni syndrome	p53	RR 7.5

RR, relative risk; SIR, standardized incidence ratio

At highest risk for developing pancreatic cancer, with a 75 to 135-fold increase, are individuals with the Peutz-Jeghers syndrome [37, 38]. This cancer susceptibility syndrome is caused by mutations in the ***STK11*** or ***LKB1*** genes that also increase the risk for gastrointestinal, lung, ovarian, and breast cancer. Patients with familial adenomatous polyposis (FAP) and

Li-Fraumeni syndrome also have a slightly increased risk of developing pancreatic cancer (4.5 and 7.5-fold, respectively [39, 40]). The risk is comparable to that of patients with Lynch syndrome, caused by mutations in one of the DNA mismatch repair genes, including ***MLH1***, ***MSH2*** and ***MSH6***, and who are at a 9-fold increased risk for developing pancreatic cancer [41].

The second and largest hereditary high-risk group consists of individuals with a strong family history of pancreatic cancer, but in whom no mutation was found in any of the known cancer susceptibility genes. This condition is referred to as familial pancreatic cancer (FPC). Depending on the number of affected relatives, the risk increases dramatically: individuals with one first-degree relative with pancreatic cancer have a 4.5 to 7-fold increased risk; those with two, a 4 to 6-fold increased risk, and those with three or more an up to 32-fold increased risk, as compared to the general population [42, 43]. When at least one family member was diagnosed below the age of 50, the relative risk increases even further (hazard ratio of 1.6 per year of decreased age of the family member) [43].

For FPC families, it is important to realize that at least half of the members are not affected, assuming a dominant inheritance pattern. Unfortunately, because the causative mutation is unknown, it is not possible to test carriership and hence increased risk of developing pancreatic cancer. Furthermore, in FPC families, the phenomenon of genetic anticipation has been observed: compared to sporadic cases, pancreatic cancer seems to occur at an earlier age (mean 72 versus 62, respectively) and within affected families, subsequent generations seem to die at an earlier age, compared to the preceding generations [44].

Besides these high-risk individuals from families in which pancreatic cancer aggregates, individuals with the incidental finding of a pancreatic cyst and suspected intraductal papillary mucinous neoplasm (IPMN) are also at high risk of developing pancreatic cancer [45]. These patients therefore qualify for surveillance too, however, there is a clear recommendation for the surveillance policy for these incidental findings (revised Sendai Consensus Guidelines [46]), as discussed below.

The International Cancer of the Pancreas Screening (CAPS) Consortium provided recommendations concerning screening and surveillance of the pancreas for pancreatic cancer in 2011 [47]. It was recommended that only individuals with an excess risk greater than 10 times that of the general population and who are eligible for surgery should be screened for pancreatic cancer (see Table 2). There was no consensus recommendation about the age when to initiate and end screening. The screening principles of colorectal cancer are mostly used, which implies to initiate surveillance of high-risk individuals from the age of

50 or 10 years earlier than the youngest affected member in the family, whichever occurs first, and end surveillance at the age of 75 [48].

Table 2. Candidates for pancreatic cancer surveillance due to a >10-fold increased risk of developing pancreatic cancer

Individuals with ≥ 2 relatives affected with pancreatic cancer, of which at least one in the first-degree
Individuals with ≥ 2 first-degree relatives affected with pancreatic cancer
Individuals with Peutz-Jeghers syndrome
BRCA2 mutation carriers with at least one first-degree relative affected with pancreatic cancer or ≥ 2 affected family members with pancreatic cancer
PALB2 or CDKN2A mutation carriers and individuals with Lynch syndrome with at least one first-degree relative affected with pancreatic cancer

What do we want to detect during surveillance?

Surveillance of asymptomatic individuals is aimed to detect an early stage of pancreatic cancer or, even more preferable, an advanced precursor lesion. Similar to the adenoma-carcinoma sequence in colorectal cancer, pancreatic cancer evolves through non-invasive precursor lesions. Known precursor lesions for pancreatic cancer are pancreatic intraepithelial neoplasias (PanINs), IPMNs and mucinous cystic neoplasms (MCNs) [49]. These precursor lesions are more common in patients with a strong family history of pancreatic cancer than in patients with sporadic disease, and precursor lesions are of a higher grade in those patients with a strong family history of pancreatic cancer [50]. In sporadic cases, it is estimated that a precursor neoplastic clone will take approximately 11 to 12 years to evolve into a malignant clone and an additional 7 years to develop metastatic subclones [51]. Although the pace of progression of pancreatic cancer in hereditary cases is not known, at least potentially, these findings provide a window of opportunity to perform a timely intervention before an advanced precursor lesion evolves into cancer. Obviously, the premise of this strategy is that these precursor lesions can reliably be identified and stratified according to their risk of malignant transformation (i.e. degree of dysplasia) by a suitable surveillance technique.

The most common precursor lesion of invasive pancreatic cancer are PanINs. PanINs arise in the smaller pancreatic ducts, are microscopic (<5 mm in diameter) and are often multifocal. They are reasonably common, particularly in the elderly (incidence of 0.1 per 100.000 at age 30; incidence of 50 per 100.000 at age 80) [52]. Based on the degree of architectural and nuclear atypia, they are classified into three grades: PanIN-1 (low-grade dysplasia), PanIN-2 (moderate-grade dysplasia) and PanIN-3 (high-grade dysplasia or carcinoma in situ). PanINs are difficult to identify on imaging, however, recent data show that PanIN

lesions are possibly associated with lobular parenchymal atrophy which correlated directly with preoperative endoscopic ultrasound changes of chronic pancreatitis [53].

IPMNs are a less frequent precursor to invasive pancreatic cancer, although they are more frequently recognized with the increasing use of abdominal imaging. De Jong et al. [54] reassessed results of 2803 MRI-scans which were performed as part of a preventive medical examination and the prevalence of pancreatic cysts was found to be 2.4% which increased with age to >10% in those aged above 70. IPMNs are cystic epithelial neoplasms (≥ 5 mm in diameter) that arise from the main pancreatic duct or its side branches and produce mucin. They are divided into three subtypes: those that involve the main duct (main-duct IPMNs), those involving side ducts (branch-duct IPMNs), and those involving both (mixed-, or combined-type IPMNs). IPMNs are also classified into low-, intermediate-, and high-grade dysplasia, based on the degree of atypia. Branch-duct IPMNs have lower malignant potential than main-duct IPMNs; the prevalence of malignancy (in situ and invasive) is much higher in main-duct IPMNs (70%) than in branch-duct IMPNs (25%) [55, 56]. Predictive signs of an invasive carcinoma in an IPMN are involvement of the main pancreatic duct, diffuse or multifocal involvement, the presence of a large mural nodule, the size of the tumor, and obstruction of the common bile duct [57]. Some IPMNs are multifocal and, importantly, up to one-third of IPMNs have an invasive component [58, 59]. The molecular alterations in IPMNs are heterogeneous and include loss of ***SMAD4***, loss of ***STK11*** gene expression, activating mutations in the ***PIK3CA*** gene, and ***KRAS*** gene mutations [60-62].

MCNs are also mucin-producing cystic lesions, but, in contrast to IPMNs, they do not involve the ductal system and have a distinctive ovarian-type stroma on pathological examination. MCNs arise almost exclusively in women and are mostly located in the distal pancreas [63]. MCNs are also classified according to degree of dysplasia, and up to one-third show an invasive component [63]. At DNA level, activating mutations in the ***KRAS2*** gene occur early, and inactivation of ***TP53*** and ***MADH4*** occur in invasive MCNs [64, 65]. Unraveling the molecular pathology of MCNs, however, poses a challenge, partly due to their rare nature.

The International CAPS Consortium defined which findings should be considered a success of surveillance: detection and treatment of early invasive cancer (T1N0M0) at baseline or follow-up, detection and treatment of multifocal PanIN 3 (no consensus was reached concerning the detection and treatment of unifocal PanIN 3) and detection and treatment of IPMN with high-grade dysplasia [66].

Which surveillance modalities should we use?

Biomarkers

Numerous efforts have been undertaken in the last years to identify new markers that are reliable and specific for pancreatic cancer. However, they currently have a limited role in diagnosing pancreatic cancer at an early stage. This is due to the low specificity and sensitivity of the current markers.

The most well-known serum marker for pancreatic cancer is the carbohydrate antigen CA 19-9. It was discovered in 1981 and has since been used for monitoring response to therapy in pancreatic cancer patients. Although CA 19-9 might be useful to detect malignancy in patients with cystic lesions [67, 68] and an increase in CA 19-9 over time may predict malignancy in patients with chronic pancreatitis [69], CA 19-9 is not suitable for screening purposes because of its poor sensitivity (41-86%) and specificity (33-100%) [70, 71]. Other serum markers that have been tested for the detection of pancreatic cancer, including CA 50, CA 72-4, CA 125 and CA 242, proved to be inferior to CA 19-9 [70]. Recent studies show promising results for MIC-1 with a sensitivity for pancreatic cancer of 90% and a specificity of 94% [47]. Other promising markers which are currently being investigated in serum or plasma, include SNAIL, osteropontin, CEACAM 1, ICAM 1, DJ 1, APRIL, HSP 70 and ULBP 2 [5]. Also, panels of biomarkers (more than two biomarkers combined) are being researched with promising first results [71, 72].

Stool markers as a detection tool for pancreatic cancer or its precursor lesions is in its infancy. Data from Kisiel et al. [73] show methylated BMP3 in stool to be a promising detector of pancreatic cancer with a sensitivity of 51% and a specificity of 90%. Combined with KRAS, results are slightly better with a possible increase of sensitivity to 64%. Currently, this group of researchers is conducting investigations in patients enrolled in screening programmes to validate this stool test as a screening tool for pancreatic cancer and its precursor lesions.

Another specimen currently being researched for biomarkers is pancreatic juice. Pancreatic juice has a higher concentration of proteins and DNA released from pancreatic cancer cells than serum or stool. It can be obtained by endoscopic retrograde cholangiopancreaticography (ERCP), or, more preferably, from duodenal collections during endoscopy after secretin-infusion [74]. Different studies have identified potential biomarkers (i.e. PAP-2, REG1α, GNAS and TP53) [74-77], however, further studies are needed to determine the clinical implications of these potential markers.

Imaging modalities

Endoscopic ultrasonography (EUS) is a well-established modality for the detection of small pancreatic neoplasms and it is currently the most promising surveillance tool. EUS yields a detection rate of pancreatic cancer of 94-100% and is accurate in determining the T-stage (82% accuracy), N-stage (64-72% accuracy) and vascular invasion (92-95%) [78-80]. Advantages of EUS are that it can visualize the entire pancreas and that, because of the close approximation of the EUS transducer to the pancreas, detailed images of the pancreas can be produced which surpass those of either computed tomography (CT) or magnetic resonance imaging (MRI)[79]. Another advantage of EUS is that, whenever a pancreatic lesion is detected, a EUS-guided fine needle aspiration (EUS-FNA) can be performed during the same procedure. EUS-FNA is 75-80% sensitive for the diagnosis of pancreatic cancer [78, 81]. Limitations of EUS are that accuracy is highly skills- and experience-dependent and that in case of chronic pancreatitis small suspicious lesions may be difficult to detect.

Spiral computed tomography (CT) is almost always obtained during the diagnostic work-up of a patient with a suspicious pancreatic lesion. However, its resolution is limited for small lesions (<1 cm), even with a multi detector computed tomography (MDCT) in which slice thickness is reduced from 10 to 2-5 millimetres. The sensitivity and specificity of conventional CT is low with 69% and 64% consecutively. MDCT has a higher sensitivity and specificity than the conventional CT, but comparable rates with different imaging modalities (see Table 3) [82-84]. However, the risk of radiation-related cancers makes CT an inferior approach for screening or surveillance.

Sensitivity and specificity of magnetic resonance imaging (MRI) combined with magnetic resonance cholangiopancreatography (MRCP) for the detection of pancreatic cancer is similar to CT (see Table 3) [83, 84]. However, MRI/MRCP is better at characterizing cystic lesions of the pancreas and is better for defining the pancreatic duct and biliary tree, neither does it use radiation. Therefore, MRI/MRCP appears suitable for routine surveillance and is widely used and tested in research surveillance programmes. Limitations of MRI/MRCP are that it is contraindicated in patients with metal parts in their body and in patients with gadolinium-allergy.

Integrated positron emission tomography/computed tomography (PET/CT) has similar sensitivity and specificity to other imaging modalities (see Table 3). Compared to MDCT, it does not provide additional information, except for a better detection of distant metastases [84]. Its usefulness in diagnosing pancreatic carcinomas of diameters <2 cm remains unclear [85]. Major disadvantage of PET/CT is the increase in false negative results when serum blood glucose levels are elevated as seen in diabetes mellitus, which is often associated with pancreatic cancer. Chronic pancreatitis may also result in false-positive PET/CT results.

Another disadvantage is the risk of radiation-related cancers when PET is combined with CT, however, without CT sensitivity drops dramatically.

Given the low sensitivity for the detection of malignant and premalignant lesions and the substantial complication risk, endoscopic retrograde cholangiopancreaticography (ERCP) should not be used for screening purposes.

Recommendations

An ideal screening or surveillance tool should be widely accessible, simple to administer, inexpensive, associated with minimal discomfort and/or morbidity, reproducible, and able to detect the preclinical phase of the disease [86]. EUS and MRI/MRCP are currently regarded as the most promising surveillance tools, since they are relatively widely accessible, have low morbidity rates, and, in particular, are best at revealing early pancreatic cancer and its precursors, since these modalities have the highest sensitivity for small lesions (see Table 3). Canto et al. [82] showed that EUS and MRI are better than CT for the detection of small pancreatic lesions during screening, with good concordance of lesion size, number and location between EUS and MRI/MRCP. The CAPS Consortium therefore recommended that for both initial screening and follow-up surveillance, EUS and MRI/MRCP should be performed [66]. A 12-month interval in the absence of pancreatic abnormalities was suggested but not agreed upon. Patients with a non-suspicious cyst should have an imaging interval of 6-12 months. Patients with a newly detected indeterminate solid lesion or an indeterminate main pancreatic duct stricture should have follow-up every 3 months.

Table 3. Sensitivity and specificity of imaging modalities for detecting pancreatic cancer

Imaging modality	Sensitivity	Specificity	Sensitivity for the detection of lesions <3 cm
EUS	94-100%	100%	93%
Conventional CT	69%	64%	53%
MDCT	76-92%	67%	>60%
MRI/MRCP	82-85%	72-100%	67%
FDG-PET/CT	73-94%	68-94%	Unclear

EUS, endoscopic ultrasonography; CT, computed tomography; MDCT, multidetector row computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; FDG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography

Whom should we offer treatment to?

The key issue is to rightfully identify lesions that have a high risk to progress into a malignancy. Individuals with benign lesions should not receive unwarranted surgery while patients with (pre)malignant lesions should not be withheld curative surgery.

The revised Sendai Consensus Guidelines recommend resection in the following cases: (i) all main-duct IPMNs; (ii) all branch-duct IPMNs with a main pancreatic duct diameter of ≥ 10 mm, with a solid component within the cyst or causing obstructive jaundice; (iii) a branch-duct IPMN with 'worrisome features' (main pancreatic duct diameter of 5-9 mm, cyst size of ≥ 30 mm, thickened or enhancing cyst walls, associated pancreatitis, presence of non-enhancing mural nodule, or an abrupt change in the calibre of the pancreatic duct with distal pancreatic atrophy); (iv) all MCNs [46]. The International Cancer of the Pancreas Screening (CAPS) Consortium agreed that these thresholds for resection should be either the same or lower in subjects with a strong family history of pancreatic cancer. For example, it was agreed upon that surgery should be considered for suspected branch-duct IPMNs from a cyst size of ≥ 20 mm (instead of ≥ 30 mm). For all other pancreatic abnormalities, no evidence-based or consensus policy exists. In these particular instances findings should be discussed in an experienced multidisciplinary pancreatic team to reach a decision for each patient individually while balancing risk versus benefit of surgery versus continued surveillance.

A variety of operations for pancreatic lesions are available, including total pancreatectomy, pancreaticoduodenectomy, distal pancreatectomy and segmental resection of the tumor. In the majority of patients, the choice of surgery will be determined by location and size of the lesion. However, IPMNs might represent, especially in these high-risk patients, a pancreatic 'field defect', i.e. all pancreatic ductal epithelial cells are at risk of dysplastic change [87]. Also, branch-duct IPMNs in the setting of FPC, may indicate the presence of high-grade PanIN lesions elsewhere in the pancreas [88]. Therefore, it has been suggested that a total pancreatectomy should be performed in these patients. However, the risk of malignancy needs to be carefully weighed against the issues that arise in apancreatic patients (endo- and exocrine insufficiency). The CAPS Consortium therefore recommended to start with minimal surgery and that further pancreatectomy should be performed intraoperatively to achieve R0 resection of cancer or PanIN 3 at the margin.

What are the outcomes of surveillance programmes so far?

Over the past decade, multiple centers have initiated surveillance programs for pancreatic cancer, to evaluate the diagnostic yield and ultimately improve survival. Results of these studies are summarized in Table 4. In the 15 studies listed in Table 4, a total of 1085 high-risk individuals underwent annual surveillance of the pancreas. Diagnostic yield differed greatly and ranged from 1 to 67%, mostly due to differences in surveillance modalities, study populations and outcome measures. EUS is used in almost all research protocols and MRI/MRCP and CT are also very commonly used. All studies combined, 94 relevant high-grade dysplastic lesions were diagnosed; an overall diagnostic yield of 9%. Seventy-one of these individuals underwent resection.

Histopathology of the resected pancreatic specimens revealed pancreatic cancer in 15 of the 71 specimens (21%), of which 9 had been detected at the first screening visit and six during follow-up (of which one patient missed the 1-year surveillance visit). Only one of the cancers had arisen from an IPMN. IPMNs were found in 25 of 71 specimens (35%), of which nine were detected at the first screening visit and four during follow-up (three of these had been present at baseline, but showed growth after 1 year). Two IPMNs showed high-grade dysplasia, 6 moderate-grade, and 8 low-grade dysplasia. Serous cystadenomas were identified in 3 of the 71 specimens (4%) and a neuroendocrine tumor was discovered in one (1%). Six of the 1085 individuals (0.6%) already had metastatic disease at diagnosis (two were detected at baseline, two after 1 year, and one after 4 years of surveillance).

Table 4. Overview of results of pancreatic cancer surveillance programs for high-risk individuals

Study	N	High risk individuals	Imaging modalities	Diagnostic yield*, N (%)
Brentnall 1999 [89]	14	FPC	EUS + CT + ERCP	7 (50)
Rulyak 2001# [90]	35	FPC	EUS; ERCP$	12 (34)
Kimmey 2002# [91]	46	FPC	EUS; ERCP$	12 (26)
Canto 2004 [92]	38	FPC, PJS	EUS ; CT$, EUS-FNA$, ERCP$	2 (5)
Canto 2006 [93]	78	FPC, PJS	EUS + CT; EUS-FNA$, ERCP$	8 (10)
Kluijt 2009 [94]	3	CDKN2A	EUS + MRI; CT$	2 (67)
Poley 2009 [95]@	44	FPC, PJS, CDKN2A, HP, BRCA, p53	EUS; CT$, MRI$	10 (23)
Langer 2009 [96]	76	FPC, CDKN2A, BRCA	EUS + MRI; EUS-FNA$	1 (1)
Verna 2010 [97]	51	FPC, PJS, CDKN2A, HP, BRCA, Lynch	EUS and/or MRI; EUS-FNA$, ERCP$	6 (12)
Ludwig 2011 [98]	109	FPC, BRCA	MRI; EUS$, EUS-FNA$	9 (8)
Vasen 2011 [99]	79	CDKN2A	MRI	16 (20)
Scheider 2011¥ [100]	72	FPC, BRCA, PALB2	EUS + MRI	9 (13)
Al-Sukhni 2012 [101]	262	FPC, PJS, CKDN2A, HP, BRCA	MRI; CT$, EUS$, ERCP$	19 (7)
Canto 2012 [82]	216	FPC, PJS, BRCA	EUS + CT + MRI; EUS-FNA$	5-92 (2-43)
Potjer 2012∞ [102]	241	FPC, CDKN2A	MRI; EUS$	15 (6)

* Yield is defined as the detection of (pre)malignant lesions (early invasive cancer T1N0M0, PanIN ≥2 or IPMN)
# Continuation of Brentnall 1999
@ Continuation of Kluijt 2009
$ Test performed only as an additional test for detected abnormalities
¥ Continuation of Langer 2009
∞ Continuation and combination of both data from Langer 2009 and Vasen 2011
FPC, familial pancreatic cancer; PJS, Peutz-Jeghers syndrome; HP, hereditary pancreatitis; EUS, endoscopic ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; ERCP, endoscopic retrograde cholangiopancreaticography; EUS-FNA, endoscopic ultrasonography-guided fine needle aspiration

Bartsch et al. [88] recently published histopathological results of surgical specimens of five patients at risk who underwent pancreatic resection because of patient preference al-

though formal criteria for surgery were not strictly met. Importantly, multifocal moderate to high-grade PanIN lesions were found in all 5 cases independently of the IPMN for which the patient was operated on. If larger series suggest that branch-duct IPMNs, even if they do not yet meet the formal criteria for resection, are an indicator for the presence of multifocal high-grade PanIN lesions, one has to reconsider the indication for pancreatic resection. According to current guidelines, these 5 patients would not have undergone surgery and in that regard their surveillance outcomes could be considered as false-negative.

How should we manage cystic tumors in high-risk individuals?

At present, there is no evidence to suggest that the natural behavior of pancreatic cystic neoplasms in individuals with a hereditary pancreatic cancer risk differs from the general population. Therefore, the revised Sendai criteria for cyst management (see Table 5 [46]) can be applied in this group, but with some modification: the Sendai criteria suggest a longer than 1-year interval for cysts smaller than 2 cm, but in patients with a hereditary risk, annual follow-up is always recommended, according to the CAPS guidelines [66].

In the general population, EUS-guided fine needle aspiration (EUS-FNA) is widely used. Although cyst fluid cytology has a high specificity for malignancy (almost 100%), the sensitivity is low [103]. Cytology, combined with tumor marker analysis (amylase, CEA and CA 19-9) can be helpful in differentiating mucinous from non-mucinous pancreatic cysts [104], but is still non-accurate in predicting malignancy. In high-risk individuals, the role of EUS-FNA is limited, as the pre-test likelihood of malignancy is so high, that clinical decision-making is less dependent on cyst fluid analysis. A lesion with morphological features suspicious for malignancy will be resected, regardless of normal FNA-results. Clearly, EUS-FNA should be reserved for those individuals in whom the results will have a direct impact on the decision to operate.

Every pancreatic cyst, suspect of advanced dysplasia or malignancy, should be resected. Limited resections or focal non-anatomic resections (excision, enucleation) may be considered for MCN or branch-duct IPMN without suspicion of malignancy. Resection should aim to achieve complete removal of the tumor, with negative margins. Per-operative frozen sections can help to achieve negative margins. In case of low-grade or moderate-grade dysplasia on the resection margin, further resection is controversial. However, when positive margins for high-grade dysplasia are present, re-operation and additional resection should be performed.

Table 5. The revised Sendai criteria for cyst management

Finding	Management
Cystic tumors with any of the following high-risk stigmata of malignancy: Obstructive jaundice in a patient with a cystic lesion in the head of the pancreas Enhancing solid component within cyst Main pancreatic duct ≥10 mm in size	Consider surgery, if clinically appropriate.
Cystic tumors with any of the following worrisome features: Clinical: pancreatitis Imaging: cyst ≥3 cm; thickened/enhancing cyst walls; main duct size 5-9 mm; non-enhancing mural nodule; abrupt change in caliber of pancreatic duct with distal pancreatic atrophy AND any of the following features on endoscopic ultrasound: Definite mural nodule Main duct features suspicious for involvement (presence of any one of thickened walls, intraductal mucin or mural nodules) Cytology: suspicious or positive for malignancy	Consider surgery, if clinically appropriate.
Cystic tumors ≥3 cm and/or inconclusive EUS results on mural nodules, main duct features or cytology	Close surveillance, alternating MRI and EUS every 3-6 months (or strongly consider surgery in young, fit patients).
Cystic tumors 2-3 cm	EUS in 3-6 months, then lengthen interval, alternating MRI with EUS (or consider surgery in young, fit patients).
Cystic tumors 1-2 cm	MRI annually during 2 years, then lengthen interval if no change.
Cystic tumors <1 cm	MRI in 2-3 years

MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography

For multifocal side branch IPMNs, the same surgical approach holds as for unifocal disease: a segmental pancreatectomy to remove the IPMNs at highest oncological risk and close monitoring of the remaining lesions. According to the revised Sendai criteria, however, in patients with a strong family history of pancreatic cancer, one should consider a total pancreatectomy, because of the increased prevalence of high-grade dysplasia elsewhere in the pancreas [88].

It is important to realize that, after partial pancreatectomy, the pancreatic remnant is still prone to develop dysplastic lesions. Therefore, continued surveillance should be performed in these patients at least annually, regardless of pathologic findings in the surgical specimen, as is continued surveillance after IPMN resection.

The true challenge in pancreatic cancer surveillance is to adequately identify both cystic (IPMN) and solid (PanIN) pre-neoplastic lesions. This means to avoid resection of early stage lesions (i.e. low or medium grade dysplastic IPMN, PanIN1 or PanIN2 lesions), and to timely resect advanced lesions, before cancer develops.

Where do we stand?

In 2010, Harinck et al. [105] applied the principles of screening for disease, as proposed by Wilson and Jungner [106], to appraise the validity of surveillance of individuals at high risk for developing pancreatic cancer. Principles and updated considerations are listed in Table 6. The majority of principles is met. Cost-effectiveness is unknown and the application of a test that is able to reliably detect relevant high-grade dysplastic lesions is under investigation and development.

The ultimate question is whether screening and surveillance programmes ultimately improve the overall survival rate of individuals at high risk for the development of pancreatic cancer. Based on present studies, it is not possible to draw a definite conclusion about the (potential) merits of surveillance to prevent pancreatic cancer death. To definitely answer this question more research is required with careful long-term follow-up of affected individuals within well-defined research programmes. Pooling of data from various (international) cohorts will be needed to acquire sufficient numbers for meaningful statistical analysis and accurate estimates of risk reduction and survival benefit. There is no doubt that it will take ample time to come up with meaningful answers regarding the potential benefit of screening high risk individuals to prevent pancreatic cancer. In that regard we should not be impatient and remember that it took twenty years to prove that screening for colorectal cancer improves survival.

Table 6. Principles of screening by Wilson and Jungner with considerations regarding surveillance of individuals at high risk for developing pancreatic cancer

Principles	Considerations
1. The condition sought should be an important health problem	Pancreatic cancer is an important health problem because of the dismal survival rates. It remains one of the most fatal human malignancies with a median survival of less than 6 months and a 5-year survival of approximately 6% [2, 4].
2. There should be an accepted treatment for patients with recognized disease	The only curative treatment for pancreatic cancer is surgery and owing to advances in surgical techniques and supportive care, mortality rates are well below 4% in high-volume centres [107].
3. Facilities for diagnosis and treatment should be available	CT, MRI and EUS are widely used and available. However, accuracy of EUS is highly skills- and experience-dependant. Also, complication rates of pancreatic surgery are lower when performed in high-volume centres [107]. Therefore, surveillance for pancreatic cancer should be centred in specialized facilities with an experienced multidisciplinary pancreatic team.
4. There should be a recognized latent or early symptomatic stage	Recognized and well-known precursor lesions of pancreatic cancer are PanIN, IPMN and mucinous cystic neoplasms [49].
5. There should be a suitable test or examination	EUS and MRI/MRCP have high sensitivity for small lesions [78-80, 83, 84]. Nevertheless, the accuracy to detect early lesions in these populations needs to be defined.
6. The test should be acceptable for the population	The majority of participants in surveillance did not experience surveillance by EUS and MRI as psychologically too burdensome, moreover, approximately 90% said that perceived disadvantages of follow-up outweighed perceived disadvantages [108].
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood	In recent years, tremendous strides are made in further understanding the natural history of pancreatic cancer [51]. It is estimated that a precursor neoplastic clone will take approximately 11 to 12 years to evolve into a malignant clone and an additional 7 years to develop metastatic subclones 51. This theoretically provides ample time for early detection.
8. There should be an agreed upon policy whom to treat as a patient	It is agreed upon to offer surgery when main-duct or branch-duct IPMNs show morphological features suspicious of malignancy [66, 105]. For all other pancreatic abnormalities, no evidence-based or consensus policy exists. In these particular instances findings should be discussed in an experienced multidisciplinary pancreatic team to reach a decision for each patient individually.
9. The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole	This is currently not established.
10. Case-finding should be a continuing process and not a 'once and for all' project	A normal single test outcome in high-risk individuals will be no guarantee that pancreatic cancer will not develop in subsequent years. Therefore, a 12-month interval in the absence of pancreatic abnormalities, and a shortened interval in the presence of abnormalities, is recommended [66].

Conclusions

Pancreatic cancer is one of the most fatal human malignancies. Overall, the incidence of pancreatic cancer is low, but a well-defined group of individuals are at high risk of developing pancreatic cancer. In the last decade, surveillance programmes have been initiated in order to detect precursor lesions or early pancreatic cancer in these high-risk individuals. Results are promising, but the true impact and optimal strategy for surveillance remains to be determined. Annual surveillance of individuals with a >10-fold increased risk of pancreatic cancer with EUS and/or MRI/MRCP should only be performed in a research setting in expert centers.

Outline of the thesis

This thesis starts with an overview of what is currently known about surveillance for pancreatic cancer (**chapter 1**). Many aspects of surveillance still remain to be investigated. This thesis assessed a few of these matters. The studies documented in this thesis consist of two major parts. The first part of the thesis (**chapters 2, 3, 4 and 5**) includes 3 studies on the clinical aspects of pancreatic cancer surveillance. The second part or this thesis (**chapters 6 and 7**) includes 2 studies on the psychosocial aspects of participating in surveillance.

The most optimal screening test for pancreatic cancer surveillance is not known. Many research protocols use EUS and MRI. In **chapter 2**, the yield of EUS and MRI for screening for pancreatic cancer was studied in high-risk individuals. We conducted a prospective multicenter comparative prospective blinded study comparing EUS and MRI for the detection of clinically relevant pancreatic lesions at first-time screening. In **chapter 3**, we studied the prevalence and progression of cystic pancreatic lesions in two distinct high-risk groups for developing pancreatic cancer (carriers of a mutation that predisposes to pancreatic cancer and individuals without a known gene mutation but with a strong family history of pancreatic cancer (FPC)), as differences between these two distinct high-risk groups might exist. Features of chronic pancreatitis and their progression were studied in **chapter 4**. These features are frequently detected in asymptomatic individuals participating in pancreatic cancer surveillance, but their significance is still unclear. In **chapter 5**, we describe the unique outcomes of surgery performed in individuals participating in pancreatic cancer surveillance programs worldwide. Few studies have described surgical pathology findings of high-risk individuals who have underwent surgery while participating in surveillance, and most of these studies included only a few cases. We created a worldwide registry to gather data more readily and reliably. We evaluated the diagnostic yield and outcomes of individuals who underwent surgical resection or progressed to invasive cancer.

In the second part of this thesis, psychosocial aspects of participating in pancreatic cancer surveillance were studied. Importantly, when assessing the effectiveness of a surveillance

program, one should also take into account the psychological aspects of repeated participation in such a surveillance program. Therefore, in **chapter 6**, the psychological burden of repeated participation in surveillance was studied by using repetitive annual questionnaires. In **chapter 7**, cancer worries were studied in more detail to study if factors could be found to timely identify individuals 'at risk' for high levels of cancer worries who would likely benefit from psychosocial support.

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PART I

Clinical aspects of surveillance

Chapter 2

A multicenter comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals

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ABSTRACT

Objective

Endoscopic ultrasonography (EUS) and MRI are promising tests to detect precursors and early-stage pancreatic ductal adenocarcinoma (PDAC) in high-risk individuals (HRIs). It is unclear which screening technique is to be preferred. We aimed to compare the efficacy of EUS and MRI in their ability to detect clinically relevant lesions in HRI.

Design

Multicenter prospective study. The results of 139 asymptomatic HRI (>10-fold increased risk) undergoing first-time screening by EUS and MRI are described. Clinically relevant lesions were defined as solid lesions, main duct intraductal papillary mucinous neoplasms and cysts ≥10mm. Results were compared in a blinded, independent fashion.

Results

Two solid lesions (mean size 9mm) and nine cysts ≥10mm (mean size 17mm) were detected in nine HRI (6%). Both solid lesions were detected by EUS only and proved to be a stage I PDAC and a multifocal pancreatic intraepithelial neoplasia 2. Of the nine cysts ≥10 mm, six were detected by both imaging techniques and three were detected by MRI only. The agreement between EUS and MRI for the detection of clinically relevant lesions was 55%. Of these clinically relevant lesions detected by both techniques, there was a good agreement for location and size.

Conclusion

EUS and/or MRI detected clinically relevant pancreatic lesions in 6% of HRI. Both imaging techniques were complementary rather than interchangeable: contrary to EUS, MRI was found to be very sensitive for the detection of cystic lesions of any size, MRI however might have some important limitations with regard to the timely detection of solid lesions.

INTRODUCTION

Despite all efforts in past decades, the prognosis of pancreatic ductal adenocarcinoma (PDAC) is still dismal. With a mean survival of <6 months and a 5-year survival of <5%, PDAC ranks among the top 5 causes of cancer-related deaths in the Western world despite its relatively low incidence [1]. Survival rates are strongly dependent on the stage at which PDAC is detected. Therefore, there is great interest in pancreatic screening to detect PDAC at an earlier and potentially curable stage or, even more preferable, to detect high-grade precursor lesions.

Screening of the general population is not feasible as we currently lack a simple, reliable and inexpensive screening tool. However, evidence is starting to accumulate that screening might be worthwhile when offered to individuals at high risk of developing PDAC [2]. High-risk individuals include mutation carriers of PDAC-prone gene mutations (eg, *CDKN2A*, *BRCA1*, *BRCA 2*, *STK11/LKB1*) and relatives of patients with familial PDAC. The risk of developing PDAC within these well-defined populations of high-risk individuals is estimated to be at least 10-fold increased compared to the general population and exceeds 76-fold in selected cases [2 3]. Previous studies have shown that screening these high-risk individuals leads to the detection of early stage PDAC and premalignant lesions [4-13].

At present, endoscopic ultrasound (EUS) and MRI are considered the most accurate techniques for pancreatic imaging within a screening setting [2 8]. Only one study [8] has prospectively compared the diagnostic yields of EUS and MRI in a blinded fashion. In this study [8], good concordance for lesion size, number and location between EUS and MRI was seen.

We conducted a prospective head-to-head blinded comparison between EUS and MRI for the detection of clinically relevant pancreatic lesions at first time screening in individuals at high risk for developing PDAC.

METHODS

Study design and sites

We conducted a multicenter prospective blinded cohort study. Participating centers were Erasmus MC-University Medical Center Rotterdam, Academic Medical Center Amsterdam, University Medical Center Groningen and the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital.

Objective

A prospective head-to-head blinded comparison between EUS and MRI for the detection of pancreatic lesions at first time screening in individuals at high risk for developing PDAC.

Participants

Data were collected within the framework of our ongoing Familial Pancreatic Cancer Surveillance Study. Eligible for inclusion are asymptomatic individuals with an estimated ≥10-fold increased familial or inherited PDAC-risk compared to the general population (see inclusion criteria below). The minimal age for inclusion is 45 years or 10 years younger than the age of the youngest relative with PDAC, whichever occurred first. For patients with Peutz Jeghers syndrome the minimal age for inclusion is 30 years or 10 years younger than the age of the youngest relative with PDAC, whichever occurred first. Potential candidates are evaluated and recruited by a clinical geneticist to check whether inclusion criteria are fulfilled. This evaluation includes (1) obtaining a detailed personal and family medical history, (2) verification of clinical diagnoses reported by patients and family members by review of medical and pathologic records and revision of histological slides whenever available, and (3) based on the medical information genetic testing for suspected gene mutation(s).

Inclusion criteria

1. Carriers of ***CDKN2A*** gene mutations, regardless of the family history of PDAC [14]
2. Peutz-Jeghers Syndrome patients (diagnosis based on a proven ***LKB1/STK11*** gene mutation [3]
3. Carriers of gene mutations in ***BRCA1***, ***BRCA2***, ***p53***, or Mismatch Repair Gene with a family history of PDAC in at least two family members [15-18]
4. First degree relatives (FDRs) of patients with familial pancreatic cancer (FPC). FPC families were defined as families affected by PDAC in at least (1) two FDRs, (2) three relatives in which the affected cases are FDR or second-degree relatives (SDRs) of each other, or (3) two SDR of whom at least one relative was aged <50 years at the time of diagnosis [8 19]. Eligible for inclusion in our study were all family members with at least one FDR with PDAC.

Exclusion criteria

Individuals with a history of PDAC, age <18, upper GI tract obstruction, severe medical illness (ASA score ≥3), or who were unable to provide informed consent due to mental retardation or language barrier were excluded.

Experimental methods

Screening techniques

Endoscopic ultrasonography

All EUS procedures were carried out by five experienced endosonographers (JWP, PF, MJB, HMvD and JEvH). Both electronic radial (Olympus UC-160 AE, Olympus Europe, Hamburg, Germany with Aloka α 5 ultrasoundprocessor, Zug, Switzerland or Pentax EG-3670 URK, Pentax Medical Europe Headquarters, Hamburg, Germany with Hitachi ultrasoundprocessor, Hitachi Medical Systems Europe, Zug, Switzerland) and curvilinear (Olympus UCT/UCP 160, Olympus Europe, Hamburg Germany with Philips HDI 5000 ultrasoundprocessor, Philips Healthcare Medical Systems, Best, The Netherlands or Aloka α 10 ultrasoundprocessor, Zug, Switzerland) instruments were used according to the personal preference of the endosonographer. Procedures were performed under conscious sedation with midazolam/fentanyl or propofol. Imaging of the pancreas was carried out from the duodenum and stomach and was digitally recorded with lossy compression (Endobase, Olympus, Hamburg). In case a relevant clinical lesion or a lesion of unknown significance was detected, both a case description and video recordings were distributed amongst all participating endosonographists for independent review. The outcome of this independent review was then presented to the local multidisciplinary hepato-pancreato-biliary team consisting of gastroenterologists, surgeons and radiologists for final decision-making regarding further management.

MRI

MRI was performed at a 1.5 or 3.0 Tesla machine (Signa HDxt, Discovery 450 or 750, GE Healthcare, Milwaukee, Wisconsin, USA; Siemens Avanto or Philips). The following sequences were obtained: coronal balanced steady state free precession imaging with 6 mm slices, coronal and axial T2-weighted single-shot fast spin echo series with 6 mm slices, axial respiratory triggered (RT) fat suppressed T2-weighted fast spin echo series with 6 mm slices, 3-D heavily T2-weighted coronal MR cholangio-pancreatography with 1.4 mm slices (with subsequent axial reconstructions) and breath-hold axial diffusion weighted imaging series including apparent diffusion coefficient mapping with 6 mm slices, using three different b-values (b=50, 400, and 800 s/mm^2). The dynamic sequence involved fat suppressed 3-D T1-weighted spoiled gradient-echo series using 2 or 3 mm slices before and after intravenous administration of gadobutrol (Gadovist 1.0 mmol/mL, Bayer Schering Pharma, Berlin, Germany) at a dose of 0.1 mmol/kg body weight using automated infusion with a power injector at a flow rate of 2 mL/s. Series were timed in the arterial, pancreatic and portal phase using bolus tracking. MRIs were scored by three highly experienced radiologists (CYN, NCK and JJH).

Image Interpretation and Reporting

Participating gastroenterologists and radiologists were blinded to the baseline results of either EUS or MRI. Reporting of imaging findings was standardized across EUS and MRI using a Case Record Form. We specifically looked for clinically relevant abnormalities defined as solid lesions of any size and cystic lesions larger than 10 mm, see also below [20]. The imaging diagnosis used for the present analysis was based on the initial description/diagnosis provided by either the attending radiologist or gastroenterologist. Whenever there was a discrepancy between the findings of EUS and MRI with respect to clinically relevant lesions, the EUS video and MR images were reviewed to determine whether the lesion(s) was (were) indeed not detectable by the other technique.

Clinically relevant lesions

In this article, we mainly focus on the detection of clinically relevant lesions. These include all solid lesions suspicious for a malignancy as well as all lesions that fulfil the revised Sendai criteria for surgery or close follow-up [20]: cysts ≥3 cm, cysts with thickened/enhancing cyst walls and/or mural nodules and/or a solid component, main branch intraductal papillary mucinous neoplasms (IPMNs) with main pancreatic duct ≥10 mm in size, and side branch IPMNs with side duct dilations/cysts >10mm.

Surgical outcomes considered 'a success'

Detection and surgical treatment of (1) invasive cancer ≥T1N0M0 with negative margins, (2) multifocal pancreatic intraepithelial neoplasia (PanIN) 3 lesions and (3) high-grade IPMNs were defined as a successful outcome of surveillance [2].

Follow-up policy

The follow-up policy was based on the agreement of an expert panel consisting of experienced endosonographists, surgeons, radiologists and pathologists and was as follows:

1. Annually, when EUS and/or MRI detected no pancreatic abnormalities or cystic lesions <10 mm.
2. Three months in case EUS and/or MRI detected a lesion for which a morphological diagnosis could not be readily made, hereinafter referred to as lesions with unknown clinical significance.
3. Six months in case of a detected cyst or side branch IPMN with a diameter >10mm and <30mm without malignant features (see below).
4. Surgical resection in case of the detection of a solid lesion morphologically suspicious for a malignancy, cystic lesion >30mm, cystic lesions with malignant features (thickened/enhancing cyst walls and/or mural nodules) or main branch IPMN with main pancreatic duct ≥10 mm [20].

Statistical methods

Descriptive statistics were generated to describe patient and lesion characteristics. To compare both imaging test results, a percentage agreement was calculated for the detection and location of lesions, and a Spearman's rho correlation coefficient was calculated for the size of lesions. We considered an agreement of 0.00 as poor, 0.01-0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial and 0.81-1.00 as almost perfect agreement [21]. All analyses were conducted using the Statistical Package for the Social Sciences (V21, SPSS Institute, Chicago, Illinois, USA).

RESULTS

Patient characteristics

At 1 September 2013, a total of 166 high-risk individuals were prospectively included in this study. Twenty-two individuals underwent some form of pancreatic screening prior to inclusion and were therefore excluded from this blinded baseline analysis. Furthermore, five high-risk individuals were excluded from this analysis because they either had underwent only EUS or only MRI (Figure 1). Therefore, a total of 139 individuals from 81 unique families were included in this blinded analysis of whom the baseline characteristics are summarized in Table 1. The mean age at inclusion was 51 years (SD 9.7, range 20-73 years). Sixteen individuals (12%) were current smokers at time of inclusion. Forty individuals (29%) had a medical history affected by cancer; in 24 of these individuals (60%) the cancer type was melanoma. Seventy-one individuals (51%) carried a pancreatic cancer-prone gene mutation, whereas the remaining individuals stemmed from FPC families. No fine needle aspiration was performed and no procedure-related adverse events occurred.

Table 1. Characteristics of asymptomatic high risk individuals who underwent baseline screening with EUS and MRI (n=139)

	Number included, n (%)	Mean age at inclusion, yrs (range)	Male gender, n (%)	Mean number of family members with PDAC (range)	Mean age of youngest family member with PDAC, yrs
Familial pancreatic cancer	68 (49)	53 (32-74)	32 (47)	2.7 (2-5)	53
Familial CMM (CDKN2A)	38 (27)	48 (20-66)	16 (42)	2.5 (0-7)	51
HBOC (BRCA1)	3 (2)	48 (43-57)	1 (33)	2.7 (2-3)	39
HBOC (BRCA2)	20 (14)	52 (39-71)	8 (40)	2.4 (2-3)	52
Peutz-Jeghers syndrome (LKB1)	7 (5)	52 (35-65)	5 (71)	0.2 (0-1)	54
Li-Fraumeni syndrome (p53)	3 (2)	43 (34-54)	1 (33%)	2 (2)	44

EUS, endoscopic ultrasonography; familial CMM, familial cutaneous malignant melanoma; HBOC, hereditary breast and ovarian cancer; PDAC, pancreatic ductal adenocarcinoma

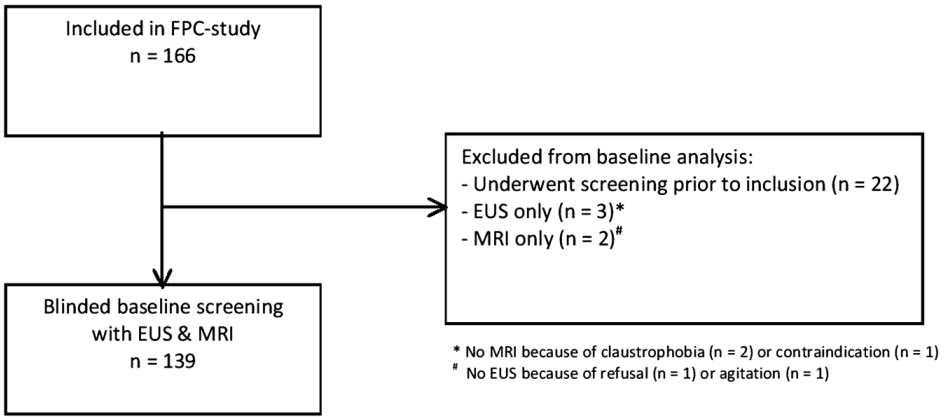

Figure 1. Flow chart. EUS, endoscopic ultrasonography; FPC, familial pancreatic cancer

Diagnostic yield

Clinically relevant lesions, as defined previously, were detected by either EUS and/or MRI in 9 out of 139 high-risk individuals (6%). Two of these nine individuals (22%) had two clinically relevant lesions. Therefore, a total of 11 clinically relevant lesions were identified in nine individuals: two solid lesions and nine cysts larger than 10 mm. Further characteristics are summarized in Table 2. Additionally, eight hypo-echoic areas with unknown clinical relevance were detected by EUS in eight individuals and two lesions with reduced signal intensity on TI-weighted series were detected by MRI in two individuals. Together with the remaining 58 cysts <10 mm (in 34 individuals) and 9 duct ectasias (in 6 individuals), a total of 88 lesions were identified in 46 out of 139 high risk individuals (33%). Characteristics of these lesions are summarized in Table 3. No difference in findings was seen between individuals that carried a PDAC-prone gene mutation and individuals that stemmed from an FPC family.

Of all 11 clinically relevant lesions, 6 (55%) were detected by both modalities. EUS detected a total of eight (73%) and MRI detected a total of nine (82%) clinically relevant lesions. When analysing all lesions (clinically relevant lesions, hypo-echoic areas of unknown clinical relevance, hypo-intense areas of unknown clinical relevance and cysts <10mm), MRI was very sensitive for the detection of cystic lesions (of all 67 cystic lesions, 60 (90%) were detected by MRI and 26 (39%) by EUS) and in specific for subcentimeter cysts (of all 58 cystic lesions <10 mm, 51 (88%) were detected by MRI and 20 (35%) by EUS). In total, there were 38 cysts <10 mm (mean 5 mm, range 2-9 mm) in 23 individuals that were detected by MRI but not by EUS. In 16 of these 23 individuals, the EUS investigation was performed using the radial scope (70%). The majority of these subcentimeter cysts therefore were missed using the radial scope and this could not be attributed to one single center or endosonographer. Conversely, EUS detected two solid lesions that were not detected by

Table 2. Characteristics of all morphologically clinically relevant lesions detected at baseline screening with EUS and MRI (n=11)

Lesion no.	Case no.	Gender, age	Genetic background (no. of affected family members with PDAC)	Tobacco use, alcohol use	Lesion type	Detection test(s)	Size EUS/ size MRI (mm)	Location on EUS / location on MRI	Remark	Outcome
#1	1	Female, 52	CDKN2A (7)	Current smoker (23 pack years), no alcohol use	Solid	EUS (radial)	11 / NA	Body / NA	Also in retrospect, the lesion was not visible on MRI	Distal pancreatectomy with splenectomy, pathology: 12mm T1N0M0 PDAC
#2	2	Male, 56	FPC (2)	No tobacco use, no alcohol use	Solid	EUS (radial)	7 / NA	Head / NA	Due to respiratory motion, the T2 sequence of MRI was of poor quality	Pancreaticoduodenectomy, pathology: multifocal PanIN2
#3	3	Female, 55	FPC (3)	No tobacco use, no alcohol use	Cystic	MRI and EUS (radial)	14 / 17	Head / Head		Unchanged at FU 12 months
#4	4	Female, 62	LKB1 (0)	Past smoker (20 pack years), current alcohol use (2 units per week)	Cystic	MRI and EUS (radial)	6 / 18	Head / Head	Endosonographist mentioned at baseline investigation that lesion would probably be >6 mm because of elongated appearance	Again detected by both EUS (linear) and MRI at FU 12 months, EUS then described it as 20 mm
#5	5	Male, 45	FPC (3)	Past smoker (16 pack years), current alcohol use (1 unit per week)	Cystic	MRI and EUS (radial)	27 / 36	Head / Head	Diagnosed as pseudocyst (history of acute pancreatitis)	Regression of the pseudocyst
#6	6	Male, 49	CDKN2A (2)	Past smoker (17 pack years), current alcohol use (7 units per week)	Cystic	MRI and EUS (linear)	12 / 12	Body / Body		Unchanged at FU 12 months

Table 2. *(continued)* Characteristics of all morphologically clinically relevant lesions detected at baseline screening with EUS and MRI (n=11)

Lesion no.	Case no.	Gender, age	Genetic background (no. of affected family members with PDAC)	Tobacco use, alcohol use	Lesion type	Detection test(s)	Size EUS/ size MRI (mm)	Location on EUS / location on MRI	Remark	Outcome
#7	6	Male, 49	CDKN2A (2)	Past smoker (17 pack years), current alcohol use (7 units per week)	Cystic	MRI and EUS (linear)	12 / 13	Tail / Tail	Same patient as #6	Unchanged at FU 12 months
#8	7	Female, 54	FPC (2)	No tobacco use, no alcohol use	Cystic	MRI and EUS (linear)	5 / 10	Tail / Tail		At FU 12 months measured at 3 mm by linear EUS and 5 mm by MRI
#9	8	Male, 69	FPC (2)	Past smoker (20 pack years), current alcohol use (3 units per week)	Cystic	MRI	NA / 24	NA / Head	Baseline and FU 12 months EUS was performed using a radial scope	At FU 12 months unchanged MRI findings, then also detected by radial EUS (8 mm)
#10	8	Male, 69	FPC (2)	Past smoker (20 pack years), current alcohol use (3 units per week)	Cystic	MRI	NA / 12	NA / Body	Same patients as #9; baseline and FU 12 months EUS was performed using a radial scope	At FU 12 months unchanged MRI findings, then also detected by radial EUS (8 mm)
#11	9	Male, 74	FPC (3)	No tobacco use, current alcohol use (1 unit per week)	Cystic	MRI	NA / 10	NA / Head	MRI described lesion in uncinate process, this area could not be visualized by EUS (radial)	At FU 12 months unchanged MRI findings, again not detected by radial EUS

EUS, endoscopic ultrasonography; FPC, familial pancreatic cancer; FU, follow-up; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma.

Table 3. Characteristics of all detected lesions at baseline screening with EUS and MRI (n=88)

	Total number detected n (%)	Number detected by EUS and MRI n (%)	Number detected by EUS only n (%)	Number detected by MRI only n (%)	Mean size, mm (range)
Solid lesions	2 (2)	-	2 (100)	-	9.0 (7-11)
Cystic lesions					
≥ 10 mm	9 (10)	6 (67)	-	3 (33)	16.9 (10-36)
< 10 mm	58 (66)	13 (22)	7 (12)	38 (66)	4.8 (2-9)
Any size (total)	67 (76)	19 (28)	7 (10)	41 (61)	5.4 (2-36)
Hypo-echoic areas with unknown relevance	8 (9)	-	8 (100)	-	5.1 (2-11)
Hypo-intense areas with unknown relevance	2 (2)	-	-	2 (100)	7.0 (5-9)
Duct ectasias	9 (10)	4 (44)	1 (11)	4 (44)	2.2 (2-3)

EUS, endoscopic ultrasonography.

MRI, also not after re-evaluation of the MRI: (1) a 11 mm solid lesion in the body of the pancreas (Table 2, lesion 1 and Figure 2A) and (2) a 7 mm solid lesion in the head of the pancreas (Table 2, lesion 2 and Figure 2C). For both lesions, resection was performed. The former lesion proved to be a 12 mm T1N0M0 moderately differentiated adenocarcinoma (Figure 2B). Although post-surgical staging suggested a favorable outcome (R0 resection of a small tumour of 12 mm) the patient developed local disease recurrence with liver and peritoneal metastases a few months later and died within 36 months after initial diagnosis. The 7 mm solid lesion in the head of the pancreas proved to be two separate 3 mm lesions very close to each other and was therefore classified as multifocal PanIN2 (Figure 2D). Characteristics of all detected lesions by EUS and MRI are summarized in Table 4.

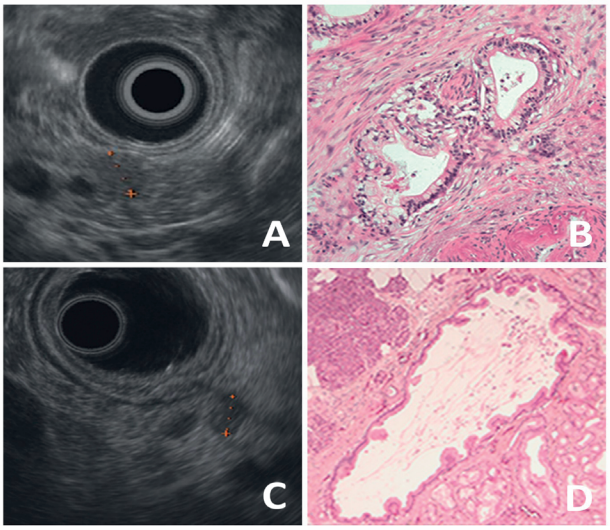

Figure 2.
(A) The still endoscopic ultrasound image of a 11 mm solid lesion of the body of the pancreas.
(B) The histological image after resection of the lesion shown in (A), which proved to be a 12 mm T1N0M0 moderately differentiated ductal adenocarcinoma.
(C) Still endoscopic ultrasound image of a 7 mm solid lesion in the head of the pancreas.
(D) The histological image after resection of the lesion shown in (C), which proved to be two separate 3 mm lesions, within 2 mm distance of each other, classified as multifocal pancreatic intraepithelial neoplasia 2.

Table 4. Characteristics of lesions detected by EUS and by MRI respectively at baseline screening

	n (%)	Mean size of lesions, mm	Location of lesions (n, %)		
			Head	Body	Tail
Detected by EUS	41	6.1	14 (34)	18 (44)	9 (22)
Solid	2 (5)	9.0	1 (50)	1 (50)	-
Cystic					
≥ 10 mm	6 (15)	12.7	3 (50)	1 (17)	2 (33)
< 10 mm	20 (49)	5.2	6 (30)	10 (50)	4 (20)
any size (total)	26 (63)	6.9	9 (35)	11 (42)	6 (23)
Unclear	8 (20)	5.1	2 (25)	4 (50)	2 (25)
Duct ectasia	5 (12)	2.0	2 (40)	2 (40)	1 (20)
Detected by MRI	70	6.1	26 (37)	24 (34)	20 (29)
Solid	-	-	-	-	-
Cystic					
≥ 10 mm	9 (13)	16.9	6 (67)	1 (11)	2 (22)
< 10 mm	51 (73)	4.8	17 (33)	19 (37)	15 (29)
any size (total)	60 (86)	6.6	23 (38)	20 (33)	17 (28)
Unclear	2 (3)	7.0	2 (100)	-	-
Duct ectasia	8 (11)	2.3	1 (13)	4 (50)	3 (38)

EUS, endoscopic ultrasonography.

Both EUS and MRI detected areas of (yet) unknown clinical relevance; these were lesions that were not cystic in nature and without the distinct morphology according to the consensus panel to be classified as a solid lesion or hypoechoic lobule. Table 5 provides a detailed description of these lesions of unknown clinical relevance. None of these cases had a history of (acute) pancreatitis or chronic ethanol overuse; only one was a heavy smoker (>15 cigarettes per day for over 40 years, case no. 5, Table 5). In all cases, except one (case no. 8, in Table 5), follow-up showed these lesions to remain stable or being not detectable anymore. In case no. 8, EUS detected two 5 mm hypo-echoic lesions (lesion #8 and #9 in Table 5). Interval screening at 3 and 6 months showed no morphological changes. However, at follow-up at 12 months, both lesions had a more solid appearance and one of these lesions discretely increased in size (from 5 to 7 mm). Based on these morphological changes, it was decided to resect both lesions. A partial spleen preserving body/tail resection was performed and pathological examination showed multifocal PanIN2 lesions.

A total of 41 out of 139 high-risk individuals (30%) had at least one feature of chronic pancreatitis: lobularity was the most frequently detected feature (19%), as well as hyperechoic pancreatic duct margins (17%) and hyperechoic stranding (15%). Twenty individuals (14%) had three or more features of chronic pancreatitis. No differences in features of chronic pancreatitis were seen between individuals that carried a PDAC-prone gene mutation and individuals that stemmed from a FPC family. Also, no correlation with the presence of cysts, alcohol use or tobacco use was found.

Table 5. Characteristics of lesions/areas of (yet) unknown clinical relevance that were detected at baseline screening (n=10)

Lesion no.	Case no.	Genetic background (no. of affected family members with PDAC)	Lesion	Detection test	Management	Pathology report	Outcome
#1	1	FPC (2)	Unclear lesion 11 mm in body of pancreas	EUS	Interval 3 months	NA	No abnormality detected at FU 3 and 12 months
#2	2	CDKN2A (3)	Unclear lesion 5 mm in head of pancreas	EUS	Interval 6 months	NA	At FU 6 and 12 months characterized as duct ectasia
#3	3	CDKN2A (0)	Unclear lesion 9 mm in head of pancreas	MRI	Standard FU at 12 months	NA	No abnormality detected at FU 12 months
#4	4	CDKN2A (5)	Unclear lesion 5 mm in tail of pancreas	EUS	Interval 3 months	NA	Lesion unchanged at FU 3 and 12 months, characterized as pronounced lobule
#5	5	FPC (3)	Unclear lesion 5 mm in body of pancreas	EUS	Interval 3 months	NA	Lesion unchanged at FU 3 and 12 months
#6	6	CDKN2A (2)	Unclear lesion 2 mm in head of pancreas	EUS	Standard FU at 12 months	NA	Lesion unchanged at FU 12 months
#7	7	BRCA2 (2)	Unclear lesion 5 mm in head of pancreas	MRI	Standard FU at 12 months	NA	No abnormality detected at FU 12 months, lesion characterized as blood vessel
#8	8	FPC (4)	Unclear lesions 5 mm in body of pancreas	EUS	Interval 3 months	Multifocal PanIN2	Lesion unchanged at FU 3 months, at FU 12 months solid component à resection
#9	8	FPC (4)	Unclear lesions 5 mm in tail of pancreas	EUS	Interval 3 months	Multifocal PanIN2	Lesion unchanged at FU 3 months, at FU 12 months solid component à resection
#10	9	FPC (3)	Unclear lesion 3 mm in body of pancreas	EUS	Interval 3 months	NA	Lesion unchanged at FU 3 months, characterized as cyst at FU 12 months

EUS, endoscopic ultrasonography; FPC, familial pancreatic cancer; FU, follow-up; PanIN, pancreatic intraepithelial neoplasia.

Agreement between EUS and MRI at baseline screening (blinded analysis)

The agreement between EUS and MRI for the detection of clinically relevant lesions (n=11) was moderate with a 55% agreement (see Table 6). Not surprisingly, the agreement was only fair for detection of all lesions regardless of size (n=88, agreement 26%). However, there was a perfect agreement between EUS and MRI for location of both clinically relevant lesions (n=6) and all lesions (n=26) (agreement 100%). Also, there was a substantial to almost perfect agreement between EUS and MRI on the size of clinically relevant lesions (Spearman's rho correlation coefficient of 0.638) and the size of all detected lesions (Spearman's rho correlation coefficient of 0.859).

Table 6. Agreement between endoscopic ultrasonography and magnetic resonance imaging for different variables and subsets of pancreatic lesions

	Clinically relevant lesions	Clinically relevant lesions + lesions with unknown relevance	All lesions	
Detection				
Baseline				
Agreement per lesion	55% (n=11)	29% (n=21)	26% (n=88)	Fair to moderate agreement
Agreement per participant	56% (n=9)	28% (n=18)	35% (n=46)	
Follow-up 12 months				
Agreement per lesion	67% (n=12)	50% (n=16)	24% (n=106)	Fair to substantial agreement
Agreement per participant	50% (n=8)	67% (n=9)	35% (n=49)	
Location				
Baseline				
Agreement per lesion	100% (n=6)	100% (n=6)	100% (n=26)	Perfect agreement
Agreement per participant	100% (n=9)	100% (n=18)	100% (n=46)	
Follow-up 12 months				
Agreement per lesion	100% (n=8)	100% (n=8)	100% (n=24)	Perfect agreement
Agreement per participant	100% (n=8)	100% (n=9)	100% (n=48)	
Size				
Baseline				
Spearman's rho per lesion	0.638 (n=6)	0.638 (n=6)	0.859 (n=26)	Substantial to almost perfect agreement
Follow-up 12 months				
Spearman's rho per lesion	0.270 (n=8)	0.518 (n=8)	0.619 (n=24)	Fair to substantial agreement

Follow-up 12 months

A total of 135 out of 139 high-risk individuals underwent repeated surveillance after 12 months; one patient developed metastatic disease (case no. 1 in Table 2) and three patients withdrew from the surveillance programme (one patient had emigrated and two patients provided no reason for withdrawal). At 12 months' follow-up, 12 clinically relevant lesions were detected in 8 individuals (6%). Also, 7 of these 12 lesions were unchanged compared

to baseline screening (lesion #3, 4, 6, 7, 9, 10 and 11, Table 2). Two lesions increased in size: in case no. 6 (Table 2) a cyst in the pancreatic head grew from 5 to 10 mm, and in another case, a 9 mm large cyst in the tail of the pancreas grew to 13 mm, both without secondary signs of malignancy. Three newly developed clinically relevant pancreatic lesions were identified: (1) case no. 6 developed a cyst of 13 mm in the body of the pancreas which was detected by both imaging modalities; (2) case no. 2, who had underwent a pancreaticoduodenectomy, developed a new 10 mm large cyst in the pancreatic tail detected by MRI; and (3) in another case, one new 10 mm large cyst in the body of the pancreas was detected by MRI, all without secondary signs of malignancy.

Agreement between EUS and MRI at follow-up 12 months (unblinded analysis)

The agreement between EUS and MRI for the detection of clinically relevant lesions increased from 55% at baseline screening (blinded results) to 67% agreement at follow-up 12 months (unblinded results).

DISCUSSION

To determine the effectiveness of EUS and MRI in their ability to detect pancreatic lesions in high-risk individuals, we conducted a multicenter prospective study in which we compared baseline results in a blinded fashion. This nationwide, blinded prospective study shows that for detection of pancreatic lesions, in this series both tests were complementary rather than interchangeable. EUS and/or MRI showed a total of 11 morphologically clinically relevant lesions at baseline screening in 6% of participating high-risk individuals.

To date, results of 12 screening studies for pancreatic cancer have been published [4-13 22 23]. Based on these results, EUS and MRI are currently regarded as the most promising screening techniques as they are relatively widely accessible, have low morbidity rates, and, in particular, are superior to any other imaging modality with regard to the detection of small pancreatic lesions. However, data on which of these two imaging techniques is to be preferred for screening purposes are largely lacking since only one of these series was conducted in a blinded fashion [8]. In this study [8], good concordance for lesion size, number and location between EUS and MRI was seen.

In our cohort, however, we found a moderate to fair agreement between EUS and MRI on the detection of both clinically relevant lesions and all pancreatic lesions, but a good to perfect agreement on size and location of detected lesions. The moderate agreement between EUS and MRI on the detection of pancreatic lesions is a reflection of the fact that

only 55% of the clinically relevant lesions (6 of 11) were detected by both EUS and MRI. For baseline imaging, both radiologist and endosonographists were blinded to the results of the competing imaging modality. Since both modalities were performed on the same day as much as possible, the order being dependent on availability and logistics, it was not possible to unblind investigators after the initial investigation. For follow-up investigations after 12 months however, radiologists and endosonographers were aware of the baseline results. The agreement per lesion between both techniques increased from 55% at baseline screening to 67% at follow-up surveillance. The disagreement between EUS and MRI lies mostly in the detection of cysts by EUS, and the detection of solid lesions by MRI. As a result, in this series both techniques were complementary rather than interchangeable.

A possible explanation for the discrepancy in findings between Canto ***et al*** [8] and our study is the use of both the radial and the linear scope for EUS investigations in all individuals in Canto's cohort, whereas only one of both scopes was used in our cohort. Performing an EUS investigation with two different endoscopes likely increases the detection of (subcentimeter) cysts, as the authors state themselves [24]. Also, since the miss rate for pancreatic lesions in high-risk individuals seems lower for linear EUS than for radial EUS [24], the frequent use of the radial scope in our cohort might have negatively influenced our reported concordance between EUS and MRI. Canto's cohort consisted of a slightly different subset of individuals (older mean age, difference in types of underlying gene mutations), however, this should not affect the comparative analysis of EUS and MRI and thus does not explain the discrepancy in findings. Both cohorts were screened in tertiary high-volume centers and by experienced endosonographers and radiologists only.

EUS proved to be particularly sensitive for the detection of small solid lesions. Two solid lesions detected by EUS, including a stage I PDAC, were not detected by MRI. When MRI investigations in both cases were re-evaluated these lesions were indeed not detectable. Our results are in line with the results of previous studies which were conducted in a clinical setting (sporadic cases) that showed EUS has the highest sensitivity for the detection of <20mm pancreatic cancers when compared to other imaging modalities including MRI [25 26].

MRI was particularly sensitive for the detection of (small) cystic lesions. All nine cystic lesions sized ≥10mm were detected by MRI, whereas EUS detected six (66%). There are multiple possible explanations why these lesions were missed by EUS. The 24 mm cyst in the head of the pancreas (Table 2, lesion #9) was composed of multiple microcysts (Figure 3). This composition influences the penetration of the ultrasound waves with the walls of the microcysts reflecting the ultrasound waves causing the lesion not to appear as a cystic lesion on EUS. However, one still would expect the lesion to be discordant compared to the

surrounding pancreatic parenchyma and thus identified as a potential 'lesion'. Indeed, at follow-up 12 months, a different endosonographer detected both lesion #9 and #10 (Table 2, case 8). The location of cyst #11 in the uncinate process (Table 2, case 9), could be the reason why this particular lesion was missed. This part of the pancreas is sometimes more challenging to visualise by EUS. Lastly, in both cases a radial scope was used. Although in this multicenter study the choice of the device was left to the discretion of the attending investigator, most endosonographists prefer a linear device to scan the pancreas.

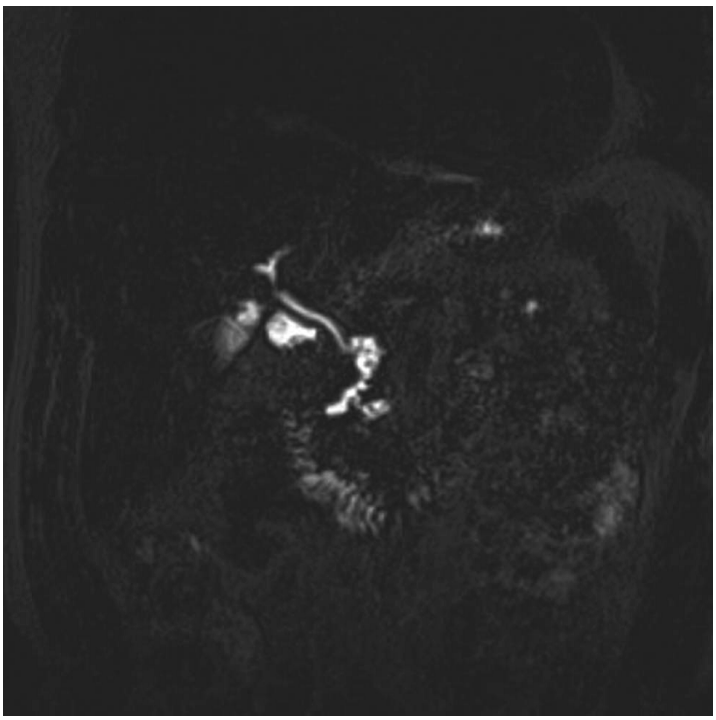

Figure 3. A 24 mm cyst in the head of the pancreas composed of multiple microcysts.

Strengths of our nationwide, multicenter, prospective study are that at baseline screening participating gastroenterologists and radiologists were blinded to the results of either EUS or MRI imaging. Moreover, as a result of the extensive genetic evaluation prior to inclusion in this study and rigid inclusion criteria, our cohort consists of individuals truly at high risk for developing PDAC.

This study is limited by the fact that we lack a definitive diagnosis of the vast majority of cases in whom an abnormality was detected, in particular if detected by one imaging modality only. As a resultant of this baseline screening, only two of all cases (1.4%) were operated. Consequently, it is yet impossible to make a final judgement with regard to

the clinical relevance of the different types and sizes of pancreatic lesions detected. For instance, the importance of the hypo-echoic areas of unknown significance that were detected by EUS but not by MRI remains to be determined. Only longer follow-up will learn whether such findings bare clinical relevance. We are currently conducting a prospective follow-up study to assess the clinical relevance of various lesions detected by EUS and MRI and whether screening high-risk individuals is truly effective in reducing PDAC-related morbidity and mortality.

The true challenge in pancreatic cancer surveillance is to adequately identify pre-neoplastic lesions to avoid resections of early stage lesions (eg, PanIN1 and 2 lesions), but timely resect advanced lesions before cancer has developed. Based on the present study, it is not possible to draw definite conclusions about the (potential) merits of surveillance to prevent pancreatic cancer death. To answer this pivotal question, long-term follow-up studies are required in a large number of individuals. In this regard, it should be recognized that it has taken many years to prove that colon cancer screening saves lives.

In conclusion, for individuals at high risk for developing pancreatic cancer that undergo screening, EUS and MRI are rather complementary than interchangeable imaging modalities in our series. For future screening therefore, we will continue to use both imaging modalities in the follow-up of our cohort of high-risk individuals. We found that, in contrast to EUS, MRI is very sensitive for the detection of even the smallest cysts . EUS seems to be most sensitive for the early detection of (small) solid lesions, which from a clinical perspective is an important property of this imaging modality. Exclusive use of linear devices is likely to improve the overall results of EUS. This should be taken into account at future revisions of recommendations regarding which imaging modality to use for surveillance.

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Chapter 3

Prevalence and progression of cystic pancreatic precursor lesions differ between groups at high risk of developing pancreatic cancer

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ABSTRACT

OBJECTIVES The aim of this study was to compare the prevalence of cystic lesions and their natural behavior in two distinct high-risk groups for developing pancreatic ductal adenocarcinoma (PDAC): (1) carriers of a mutation that predisposes to PDAC and (2) individuals without a known gene mutation but with a family history of PDAC (familial pancreatic cancer (FPC)).

METHODS Pancreatic surveillance by annual magnetic resonance imaging and endoscopic ultrasound was performed in individuals with an estimated lifetime risk of developing PDAC of 10% or greater. Progression of a lesion was defined as growth 4 mm or greater or the development of worrisome features.

RESULTS We included 186 individuals: 98 mutation carriers and 88 FPC individuals (mean follow-up 51 months). Individuals with FPC were significantly more likely than mutation carriers to have a pancreatic cyst 10 mm or greater (16% vs 5%, $P = 0.045$). Pancreatic cysts detected in mutation carriers, however, were significantly more likely to progress than those in FPC individuals (16% vs 2%, $P = 0.050$).

CONCLUSIONS This study provides evidence that the prevalence and growth characteristics of pancreatic cysts differ between distinct high-risk groups: individuals with FPC have a higher prevalence of pancreatic cysts 10 mm or greater, whereas cysts in mutation carriers are more likely to progress. These observations may help to develop more optimally tailored surveillance strategies in specific high-risk populations.

INTRODUCTION

Despite recent improvements in surgical techniques and treatment options for patients with pancreatic ductal adenocarcinoma (PDAC), the prognosis has not significantly improved over the past decades, with a 5-year survival rate still less than 6% [1]. In order to improve prognosis, there is a growing interest toward screening and surveillance so that PDAC or, more preferably, its precursor high-grade dysplastic lesions can be detected at an early stage. However, screening and surveillance of the entire population for PDAC are unlikely to be feasible because of the relatively low incidence (10-12 new cases per 100,000 persons per year [2-4]) and because of the lack of an affordable, reliable and non-invasive surveillance tool. Nevertheless, surveillance of well-defined high-risk groups for PDAC might be feasible and effective.

Two separate groups of individuals are considered to be at an inherited high risk of developing PDAC: (1) mutation carriers of hereditary syndromes that increase the risk of developing PDAC (ie, carriers of mutations in the ***CDKN2A***, ***BRCA1, BRCA2,*** or TP***53*** gene, and individuals with Peutz-Jeghers or Lynch syndrome), and (2) individuals who have no known gene mutation but who have a strong family history of PDAC (familial pancreatic cancer (FPC)). In these high-risk individuals, the risk of developing PDAC can be up to 135-fold higher than in the general population [5-12].

Over the past decade, multiple studies into the effectiveness of surveillance for PDAC in high-risk individuals have been performed [13-23]. These studies have revealed frequent detection of cystic lesions of the pancreas, which are considered possible precursor lesions to PDAC: up to 42% of high-risk individuals have a pancreatic cyst, predominantly intraductal papillary mucinous neoplasm (IPMN)-like lesions, whereas the prevalence of pancreatic cysts in the general population is estimated to be only 0 to 10%, depending on age [24 25]. However, it is still unclear whether the prevalence and growth characteristics of cystic lesions are equal within the 2 distinct high-risk groups.

Only 1 study [23] has compared the prevalence and natural behavior of precursor lesions between risk groups: significantly more individuals in a mixed group – consisting of FPC individuals, ***BRCA2*** and ***PALB2*** mutation carriers – received a diagnosis of a cystic lesion than did carriers of a ***CDKN2A*** mutation. However, the cystic lesions detected in the ***CDKN2A*** mutation carriers were more likely to become malignant.

It is important to gain more insight into the prevalence and natural behavior, including malignant progression, of cystic lesions within the 2 high-risk groups, in order to better adjust surveillance strategies within specific risk populations. This not only tailors the intensity

and burden of surveillance according to the actual risk, but also facilitates a cost-effective utilization of limited and costly health care resources. Therefore, the aim of this study was to study the incidence, prevalence and natural course of cystic pancreatic lesions in these 2 distinct high-risk populations participating in an annual pancreatic cancer surveillance program.

MATERIALS AND METHODS

Study design and sites

We extracted data from an ongoing multicenter prospective cohort study that is being performed in tertiary care medical centers in the Netherlands. Participating centers are the Erasmus MC University Medical Center Rotterdam, Academic Medical Center Amsterdam, University Medical Center Groningen, University Medical Center Utrecht and the Netherlands Cancer Institute. Detailed information on study design and methods was described previously [26]. The study protocol was approved by the Ethical Committee of all participating centers, and the study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to the performance of study procedures.

Participants

Data of all individuals with at least 1 year of follow-up participating in our ongoing Pancreatic Cancer Surveillance study were used. Eligible for inclusion in this study are asymptomatic individuals with an estimated familial or inherited lifetime risk of developing PDAC 10% or greater (see inclusion criteria in Table 1). The minimal age for inclusion between 2008 and 2013 was 45 years of age (or 30 in case of Peutz-Jeghers syndrome) or 10 years younger than the age of the youngest relative with PDAC, whichever age occurred first. Since 2013, the minimal age for inclusion is 50 years or 10 years younger than the age of the youngest relative with PDAC. Surveillance ends at the age of 75 years. Potential candidates are evaluated by a clinical geneticist. A detailed personal and family medical history is taken, cancer diagnoses of relatives are verified by review of medical records, and, if indicated, genetic testing for suspected gene mutation(s) is performed.

Surveillance strategy

Annual surveillance of the pancreas is performed using both endoscopic ultrasonography (EUS), carried out by experienced endosonographers, and magnetic resonance imaging (MRI) with intravenous administration of gadobutrol. Follow-up policy is based on the agreement of an expert panel consisting of endosonographists, surgeons, radiologists and pathologists and is as follows:

Table 1. Inclusion criteria

Carriers of CDKN2A gene mutations, regardless of the family history of PDAC
Peutz-Jeghers syndrome patients (diagnosis based on a proven LKB1/STK11 gene mutation or clinical signs), regardless of the family history of PDAC
Carriers of gene mutations in BRCA1, BRCA2, TP53, or DNA Mismatch Repair genes with a family history of PDAC* in ≥ 2 family members
Individuals with ≥ 2 relatives affected by PDAC* who were related in the first degree to each other, of which at least one was related in the first degree to the eligible individual
Individuals with ≥ 3 relatives affected by PDAC* who were related in the first or second degree to each other, of which at least one was related in the first degree to the eligible individual
Individuals with ≥ 2 relatives affected by PDAC* who were related in the second degree to each other, of which at least one was related in the first degree to the eligible individual and was aged under 50 years at time of diagnosis

PDAC, pancreatic ductal adenocarcinoma

* at least one case of PDAC must have been histologically confirmed

(1) Annual surveillance when either cystic lesions less than 10 mm or no pancreatic abnormalities are detected;
(2) Interval surveillance after 6 months when a novel cystic lesion is detected with a diameter of 10 to 30 mm without worrisome features;
(3) Interval surveillance after 3 months when a lesion of unknown significance is detected for which there is no unanimous opinion among members of the expert panel;
(4) Surgical resection in accordance with the study protocol and international consensus guideline for young, fit patients [27] in case of (1) a solid lesion that is considered suggestive of malignancy, (2) a cystic lesion 30 mm or greater, (3) a cystic lesion with worrisome features (thickened/enhanced cyst wall and/or mural nodules), or (4) a main-branch IPMN (main pancreatic duct ≥ 10 mm).

Cystic lesions

Cystic lesions are defined as hypoechoic lesions detected by EUS and hypointense lesions or hyperintense lesions detected by MRI on T1 or T2 sequences, respectively. An individual was scored as having a pancreatic cyst if either EUS or MRI described such a lesion. Cystic lesions were subdivided into lesions less than 10 mm and lesions 10 mm or greater, and into (1) main-branch IPMNs, (2) side-branch IPMNs (lesions with a clear connection to the pancreatic duct), and (3) other cystic lesions such as lesions without a certain or unclear connection to the pancreatic duct.

Progression of cystic lesions

Prior to our analysis and after elaborate discussion, we defined progression of cystic lesions as either (1) the development of worrisome features (solid component, mural nodule(s), or thickened/enhancing cyst walls) or (2) growth of 4 mm or greater during follow-up.

Statistical analysis

Descriptive statistics were used to illustrate patient and lesion characteristics. Categorical variables were compared using a χ^2 test or, when indicated, a Fisher exact test. Continuous variables were compared using the independent-samples ***t*** test. Adjusting for difference in baseline age was done using multivariate regression analysis. $P \leq 0.05$ was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (version 21; SPSS Institute, Chicago, Ill).

RESULTS

Patient characteristics

On May 6, 2015, 215 high-risk individuals were included in this study, of which 186 individuals (87%) from 105 unique families had had at least 1 year of follow-up. A total of 98 (53%) of these 186 individuals were carrier of a gene mutation, and a total of 88 individuals (47%) had a strong family history of pancreatic cancer, but no gene mutation could be detected in these individuals (FPC individuals). Baseline characteristics of these 2 groups of high-risk individuals as well as for all 215 individuals are summarized in Table 2.

Individuals with FPC were significantly older than mutation carriers (54 vs 49 years of age, $P = 0.002$) and had more relatives who were affected by PDAC (2.6 vs 2.1, $P = 0.004$). Mutation carriers were more likely to have been treated for any type of cancer (44% of mutation carriers vs 9% of FPC individuals, $P < 0.001$), mainly for melanoma. The mean follow-up time was 51 months, 49 months for the mutation carriers and 53 months for the FPC individuals ($P = 0.286$).

Cystic lesions

A total of 100 out of the 186 individuals (54%) had at least 1 pancreatic cystic lesion detected on EUS and/or MRI: 46 (47%) of 98 proven mutation carriers and 54 (61%) of 88 FPC individuals ($P = 0.049$). Nineteen individuals (10%) had a cystic lesion 10 mm or greater, 5 (5%) of 98 mutation carriers and 14 (16%) of 88 FPC individuals ($P = 0.015$). A total of 34 (18%) out of 186 individuals had a cystic lesion with a clear visible connection to the pancreatic duct (presumed side-branch IPMN), 16 mutation carriers (16%) and 18 FPC individuals (21%) ($P = 0.467$). No main-branch IPMNs were detected by EUS and/or MRI. There were no differences between the 2 groups in the mean number of cystic lesions per individual (2 in mutation carriers vs 3 in FPC individuals), in the mean largest size of cystic lesions per individual (7 mm in mutation carriers vs 8 mm in FPC individuals), or in the mean age at first diagnosis of a cystic lesion (55 years of age in mutation carriers vs 56

Table 2. Baseline characteristics of the 2 groups of high-risk individuals

	All individuals included in the study (n=215), n (%)	Individuals with at least one year of follow-up (n=186)		
		Mutation carriers (n=98), n (%)	FPC individuals (n=88), n (%)	P-value (mutation carriers vs FPC)
Sex, male	89 (41%)	44 (45%)	37 (42%)	0.695
Age at inclusion, mean (range, SD), y	52 (19-75, 10.1)	49 (19-75, 9.8)	54 (31-73, 9.6)	**0.002**
Underlying gene mutation				
CDKN2A mutation	64 (30%)	53 (54%)	-	
BRCA1 mutation	4 (2%)	4 (4%)	-	
BRCA2 mutation	33 (15%)	26 (27%)	-	
LKB1/STK11 mutation	12 (6%)	11 (11%)	-	
TP53 mutation	4 (2%)	4 (5%)	-	
Unknown (FPC)	98 (46%)	-	98 (100%)	N/A
No. of relatives with PDAC, mean (range, SD)	2.4 (0-7, 1.3)	2.1 (0-7, 1.6)	2.6 (2-5, 0.8)	**0.004**
Ever treated for cancer	65 (30%)	43 (44%) (30 melanoma, 9 breast cancer, 2 basal cell carcinoma, 1 malignant hamartoma, 1 prostate cancer)	8 (9%) (3 breast cancer, 2 cervix cancer, 1 basal cell carcinoma, 1 esophagus cancer, 1 bladder cancer)	**< 0.001**
Diabetes	6 (3%)	2 (2%)	3 (4%)	0.668
Smoking behavior				
Current smoker	26 (12%)	9 (11%)	10 (13%)	
Past smoker	63 (29%)	33 (39%)	21 (26%)	0.206
Excessive alcohol use (≥ 3 units/day)				
Current excessive user	3 (1%)	1 (1%)	1 (1%)	
Past excessive user	2 (1%)	1 (1%)	0 (0%)	0.619
Underwent surveillance with				
EUS and MRI	201 (94%)	90 (92%)	83 (94%)	
EUS only	3 (1%)	3 (3%)	1 (1%)	
MRI only	11 (5%)	5 (5%)	4 (5%)	0.651
Follow-up, mean (range, SD), mo	44 (0-120, 30.6)	49 (12-120, 26.9)	53 (12-120, 27.3)	0.286

P values (≤ 0.05) in bold font were considered statistically significant.

FPC, familial pancreatic cancer; SD, standard deviation; y, years; mo, months; N/A, not applicable; PDAC, pancreatic ductal adenocarcinoma; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging.

years of age in FPC individuals). Details are also summarized in Table 3. A total of 250 cystic lesions were identified in these 100 individuals.

Table 3. Cystic lesions detected in the 2 groups of high-risk individuals

	Mutation carriers (n=98), n (%)	FPC individuals (n=88), n (%)	P-value (univariate analysis)	P-value (after adjusting for difference in baseline age, multivariate analysis)
Cystic lesions detected				
All cystic lesions	46 (47)	54 (61)	**0.049**	0.207
Cystic lesion < 10 mm	45 (46)	50 (57	0.138	0.434
Cystic lesion ≥ 10 mm	5 (5)	14 (16	**0.015**	**0.045**
Presumed side-branch IPMNs	16 (16)	18 (21	0.467	0.169
Number of cystic lesions per individual, mean (range, SD)	2.2 (1-5, 1.4)	2.7 (1-6, 1.4)	0.088	0.111
Largest size of cystic lesions per individual, mean (range, SD), mm	6.8 (2-24, 4.8)	7.7 (2-36, 6.2)	0.465	0.524
Age at first diagnosis of a cystic lesion, mean (range, SD), y	55 (34-72, 8.6)	56 (38-73, 8.9)	0.507	0.493

P values (≤ 0.05) in bold font were considered statistically significant.
FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm; SD, standard deviation.

Because FPC individuals were statistically significantly older than the mutation carriers at study inclusion, we adjusted for this difference to exclude an age effect. The higher prevalence of cystic lesions of any size in FPC individuals was no longer statistically significant after adjusting for baseline age (***P*** = 0.207). However, cystic lesions 10 mm or greater were still significantly more prevalent in FPC individuals than in proven mutation carriers (16% vs 5%, respectively, ***P*** = 0.045).

Progression of lesions

Of the 100 individuals with a cystic lesion, 85 had had follow-up of their cystic lesion (37 mutation carriers and 48 FPC individuals). In 7 or these 85 individuals (8%), a lesion progressed during follow-up, 6 of which were detected in mutation carriers (6/37 (16%)) versus only 1 in an FPC individual (1/48 (2%); ***P*** = 0.040, ***P*** = 0.050 after adjusting for baseline age). All 7 progressed cases underwent surveillance with both EUS and MRI.

Characteristics of the 7 lesions that progressed during follow-up are shown in Table 4. In 4 individuals, a lesion had grown 4 mm or greater (patients 1, 2, 4 and 7 in Table 4). In 2 individuals, gradual growth of a lesion was observed, which did not yet require a change in management policy (patients 1 and 2). Also in patient 4, in whom we saw slight growth of

Table 4. Characteristics of cystic lesions that progressed during follow-up

Case no.	Genetic background (no. of affected family members with PDAC)	Sex, age at diagnosis of cyst (y)	Lesion	Progression	Management	Pathology report of resected specimen
1	TP53 (2)	F, 40	Multifocal SB-IPMN from baseline (7-mm cyst in the head, and two 4-mm cysts in the tail of the pancreas)	Gradual growth of the lesion in the head in the pancreas from 7 to 17 mm at follow-up 84 mo	Standard follow-up (annually)	N/A
2	BRCA2 (3)	M, 72	4-mm SB-IPMN in the tail of the pancreas from 12-mo follow-up	Gradual growth from 4 to 9 mm at follow-up 48 mo	No longer in follow-up after reaching the study end-age (75 y)	N/A
3	LKB1 (0)	F, 62	SB-IPMN in the head of the pancreas from baseline (18 mm)	Gradual growth from 18 to 24 mm, development of a solid component and hypo-echoic area around the cyst at follow-up 36 mo	Intended pancreatico-duodenectomy, but during surgery distant lymph node metastasis was detected	N/A
4	LKB1 (0)	F, 52	Multifocal SB-IPMN from baseline (4-mm cyst in the head, 5-mm cyst in the body, and 6-mm cyst in the tail of the pancreas)	Growth of the lesions in the head and body of the pancreas from 4 and 5 to 9 mm at follow-up 36 mo	Standard follow-up (annually)	N/A
5	CDNK2A (2)	M, 48	Multifocal SB-IPMN from baseline (5-mm cyst in the head, 12-mm cyst in the body, and 13-mm cyst in the tail of the pancreas)	Growth of the lesion in the tail of the pancreas from 13 to 23 mm and development of a solid component at follow-up 24 mo	Tail resection	12-mm T3 N1 M0 PDAC in pancreatic tail, arising from an IPMN of intestinal and gastric type with focal high-grade dysplasia

Table 4. *(continued)* Characteristics of cystic lesions that progressed during follow-up

Case no.	Genetic background (no. of affected family members with PDAC)	Sex, age at diagnosis of cyst (y)	Lesion	Progression	Management	Pathology report of resected specimen
6	FPC (4)	M, 45	Multifocal SB-IPMN from baseline (3-mm cyst in the head, 5-mm cyst in the body, and 9-mm cyst in the tail of the pancreas)	Development of solid component in the cystic lesions in the body and tail of the pancreas at follow-up 12 mo	Body-tail resection	Diffuse multifocal PanIN2
7	BRCA2 (2)	F, 45	7-mm cystic lesion in the tail of the pancreas from baseline, hard to distinguish between a SB-IPMN or MB-IPMN	Growth of lesion in the tail from 7 to 14 mm at 12-mo follow-up	Tail resection	MB-IPMN of gastric type with moderate-grade dysplasia

No, number; y, years; PDAC, pancreatic ductal adenocarcinoma; F, female; M, male; FPC, familial pancreatic cancer; SB-IPMN, side-branch intraductal papillary mucinous neoplasm; mo, months; N/A, not applicable; PanIN, pancreatic intraepithelial neoplasia; MB-IPMN, main-branch intraductal papillary mucinous neoplasm.

2 cystic lesions, management policy was not yet altered. Only in patient 7, in whom a cystic lesion located in the tail of the pancreas grew from 7 to 14 mm within 1 year of follow-up, a distal pancreatectomy was performed. The pathology of the resected specimen showed a main-branch IPMN with moderate grade dysplasia. In 3 remaining individuals, worrisome features had developed during follow-up (patients 3, 5 and 6 in Table 4). In patient 3, an 18-mm side-branch IPMN was detected in the head of the pancreas at baseline imaging, without the presence of a worrisome feature. At 12-month follow-up, a small nodule (4 mm) had developed within the cyst. At 24-month follow-up, the cyst had shrunk to 9 mm with the solid component grown to 6 mm. Fine-needle aspiration was performed on 2 different occasions 3 months apart and showed no malignant cells. At 36-mont follow-up, the lesion had grown to 24 mm, and a hypoechoic area around the cyst was visualized with EUS. A pancreaticoduodenectomy was performed where a pancreatic cancer was found. The cancer was unfortunately unresectable because of a pathologically proven distant lymph node metastasis during surgery (adenocarcinoma of pancreaticobiliary origin). In patient 5, a morphologically multifocal side-branch IPMN was detected at baseline imaging with unchanged characteristics at 12-month follow-up (no worrisome features). One of the lesions, a tail lesion, had grown from 13 to 23 mm at follow-up at 24 months and also developed a solid component measuring 11 mm in diameter and appearing predominantly hypovascular on contrast-enhanced EUS. A distal pancreatectomy was performed. Pathology of the resected specimen showed a T3 N1 M0 PDAC. Patient 6 developed distinct solid components, 6 and 4 mm, and hypovascular on contrast-enhanced EUS, in 2 separate cystic lesions 1 year after detection of these cysts. A body-tail resection was performed. Pathology of the resected specimen showed multifocal pancreatic intraepithelial neoplasia grade 2 (the lesions were <1 cm on pathological examination, so they did not fulfill the pathological criteria for IPMN). In this cohort, none of the individuals without a progressed lesion underwent resection.

DISCUSSION

In this multicenter prospective study, we compared the incidence, prevalence and the natural behavior of cystic pancreatic lesions in 2 distinct groups of individuals at high risk of developing pancreatic cancer. Individuals with FPC were significantly more likely than mutation carriers to have a pancreatic cyst 10 mm or greater. Pancreatic cysts detected in mutation carriers, however, were more likely to progress during follow-up.

Over the past decade, centers in different countries around the world have initiated surveillance programs for pancreatic cancer aiming to improve the survival of PDAC [13-23]. One way of optimizing the diagnostic yield of such surveillance programs, that is, the detection of

early-stage PDAC or an advanced precursor lesion, is to restrict the program to high-risk individuals with a clear genetic or familial background. Little is known about the possible differences in the incidence, prevalence and natural behavior of the abnormalities detected between these 2 distinct high-risk groups.

To date, there is only 1 report comparing findings between 2 high-risk groups [23]. In this study, 1 high-risk group consisted of ***CDKN2A*** mutation carriers, namely, ***p16-Leiden*** mutation carriers, whereas the other high-risk group was a mixed group consisting of FPC individuals, ***BRCA2*** and ***PALB2*** gene mutation carriers. This study demonstrated a high incidence of cystic lesions in the mixed group (42%), however, with a low incidence of PDAC (0.8%) and progression of cystic lesions in only a small fraction of these individuals during follow-up (8%). In contrast, the ***p16-Leiden*** mutation carriers had a lower incidence of cystic lesions (16%), but a higher incidence of PDAC (7%) and a substantial proportion of their cystic lesions (17%) were seen to grow or develop into malignancy during follow-up.

We report a very high incidence of cystic lesions in both groups: 61% in FPC individuals and 47% in mutation carriers. Such high numbers of cystic lesions in the pancreas have been detected before in multiple studies into the effectiveness of surveillance for PDAC in high-risk individuals [13-23]. In contrast, the estimated prevalence of cystic lesions in the general population is estimated to be only 3% [24 25].

One of the notable differences that we found between the 2 high-risk groups was the prevalence of cystic lesions: one might have expected a lower prevalence of cystic lesions in FPC individuals because we can neither prove nor rule out that these individuals carry a yet unknown gene mutation. Because of the presumed autosomal dominant inheritance pattern observed in FPC families, half of these FPC individuals do not carry a gene mutation and will therefore also not be at increased risk of developing PDAC. This is in contract to our proven mutation carriers in whom an increased risk for PDAC was confirmed by genetic testing.

With regard to the significantly higher prevalence of cystic lesions in the group of FPC individuals, it is tempting to speculate that this might be indicative of a difference in pathophysiology or in molecular subtypes of PDAC [28] between the 2 high-risk groups. An even more important observation is the fact that almost no progression of cystic lesions was seen in FPC individuals (no single PDAC developed within the FPC cohort), whereas lesions in mutation carriers did progress in a significant proportion of individuals (PDAC incidence 2%). In line with current guidelines where progression of a cyst in either size or development of worrisome features is considered a sign of increased malignant potential, this difference in progression between the 2 groups eventually might have important

implications for surveillance strategies, such as applying differential strategies with shorter or longer surveillance intervals between groups.

This multicenter prospective study has several strengths. First, all individuals were counseled by a clinical geneticist prior to inclusion, and DNA testing was performed, if indicated. In FPC individuals, or their affected relatives, no mutation in one of the PDAC-related genes could be identified. This makes the group of FPC individuals truly distinct from the proven mutation carriers. Second, as we have a large group of individuals participating in our annual surveillance, all mutations known to increase the risk of developing PDAC are well represented in our cohort.

A limitation of this study is that for the majority of individuals in whom a cystic lesion was detected a definitive pathological diagnosis is lacking: confirmation was in only 3 resected lesions. Consequently, it is not yet possible to judge the true clinical relevance of the detected lesions. Only longer-term follow-up will provide more insight into the relevance of these lesions. Another limitation of this study is that the age at inclusion differed significantly between the 2 high-risk groups: the FPC individuals were slightly older than the mutation carriers. From literature, it is well known that cystic lesions become more prevalent with increasing age [24]. Nevertheless, when comparing the 2 groups, we adjusted for this difference in baseline age and still found a higher prevalence of cystic lesions 10 mm or greater in FPC individuals.

In conclusion, this observational cohort study provides evidence that the prevalence and growth characteristics of pancreatic cysts differ between distinct groups of individuals at high risk of developing PDAC. Individuals with FPC have a higher prevalence of pancreatic cysts 10 mm or greater, whereas cysts in mutation carriers are more likely to progress. These observations may help to develop more optimally tailored effective and cost-effective surveillance strategies in specific risk populations at high risk of developing PDAC.

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Chapter 4

Evolution of features of chronic pancreatitis during endoscopic ultrasound-based surveillance of individuals at high risk for pancreatic cancer

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ABSTRACT

Background and study aims

During endoscopic ultrasound (EUS)-based pancreatic ductal adenocarcinoma (PDAC)-surveillance in asymptomatic individuals, features of chronic pancreatitis (CP) are often detected. Little is known about the prevalence and progression of these features. The aim of this study was to quantify these features, assess the interobserver agreement, assess possible associated factors, and assess the natural course during 3 years of follow-up.

Patients and methods

Two experienced endosonographers reviewed anonymized sequential EUS videos of participants in PDAC surveillance that were obtained in 2012 and 2015 for features of CP. Descriptives, agreement analyses, univariate and multivariate analyses for possible risk factors, and repeated measures analyses to assess intra-individual changes over time were performed.

Results

A total of 42 EUS videos of 21 participants were reviewed. Any feature of CP was present in 86% (2012) and 81% (2015) of participants, with a mean of 2.5 features per individual. The overall interobserver agreement was almost perfect at 83%. No baseline factors were significantly associated with features of CP. Features did not change over time, except for hyperechoic foci without shadowing, which decreased intra-individually (β=-1.6, P=0.005).

Conclusions

This blinded study shows features of CP to be highly prevalent in individuals at high risk of developing pancreatic cancer. No baseline factors were associated with presence of these features. CP features did not increase intra-individually over a 3-year period. Longer follow-up and pathological examination of pancreatic resection specimens will be essential to learn whether the EUS detection and follow-up of these CP features bear clinical relevance.

INTRODUCTION

Over the past decades, multiple centers have initiated surveillance programs in individuals at high risk of developing pancreatic ductal adenocarcinoma (PDAC) to evaluate the diagnostic yield of such surveillance programs and to ultimately improve the poor survival of PDAC [1-13]. As recommended by the Cancer of the Pancreas Screening (CAPS) Consortium, most surveillance programs entail annual magnetic resonance imaging (MRI) as well as endoscopic ultrasound (EUS) imaging of the pancreas [14]. The diagnostic yield for the detection of high-grade dysplastic precursor lesions (i.e., pancreatic intraductal neoplasia (PanIN)-3 and intraductal papillary mucinous neoplasms (IPMN) with high-grade dysplasia) or early stage PDAC varies between studies with an overall diagnostic yield of about 10% [15].

During EUS-based PDAC surveillance, not only cystic or solid lesions can be detected and features of chronic pancreatitis (CP) also are frequently observed. The clinical significance of these CP features in asymptomatic individuals is still unclear. Research suggests that these features might be related to emerging PanIN and IPMN lesions [16,17], however, little is known about the prevalence and progression of these CP features detected in asymptomatic high-risk individuals. Therefore, the aim of this study was to quantify CP features in individuals participating in our EUS/MRI-based surveillance program by reviewing stored videos of sequential EUS examinations and assess their progress over a 3-year period. We also aimed to study interobserver agreement in our series and assess possible factors associated with presence of these CP features.

PATIENTS/MATERIAL AND METHODS

Our PDAC-surveillance program has been described in detail before [13]. In summary, annual surveillance is performed using EUS and MRI/MRCP in individuals at inherited or familial increased risk of developing PDAC (≥ 10% life-time risk, i.e. all carriers of ***CDKN2A*** gene mutations, all Peutz-Jeghers syndrome patients, carriers of gene mutations in ***BRCA1***, ***BRCA2***, ***TP53*** or mismatch repair genes with a family history of PDAC in at least two family members, and first-degree relatives of patients with familial pancreatic cancer (FPC)). All EUS-investigations are performed under conscious sedation with midazolam/fentanyl by experienced endosonographers using a curvilinear device. Images of the pancreas are obtained from the duodenum and stomach and are digitally recorded in real time with lossy compression.

For this study, all participants in PDAC surveillance at the Erasmus University Medical Center Rotterdam, The Netherlands, were included for whom two EUS videos were available 3 years apart (2012 and 2015). The images were anonymized for patient ID and date of investigation. Two highly experienced endosonographers (MB and JWP, each over 3500 career EUS investigations) individually reassessed the videos for features of CP: parenchymal features [18] were scored in the head, body and tail of the pancreas and ductal features features [18] were scored in the body and tail, using a standardized Case Record Form. The EUS videos were randomly assigned a video number and were thus assessed in an order for which no correlation could be made between patient ID or date of investigation. Both endosonographers scored the videos separately, after which a consensus meeting was held to discuss individuals in whom there was a difference in scored features.

The study was approved by the local Ethical Committee and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to the performance of any study procedures.

Statistical methods

Descriptive statistics were used to describe participants' characteristics. A proportion of agreement was calculated to assess interobserver agreement for each feature of CP. We considered an agreement of 0.00 as poor, 0.01-0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial and 0.81-0.99 as almost perfect agreement and 1.00 as perfect agreement [19].

Data after consensus agreement were analyzed using descriptive statistics and univariate (Chi-square test, Fisher's exact test and independent ***t***-test where appropriate) and multivariate analyses, to detect participants' characteristics associated with a mean of ≥ 4 CP features on EUS assessments. Intra-individual changes over time were assessed with repeated measures, generalized estimated equations for ordinal outcomes, and with mixed-effect models (growth curve models) with maximum likelihood estimator and unstructured covariance matrix for longitudinal data (non-proportional analyses). To correct for multiple testing, we only report ***P***-values of <0.01 as statistically significant. For all statistical analyses, the Statistical Package for the Social Sciences was used (version 23.0, SPSS Institute, Chicago, IL).

RESULTS

Participant characteristics

In 2012, EUS videos of 26 individuals participating in surveillance were stored, of which 21 individuals had a follow-up EUS video available in 2015. These 21 individuals were included in the study, whose characteristics are summarized in Table 1. The mean age of the 21 included individuals was 52, they were predominantly female and there were no excessive alcohol consumers or diabetic participants.

Table 1. Baseline characteristics of included individuals

	All individuals included in the study (n=21) N (%)
Sex, male	4 (19%)
Age at inclusion (years), mean (range, SD)	52 (41-68, 7.1)
Body Mass Index, mean (range, SD)	26 (16-40, 5.4)
Underlying gene mutation	
CDKN2A mutation	6 (29%)
BRCA2 mutation	1 (5%)
LKB1/STK11 mutation	1 (5%)
Unknown (FPC)	13 (62%)
No. of relatives affected by PDAC, mean (range, SD)	2 (0-6, 1.5)
Age of youngest relative affected by PDAC, mean (range, SD)	50 (42-72, 9.1)
Diabetes	0 (0%)
Smoking	
Current smoker	3 (14%)
Past smoker	3 (14%)
Never smoker	15 (71%)
≥ 20 pack years of smoking	3 (14%)
Alcohol consuming	
Current alcohol consumer	16 (76%)
Current excessive alcohol consumer (≥ 3 units/day)	0 (0%)
Past alcohol consumer	1 (5%)
Past excessive alcohol consumer (≥ 3 units/day)	0 (0%)
Never alcohol consumer	4 (19%)
Features of chronic pancreatitis	
Individuals with features present at first available EUS video	18 (86%)
Individuals with features present at second available EUS video	17 (81%)

SD, standard deviation; FPC, familial pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; EUS, endoscopic ultrasound.

Review of the first EUS video showed any feature of chronic pancreatitis in 18 of 21 (86%) participants, and in 17 (81%) at review of the second video, 3 years later (as specified in Table 2). The mean number of CP features per participant was 2.5 (range 0-7). When the

Rosemont classification [18] was applied, only 52% of screened individuals had a normal EUS examination and three (7%) fulfilled criteria for CP.

Table 2. Overview of detected features of chronic pancreatitis

Table 2. *(continued)* Overview of detected features of chronic pancreatitis

Features of chronic pancreatitis	All available EUS videos (n=42)	First available EUS video (2012, n=21)	Second available EUS video (2015, n=21)	Intra-individual change (2012 vs 2015)		
				B	SE	P
Hyperechoic foci with shadowing	3 (7%)	2 (10%)	1 (5%)	-0.74	1.3	0.570
Head	1 (2%)	0 (0%)	1 (5%)	-	-	-
Body	3 (7%)	2 (10%)	1 (5%)	-0.74	1.3	0.570
Tail	2 (5%)	1 (5%)	1 (5%)	-	-	1.000
Hyperechoic foci without shadowing	20 (48%)	14 (67%)	6 (29%)	-1.61	0.6	**0.006**
Head	15 (36%)	12 (57%)	3 (14%)	-2.08	0.7	**0.005**
Body	10 (24%)	8 (38%)	2 (10%)	-1.77	0.8	0.035
Tail	8 (19%)	5 (24%)	3 (14%)	-0.63	0.8	0.414
Lobularity with honeycombing	5 (12%)	3 (14%)	2 (10%)	-0.46	0.8	0.564
Head	1 (2%)	1 (5%)	0 (0%)	-	-	-
Body	5 (12%)	3 (14%)	2 (10%)	-0.46	0.8	0.564
Tail	4 (10%)	2 (10%)	2 (10%)	-	-	1.000
Lobularity without honeycombing	13 (31%)	8 (38%)	5 (24%)	-0.68	0.6	0.251
Head	6 (14%)	4 (19%)	2 (10%)	-0.80	0.8	0.318
Body	7 (17%)	5 (24%)	2 (10%)	-1.09	1.0	0.265
Tail	6 (14%)	2 (10%)	4 (19%)	0.80	0.8	0.318
Cysts	9 (21%)	5 (24%)	4 (19%)	-0.28	0.8	0.705
Head	5 (12%)	2 (10%)	3 (14%)	0.46	1.0	0.656
Body	5 (12%)	3 (14%)	2 (10%)	-0.46	0.8	0.564
Tail	5 (12%)	3 (14%)	2 (10%)	-0.46	0.8	0.564
Stranding	30 (71%)	14 (67%)	16 (76%)	0.47	0.6	0.411
Head	26 (61%)	12 (57%)	14 (67%)	0.41	0.6	0.477
Body	15 (36%)	6 (29%)	9 (43%)	0.63	0.5	0.167
Tail	12 (29%)	5 (24%)	7 (33%)	0.47	0.6	0.411
MPD calculi	1 (2%)	0 (0%)	1 (5%)	-	-	-
Head	1 (2%)	0 (0%)	1 (5%)	-	-	-
Body	0 (0%)	0 (0%)	0 (0%)	-	-	-
Tail	0 (0%)	0 (0%)	0 (0%)	-	-	-
Irregular MPD contour	0 (0%)	0 (0%)	0 (0%)	-	-	-
Body	0 (0%)	0 (0%)	0 (0%)	-	-	-
Tail	0 (0%)	0 (0%)	0 (0%)	-	-	-
Dilated side branches	5 (12%)	2 (10%)	3 (14%)	0.46	0.8	0.564
Body	2 (5%)	1 (5%)	1 (5%)	-	-	1.000
Tail	5 (12%)	2 (10%)	3 (14%)	0.46	0.8	0.564

Table 2. *(continued)* Overview of detected features of chronic pancreatitis

Features of chronic pancreatitis	All available EUS videos (n=42)	First available EUS video (2012, n=21)	Second available EUS video (2015, n=21)	Intra-individual change (2012 vs 2015)		
				B	SE	P
MPD dilatation	1 (2%)	0 (0%)	1 (5%)	-	-	-
Body	0 (0%)	0 (0%)	0 (0%)	-	-	-
Tail	1 (2%)	0 (0%)	1 (5%)	-	-	-
Hyperechoic MPD margin	15 (36%)	8 (38%)	7 (33%)	-0.21	0.6	0.739
Body	14 (33%)	7 (33%)	7 (33%)	-	-	1.000
Tail	8 (19%)	4 (19%)	4 (19%)	-	-	1.000
Mean number of features of CP (range, SD)	2.5 (0-7, 1.5)	2.7 (0-5, 1.4)	2.2 (0-7, 2.2)	-0.43	0.4	0.328
Rosemont classification				0.956	4.4	0.029
Normal	22 (52%)	9 (43%)	13 (62%)			
Indeterminate for CP	13 (31%)	7 (33%)	6 (29%)			
Suggestive of CP	4 (10%)	3 (14%)	1 (5%)			
Consistent with CP	3 (7%)	2 (10%)	1 (5%)			

EUS, endoscopic ultrasound; MPD, main pancreatic duct; SE, standard error.
Bold ***P***-values (< 0.01) were considered statistically significant.

Interobserver agreement

Results of the interobserver agreement analyses are shown in Table 3. On almost all CP features, there was an almost perfect to perfect agreement between the two reviewers. Substantial agreement was reached for hyperechoic foci without shadowing overall (69% agreement), in the head (69% agreement) and in the tail of the pancreas (79% agreement), for lobularity without honeycombing overall (71% agreement) and in the body of the pancreas (71% agreement), and for hyperechoic main pancreatic duct margins overall (71% agreement), and in the body of the pancreas (79% agreement). Only moderate agreement was reached for stranding overall, and in the head of the pancreas (59.5 and 52.4% agreement, respectively). Agreement for all CP features (taken together, all possible CP features in any location of the pancreas, i.e. the 29 items from Table 3) rated as almost perfect at 83%.

Characteristics associated with features of chronic pancreatitis

Table 4 shows the results of univariate and multivariate analyses regarding possible risk factors associated with detection of a mean of ≥ 4 features of CP on EUS. On univariate analysis, 'age of the youngest relative affected by PDAC' was the only identified risk factor (***P*** = 0.002), but it was not sustained after multivariate analysis.

Intra-individual change in detected features of chronic pancreatitis

Results of the repeated measures generalized estimated equations analyses of intra-individual change in CP features are shown in Table 2. Except for hyperechoic foci without

Table 3. Interobserver agreement per feature of chronic pancreatitis

Features of chronic pancreatitis	% agreement between two reviewers	Interpretation of % agreement
Hyperechoic foci with shadowing	85.7	Almost perfect agreement
Head	90.5	Almost perfect agreement
Body	88.1	Almost perfect agreement
Tail	95.2	Almost perfect agreement
Hyperechoic foci without shadowing	69.0	Substantial agreement
Head	69.0	Substantial agreement
Body	85.7	Almost perfect agreement
Tail	78.6	Substantial agreement
Lobularity with honeycombing	88.1	Almost perfect agreement
Head	97.6	Almost perfect agreement
Body	88.1	Almost perfect agreement
Tail	88.1	Almost perfect agreement
Lobularity without honeycombing	71.4	Substantial agreement
Head	83.3	Almost perfect agreement
Body	71.4	Substantial agreement
Tail	83.3	Almost perfect agreement
Cysts	92.9	Almost perfect agreement
Head	95.2	Almost perfect agreement
Body	92.9	Almost perfect agreement
Tail	85.7	Almost perfect agreement
Stranding	59.5	Moderate agreement
Head	52.4	Moderate agreement
Body	83.3	Almost perfect agreement
Tail	85.7	Almost perfect agreement
MPD calculi	100.0	Perfect agreement
Head	100.0	Perfect agreement
Body	100.0	Perfect agreement
Tail	100.0	Perfect agreement
Irregular MPD contour	97.6	Almost perfect agreement
Body	100.0	Perfect agreement
Tail	97.6	Almost perfect agreement
Dilated side branches	83.3	Almost perfect agreement
Body	92.9	Almost perfect agreement
Tail	88.1	Almost perfect agreement
MPD dilatation	97.6	Almost perfect agreement
Body	100.0	Perfect agreement
Tail	97.6	Almost perfect agreement
Hyperechoic MPD margin	71.4	Substantial agreement
Body	78.6	Substantial agreement
Tail	83.3	Almost perfect agreement
Overall (taken together all 29 items above)	83.3	Almost perfect agreement

MPD, main pancreatic duct

Table 4. Univariate and multivariate analyses for factors possibly associated with a mean ≥ 4 features of chronic pancreatitis

Factors	Univariate analyses P-value	Multivariate analysis P-value
Sex	0.546	0.999
Age	0.504	0.625
Body Mass Index	0.646	
Underlying gene mutation	0.890	
Number of relatives affected by PDAC	0.388	0.938
Age of youngest relative affected by PDAC	**0.002**	0.367
Smoking	0.574	
Number of pack years of smoking	0.371	0.677
Alcohol consuming	0.849	
Number of alcohol units per week	0.691	

PDAC, pancreatic ductal adenocarcinoma.
Bold ***P***-values (< 0.05) were considered statistically significant.

shadowing, which decreased intra-individually (overall (β = - 1.6, standard error (SE) 0.6, ***P*** = 0.006) and, more specifically, in the head of the pancreas (β = - 2.1, SE 0.7, ***P*** = 0.005)), CP features did not change in the 3 years. Also, the mean number of CP features and the Rosemont classification did not change. However, there was one individual, a 60-year old woman without a known gene mutation (FPC), in whom in 2012 only 1 feature of CP was present (a cyst in the head of the pancreas), while in 2015, no less than 7 features

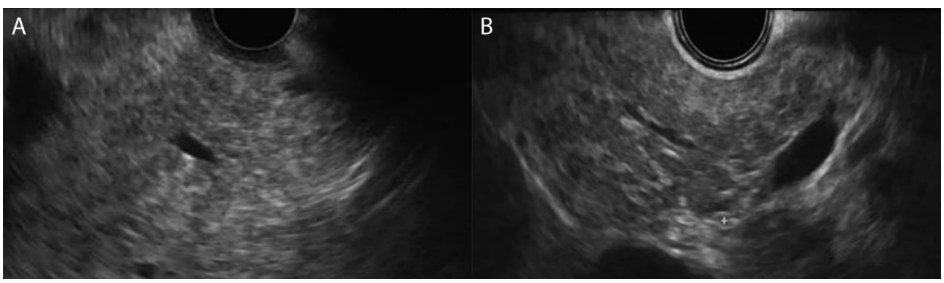

Figure 1. Serial still images of endosonography in a participant with marked progression of features of chronic pancreatitis
A. Still image of the endoscopic ultrasound examination in 2012, showing an unremarkable pancreas.
B. Still image of the endoscopic ultrasound examination in 2015 in the same individual, showing multiple features of chronic pancreatitis (hyperechoic foci, lobularity, stranding, and a hyperechoic main pancreatic duct margin).

were detected (hyperechoic foci with and without shadowing, lobularity with and without honeycombing, stranding, MPD calculi, and hyperechoic MPD margins), see Figure 1. Unfortunately, this patient subsequently died of a trauma.

None of the individuals in this series underwent surgery between 2012 and 2015. One individual, a 50-year old male without a known gene mutation (FPC), had already undergone a distal pancreatectomy in 2011 as a consequence of two EUS-detected solid lesions. Prior to surgery, no features of CP were detected. The resection specimen harbored a panIN-2 lesion and diffuse foci with panIN-1B. The EUS videos of the remnant pancreas from 2012 and 2015 showed hyperechoic foci without shadowing and hyperechoic MPD margins in 2012; in 2015 only stranding was detected.

DISCUSSION

This study shows CP features to be highly prevalent in asymptomatic participants in PDAC surveillance, with a substantial to almost perfect interobserver agreement. Also, these features hardly changed over a 3-year course of follow-up.

Since the start of our PDAC surveillance program in 2008, features of CP were often detected, but their clinical relevance was unclear. They have been associated with incipient or emerging PanIN and IPMN lesions producing lobular parenchymal atrophy resulting in CP-like changes [16,17]. Therefore, to assess the detection of features of CP, interobserver agreement for these features, factors associated with them, and above all, the natural course of these features over time during EUS-based surveillance for PDAC in high-risk individuals, we conducted this blinded single-center study in which we reviewed stored videos from EUS examinations in 2012 and 2015.

In our series, we showed CP features to be highly prevalent: 86% (in 2012) and 81% (in 2015) of individuals had an EUS feature of CP; only 52% of individuals fell into the category 'normal' when the Rosemont classification [18] was applied. This prevalence is much higher than described in a non-high risk cohort. Petrone et al. [20] described 16.8% of asymptomatic individuals undergoing EUS for an indication not related to pancreaticobiliary disease as having at least one ductal or parenchymal abnormality present. As the prevalence of CP features in our cohort at high risk of developing PDAC is this high, the alleged association between (progression) of specific EUS features and presence of PanIN or IPMN lesions bears particular interest.

Assessing the intra-individual change in CP features over our 3-year study period, the number of CP features, individual CP features and Rosemont classification did not change, except for a statistically significant intra-individual decrease in hyperechoic foci without shadowing. However, development and progression of precursor lesions into PDAC may take multiple years [21]. Continued follow-up of these individuals therefore is of pivotal

importance. Eventually, pathological examination of resected pancreatic specimens, not yet available from individuals in the current study, are needed to further clarify the association and clinical relevance of EUS detection of CP features.

Our study revealed no baseline factors significantly associated with the detection of a mean of ≥ 4 CP features. Even factors that are known to be associated with CP, including smoking and alcohol consumption [22,23], were not associated with the detection of CP features in our cohort. Although speculative, this could be related to the underlying pathophysiologic mechanism of chronic pancreatitis-like changes in individuals at high risk of developing pancreatic cancer. Studies suggest that (multifocal) PanIN and IPMN lesions produce obstructive lobular atrophy or the pancreatic parenchyma which is likely the source of the CP-like changes that follow in these patients [16,17].

Our analyses into the interobserver agreement for detection of CP features showed an excellent agreement for most of the CP features. Overall agreement between the two expert endosonographers was 83% and rated as almost perfect. This is somewhat better than described in previous reports where a moderate to substantial agreement was described [24-26] (kappa-values of 0.46, 0.65 and agreement of 68%, respectively). Our high interobserver agreement might be explained by the fact that our two reviewers are highly trained and experienced endosonographers.

To our knowledge, this is the first study to longitudinally assess features of CP in asymptomatic high-risk individuals participating in an EUS-based PDAC surveillance program. Another strength of this study is that two expert endosonographers reviewed the EUS recordings in a blinded fashion using a standardized case record form. However, this study also has some limitations. The number of participants was limited and the follow-up comprised 3 years. None of the participating individuals underwent surgery and we therefore lack definite diagnoses and pathological correlates. Consequently, it is not possible to determine the clinical relevance of the different EUS features of CP that were detected. Also, the Rosement classification was applied in our cohort. This classification was not designed for the purpose of diagnosing CP in asymptomatic patients at high risk of developing PDAC. Although individual criteria can be readily applied and followed in an asymptomatic cohort of high-risk individuals undergoing PDAC surveillance, its clinical relevance in this setting remains unclear. The total score also may be less relevant than development of individual features over time.

CONCLUSION

In conclusion, this blinded study, reviewing EUS videos of asymptomatic high-risk individuals participating in EUS-based PDAC surveillance, showed features of CP to be highly prevalent but stable over a 3-year period, with a high interobserver agreement. We could not associate any baseline factors with detection of these CP features. Longer follow-up and, if available, pathological examination of pancreatic resection specimens will be essential to understanding the relationship between these CP features and development of malignancy, and whether detection of these features bears clinical relevance, for example, in setting the indication for resection or serving as a criterion of influence in determining the screening interval.

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Chapter 5

Detection and outcome of pancreatic cancer surveillance in high-risk individuals: results from the CAPS Consortium

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On behalf of the International CAncer of the Pancreas Screening (CAPS) Consortium

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Submitted

ABSTRACT

Background

Surveillance of high-risk individuals (HRI) for pancreatic ductal adenocarcinoma (PDAC) and its precursors is being evaluated for its ability to improve outcomes. The aim of this study was to determine prevalence and outcomes of PDAC and high-risk neoplastic precursor lesions (HRN) among HRI participating in PDAC-surveillance.

Method

A multicenter retrospective study was conducted through the International CAPS Consortium Registry to identify HRI who had undergone pancreatic resection or progressed to advanced PDAC while under surveillance. HRN were defined as PanIN-3, IPMN with high-grade dysplasia and pancreatic neuroendocrine tumors (PanNET) ≥2 cm.

Results

Seventy-six HRI were included from 11 surveillance programs; 71 had undergone surgery, 5 were diagnosed with inoperable PDAC. Thirty-two of the 71 resected pancreata (45%) had PDAC or HRN: 19 PDAC, 4 MD-IPMN, 4 BD-IPMN, and 5 PanIN-3; the remainder of cases had lower-risk neoplasia. Age ≥65, female gender, carriage of a gene mutation and location of a lesion in the head/uncinate region were associated with HRN or PDAC. The survival between HRI with low-risk neoplastic lesions versus HRI with HRN did not differ; survival was worse among patients with PDAC. There was no surgery-related mortality.

Conclusion

A high proportion of HRI who undergo surgical resection for screening-detected pancreatic lesions have HRN or PDAC. Survival was best and equal for HRI with low-risk neoplastic lesions and HRI with HRN. While all screening programs carry the risk of overtreatment, our results suggest that surveillance of HRI leads to the treatment of an acceptable mix of lesions.

INTRODUCTION

Despite improvements in treatment options for pancreatic ductal adenocarcinoma (PDAC), PDAC remains the third leading cause of cancer deaths in the United States (U.S.) with a 5-year survival of only 8% [1]. By 2030, PDAC is projected to become the second leading cause of cancer-related death in the U.S. [2]. Advances in screening, prevention, and treatment have the potential to change pancreatic cancer incidence and/or death rates, but significant reductions in mortality will require a concerted effort by the research and healthcare communities to effect a substantial change [2]. Inherited susceptibility is thought to be a major factor in PDAC susceptibility, accounting for 5-10% of cases [3]. Surveillance for PDAC and its precursor lesions in asymptomatic high-risk individuals (HRI) is increasingly being performed worldwide [4-15]. HRI can be categorized into two groups: (1) carriers of known PDAC-associated gene mutations (especially carriers of deleterious mutations in ***CKDN2A,BRCA2, BRCA1, ATM, TP53***, a Lynch syndrome gene, ***PRSS1*** or ***STK11***), and (2) first-degree relatives of familial PDAC cases (clustering of at least two first-degree blood relatives with PDAC) [16]. The goals of pancreatic surveillance of HRI have been previously described by the CAncer of the Pancreas Screening (CAPS) Consortium [17]. These include the detection and treatment of early invasive pancreatic cancer (T1N0M0) at baseline or follow-up; detection and treatment of any invasive resectable cancer at baseline screening; detection and treatment of multifocal pancreatic intraepithelial neoplasia 3 (PanIN-3); and the detection and treatment of intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia.

Few studies have described the surgical pathology findings of HRI who have undergone surgery [15 18], and most of these included only a few cases. The CAPS Consortium Registry was created to more rapidly gather information about the experience of surveillance of HRI. In this study, we evaluated the diagnostic yield and outcomes of HRI who underwent surgical resection or progressed to invasive cancer, and examined the characteristics of HRI that developed high-risk neoplastic precursor lesions (HRN) or PDAC.

METHODS

All participating centers in the CAPS Consortium (36 centers from nine countries across the world, see acknowledgements) were requested to enter patient information data for HRI participating in their PDAC-surveillance program who either underwent pancreatic surgery because of the detection of a suspicious pancreatic lesion, or who had progressed to advanced non-resectable malignant disease while participating in PDAC surveillance. Data were retrospectively collected through the use of web-based data collection software (Om-

niComm Electronic Data Capture). Anonymized clinical and demographic information was collected (gender, age, tobacco and alcohol use, diabetes mellitus, history of pancreatitis, body mass index (BMI), known gene mutations, and family history of PDAC), pancreatic imaging modalities that detected the lesions, characteristics of the lesions detected by imaging, timing of detection, therapy, pathology and outcomes after surgery or diagnosis of advanced PDAC. Research protocols of all participating centers have been largely based on the consensus statements of the Cancer of the Pancreas Screening (CAPS) Consortium [17]. However, given the retrospective nature and large time span of this study, it is inevitable that differences between protocols of screening centers worldwide existed, in particular for the period before publication of the CAPS consensus statements in 2013. The index examinations and follow-up examinations were carried out using MRI and/or endoscopic ultrasonography. However, when suspect lesions were detected, other modalities, such as CT imaging, were often used for further characterization and staging. All individuals in this study provided written informed consent for their participation in the respective PDAC-surveillance programs as approved by the Ethical Committees of the participating centers and the study was conducted in accordance with the Declaration of Helsinki.

For analyses, participants with pathologically proven high-risk neoplastic precursor lesions (HRN) or pathologically proven PDAC were compared to participants who underwent surgery but in whom the resection specimen harbored no HRN or PDAC. HRN were defined as multifocal PanIN-3 lesions, main-duct IPMNs, and branch-duct IPMNs with high-grade dysplasia. We also classified unifocal PanIN-3 lesions and PanNETs ≥ 2 cm as HRN [19 20].

Statistical methods

Descriptive statistics were performed to describe patient and lesion characteristics. Univariate analyses (Chi square, or Fisher's exact test where indicated) were performed on possible risk factors associated with PDAC or HRN in the operated cases. All variables with a ***P***-value <0.200 in the univariate analyses were included in the multivariate analysis. A Kaplan-Meier curve was plotted to compare survival for different subgroups, a hazard ratio was calculated using the Log Rank. All analyses were conducted using the Statistical Package for the Social Sciences (V.21, SPSS Institute, Chicago, Illinois, USA).

RESULTS

Patient characteristics

A total of 76 HRI were included from 11 prospective PDAC-surveillance programs in 4 countries (62 HRI from 7 centers in the United States, 9 HRI from 2 centers in The Netherlands, 3 HRI from one center in Israel, and 2 HRI from one center in Italy). In the 11 centers,

approximately 1700 HRI underwent surveillance, of whom approximately 70% were female, mean ages ranged from 53 to 75, and follow-up ranged from one to 10 years. Of the 76 HRI included, 5 were diagnosed with advanced disease during surveillance and 71 underwent surgery for a suspected lesion of whom two were diagnosed with inoperable disease during surgery. Baseline characteristics of all 76 HRI are summarized in Table 1.

Table 1. Baseline characteristics of all high-risk individuals who underwent surgery due to the detection of a suspicious pancreatic lesion or who were diagnosed with advanced pancreatic cancer during participation in PDAC surveillance.

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)
Age at surgery or diagnosis of advanced PDAC, mean (median, range, SD)	60.3 (59.8, 36-80, 11.6)	70.5 (65-80, 6.6)
Gender, male	37 (52.1%)	1 (20.0%)
Race		
White	67 (94.4%)	5 (100.0%)
Black	3 (4.2%)	-
Other	1 (1.4%)	-
Genetic background		
Familial pancreatic cancer (FPC)	52 (73.2%)	4 (80.0%)
CDKN2A (FAMMM syndrome)	7 (9.9%)	-
BRCA2 (HBOC)	3 (4.2%)	-
Peutz-Jeghers syndrome	3 (4.2%)	1 (20.0%)
BRCA1 (HBOC)	1 (1.4%)	-
TP53 (Li Fraumeni syndrome)	1 (1.4%)	-
MMR (Lynch syndrome)	1 (1.4%)	-
APC	1 (1.4%)	-
ATM	1 (1.4%)	-
PRRS1 (hereditary pancreatitis)	1 (1.4%)	-
Number of FDR with PDAC, mean (median, range, SD) Number of SDR with PDAC, mean (median, range, SD)	1.5 (1.0, 0-3, 0.8) 1.1 (1.0, 0-4, 1.0)	1.4 (0-2, 0.9) 0.3 (0-1, 0.6)
Youngest family member affected by PDAC, mean (range, SD)	55.5 (33-77, 10.8)	63.3 (52-68, 7.5)
Body mass index, mean (median, range, SD)	27.3 (26.6, 18-48, 5.1)	26.1 (23-31, 3.7)
Personal history of diabetes	11 (15.5%)	2 (40.0%)
Number of months of diabetes prior to surgery or diagnosis of advanced PDAC, mean (median, range, SD)	36.6 (45.0, 0-63, 23.7)	66 (12-120, 76.4)
Personal history of pancreatitis	9 (12.7%)	1 (20.0%)

Table 1 (continued). Baseline characteristics of all high-risk individuals who underwent surgery due to the detection of a suspicious pancreatic lesion or who were diagnosed with advanced pancreatic cancer during participation in PDAC surveillance.

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)
Smoking behavior		
Never smoker	46 (64.8%)	3 (60.0%)
Former smoker	20 (28.2%)	2 (40.0%)
Current smoker	3 (4.2%)	-
No data	2 (2.8%)	
≥ 10 pack years in total	11 (15.5%)	1 (20.0%)
≥ 20 pack years in total	4 (5.6%)	-
Alcohol consumption		
Never consumer	38 (53.5%)	2 (40.0%)
Former consumer	12 (16.9%)	1 (20.0%)
Current consumer	19 (26.8%)	2 (40.0%)
No data	2 (2.8%)	-
≥ 10 units per week (current or past)	5 (7.0%)	-
≥ 20 units per week (current or past)	2 (2.8%)	-

PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation; FAMMM, familial atypical multiple mole melanoma syndrome; HBOC, hereditary breast and ovarian cancer; MMR, mismatch repair genes; APC, adenomatous polyposis coli; ATM, ataxia telangiectasia mutated; FDR, first degree relative; SDR, second degree relative.

High-risk neoplastic precursor lesions and (advanced) pancreatic ductal adenocarcinoma

HRN or PDAC were present in the pancreatic specimen of 32 (45%) of the 71 HRI who underwent surgery: 5 (7%) cases had PanIN-3 lesions as the highest grade neoplastic lesion, 4 (6%) a branch-duct IPMN with high-grade dysplasia, 4 (6%) a main-duct IPMN, and 19 (27%) PDAC. Pathology findings in all 71 HRI who underwent surgery are summarized in Table 2, as well as lesion characteristics and type of surgery.

In 39 of the HRI (55%) the indication for surgery was detected at the baseline screening evaluation. Of the remaining 32 (45%) cases, the lesion was detected at follow-up investigation. In 9 of these 32 cases a lesion was already present at previous investigations a mean 9 months prior to resection. These lesions originally did not meet resection criteria. However, their appearance changed over time at close follow-up for which resection was then performed. Ten of these 32 cases were a mean 7 months overdue for their recommended screening interval (recommended screening intervals ranged from 3-24 months, depending on the visualization of a lesion and if so, the type of lesion). EUS detected the vast majority of lesions (87.3%). A total of 93 suspicious lesions were detected in the 71 HRI who underwent surgery, of which 44 (47%) were cystic and 33 (36%) solid in appearance. Mean size of these 93 lesions was 14 mm, ranging between 3 to 51 mm.

Table 2. Overview of lesion characteristics, type of surgery and pathology in all high-risk individuals who underwent surgery (n=71) and all high-risk individuals who were diagnosed with advanced disease (n=5) while participating in pancreatic cancer surveillance

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)
Lesion characteristics		
Time point of lesion detection:		
Baseline	39 (54.9%)	2 (40.0%)
Follow-up	32 (45.1%)	3 (60.0%)
Present at previous investigations	9 (12.7%)	1 (20.0%)
Mean months of lesion visualization prior to resection/diagnosis (median, range, SD)	8.7 (5.0, 1-32, 9.5)	41 (41, 41, -)
Case overdue for recommended screening	10 (14.1%)	1 (20.0%)
Mean months overdue for recommended screening (median, range, SD)	6.7 (6.0, 1-12, 3.4)	3 (3, 3,-)
Modality that detected the lesion (≥1 option possible):		
EUS	62 (87.3%)	2 (40.0%)
MRI/MRCP	29 (40.8%)	3 (60.0%)
CT / PET-CT	28 (39.4%)	2 (40.0%)
ERCP	8 (11.3%)	-
Lesion type of lesions that were reason for surgery (n=93)		
Cystic	44 (47.3%)	
Solid	33 (35.5%)	
Hypoechoic	3 (3.3%)	
Dilated pancreatic duct	2 (2.2%)	
Features of chronic pancreatitis	1 (1.1%)	
Other	10 (10.8%)	
Lesion location (n=93)		
Head/uncinate region	35 (37.6%)	
Body	20 (21.5%)	
Tail	29 (31.2%)	
No data	9 (9.7%)	
Lesion size in mm, mean (median, range, SD)		
All lesions (n=93)	14.0 (11.9, 3-51, 8.8)	
Cystic lesions (n=44)	13.6 (11.6, 3-40, 8.0)	
Solid lesions (n=33)	15.5 (13.0, 4-51, 10.0)	
Neoadjuvant therapy	4 (5.6%)	N/A
Type of surgery		
Distal pancreatectomy	36 (50.7%)	
Pancreaticoduodenectomy	18 (25.4%)	
Total pancreatectomy	9 (12.7%)	N/A
Pancreaticoduodenectomy followed by completion pancreatectomy	4 (5.6%)	
Central pancreatectomy	2 (2.8%)	
Diagnosis of non-resectable disease during surgery	2 (2.8%)	

Table 2 (continued). Overview of lesion characteristics, type of surgery and pathology in all high-risk individuals who underwent surgery (n=71) and all high-risk individuals who were diagnosed with advanced disease (n=5) while participating in pancreatic cancer surveillance

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)
Complications of surgery (≥1 option possible)		
None	37 (52.1%)	
Infectious complications	10 (14.1%)	
Delayed gastric emptying	6 (8.5%)	
Pancreatic fistula	4 (5.6%)	N/A
Bile leak	2 (2.8%)	
Peri-pancreatic fluid collection	1 (1.4%)	
Other	6 (8.5%)	
No data	7 (9.9%)	
Pathology (≥1 could be present)		
PDAC	19 (26.8%)	5 (100.0%)
Main-duct IPMN with high-grade dysplasia	1 (1.4%)	-
Main-duct IPMN with moderate-grade dysplasia	4 (5.6%)	-
Main-duct IPMN with low-grade dysplasia	1 (1.4%)	-
Mixed-duct IPMN with high-grade dysplasia	1 (1.4%)	-
Mixed-duct IPMN with moderate-grade dysplasia	-	-
Mixed-duct IPMN with low-grade dysplasia	-	-
Branch-duct IPMN with high-grade dysplasia	5 (7.0%)	-
Branch-duct IPMN with moderate-grade dysplasia	9 (12.7%)	-
Branch-duct IPMN with low-grade dysplasia	16 (22.5%)	-
PanIN-3, multifocal	3 (4.2%)	-
PanIN-3, unifocal	3 (4.2%)	-
PanIN-2, multifocal	35 (49.3%)	-
PanIN-2, unifocal	10 (14.1%)	-
PanIN-1, multifocal	32 (45.1%)	-
PanIN-1, unifocal	4 (5.6%)	-
Pancreatic neuroendocrine tumor ≥ 2 cm	-	-
Pancreatic neuroendocrine tumor < 2 cm	8 (11.3%)	-
Incipient IPMN	5 (7.0%)	-
Serous cystadenoma	2 (2.8%)	-
Vascular malformation	1 (1.4%)	

Table 2 (continued). Overview of lesion characteristics, type of surgery and pathology in all high-risk individuals who underwent surgery (n=71) and all high-risk individuals who were diagnosed with advanced disease (n=5) while participating in pancreatic cancer surveillance

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)
Highest grade of neoplastic lesion per HRI		
PDAC	19 (26.8%)	5 (100%)
Stage I/II PDAC	16 (22.5%)	0 (0%)
Stage III/IV PDAC	3 (4.2%)	5 (100%)
Main-duct IPMN with high-grade dysplasia	1 (1.4%)	-
Main-duct IPMN with moderate-grade dysplasia	2 (2.8%)	-
Main-duct IPMN with low-grade dysplasia	1 (1.4%)	-
Branch-duct IPMN with high-grade dysplasia	4 (5.6%)	-
Branch-duct IPMN with moderate-grade dysplasia	7 (9.9%)	-
Branch-duct IPMN with low-grade dysplasia	9 (12.7%)	-
PanIN-3, multifocal	3 (4.2%)	-
PanIN-3, unifocal	2 (2.8%)	-
PanIN-2, multifocal	9 (12.7%)	-
PanIN-2, unifocal	7 (9.9%)	-
PanIN-1, multifocal	1 (1.4%)	-
PanIN-1, unifocal	1 (1.4%)	-
Pancreatic neuroendocrine tumor < 2 cm	3 (4.2%)	-
Serous cystadenoma	2 (2.8%)	-

PDAC, pancreatic ductal adenocarcinoma; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; IPMN, intraductal papillary mucinous neoplasm; PanIN, pancreatic intraepithelial neoplasia; N/A, not applicable.

Distal pancreatectomy was performed in 36 cases (51%) and a pancreaticoduodenectomy in 18 (25%) cases. Thirty-four HRI (48%) had complications of surgery. The most common complications were infections (in 14% of cases), delayed gastric emptying (in 9% of cases) and pancreatic fistula (in 6% of cases). There were no surveillance or surgery-related deaths.

Of the five cases diagnosed with advanced disease during surveillance, 3 (60%) were diagnosed at a follow-up visit, the other two were detected at baseline evaluation; one of these cases was 3 months overdue for recommended screening (surveillance was performed at 9 months after the previous surveillance, while a 6-month interval was recommended).

Outcomes

The outcomes of both risk groups are summarized in Table 3. Of all 76 HRI who were included in this study, 61 (80%) are still alive, a mean 52 months after surgery or diagnosis of advanced PDAC. Fifty-nine of 71 HRI (83%) who underwent surgery are still alive after

surgery (a mean 54 months); 12 HRI died, of which 8 were PDAC-related. Two of the 5 cases with advanced PDAC are still alive (mean 10 months after diagnosis), three cases died a mean 11 months after diagnosis. Survival was significantly poorer for individuals with advanced PDAC as compared to the individuals who underwent surgery (survival 40% vs 83%, ***P***=0.05; mean 10 vs 54 months, ***P*** <0.001). Only 2 out of 71 HRI (3%) who underwent surgery died within a year (all-cause 1-year mortality), as compared to 2 out of 5 (40%) HRI with advanced PDAC; 52% survived more than 3 years after surgery.

Table 3. Outcomes in all high-risk individuals who underwent surgery (n=71) and all high-risk individuals who were diagnosed with advanced disease (n=5) while participating in pancreatic cancer surveillance

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)	P-value
Follow-up time in mean months (median, range, SD)	51.6 (42.0, 0-168, 45.1)	8.2 (3.0, 3-28, 11.1)	< 0.001
Survival			
Alive	59 (83.1%)	2 (40.0%)	**0.050**
Mean months after surgery/diagnosis (median, range, SD)	54.3 (44.0, 0-168, 45.9)	9.5 (3.5, 3-28, 12.3)	**< 0.001**
Long-term survival (≥ 3 years)	37 (52.1%)	0	
Mortality			
Died	12 (16.9%)	3 (60.0%)	**0.050**
Mean months after surgery/diagnosis (median, range, SD)	54.3 (28.5, 5-164, 56.0)	11.3 (3.0, 3-28, 14.4)	0.221
Short-term mortality (≤ 1 year)	2 (2.8%)	2 (40.0%)	0.154
PDAC-related	8 (11.3%)	3 (60.0%)	0.506
Non-PDAC-related	2 (2.8%)	0	
Unknown cause of death	2 (2.8%)	0	

PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation
Bold ***P***-values were considered statistically significant

Risk factors

Univariate analyses for factors associated with HRN or PDAC in the resection specimen (see Table 4) included age ≥ 65 at the time of surgery (OR 4.1, ***P*** = 0.007) and female gender (OR 3.8, ***P*** = 0.007). In the multivariate analysis, four factors were significantly associated with the presence of HRN or PDAC in the pancreatic resection specimen: age ≥ 65 at the time of surgery (OR 7.5, ***P*** = 0.010), female gender (OR 5.8, ***P*** = 0.017), carriage of a deleterious mutation in a known pancreatic cancer susceptibility gene (OR 4.9, ***P*** = 0.040) and location of a lesion in the head/uncinate region of the pancreas (OR 4.2, ***P*** = 0.041).

We also analyzed the variable 'surgery after 2011' (n=23), to analyze if surgery in more recent years yielded more HRN or PDAC in the resection specimens as compared to prior years when surveillance was just being implemented ('the learning curve'). There was a trend towards more HRN or PDAC in recent years, however, this difference was not statistically significant (OR 1.5, ***P*** = 0.448).

Survival analysis

The pancreatic neoplasia grade was significantly associated with overall survival in HRI. Figure 1 shows the Kaplan-Meier curve for different pathologic subgroups. HRI with no or low-risk neoplastic lesions (group A, N=39) and HRI with HRN (group B, N=13) had the best survival, followed by HRI with stage I or II PDAC (group C, N=16), and HRI with stage III or IV PDAC (group D, N=8). The hazard ratio for group B compared to group A was 4.5 (***P*** = 0.163), for group C 13.1 (***P*** = <0.001) and for group D 25.3 (***P*** = <0.001).

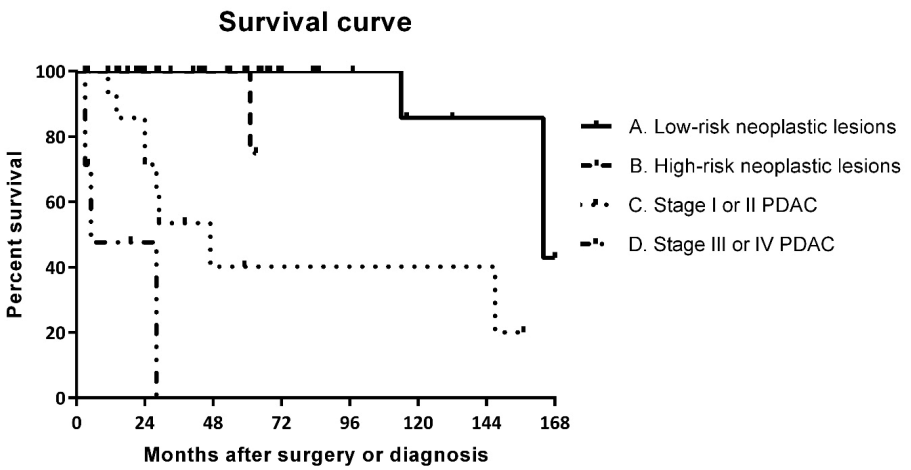

Figure 1. Kaplan-Meier survival curve per subgroup

A. Low-risk neoplastic lesions including pancreatic neuroendocrine tumors (PanNETs) <2 cm (n=39)
B. High-risk neoplastic lesions including all main-duct intraductal papillary mucinous neoplasms (IPMNs), branch-duct IPMNs with high-grade dysplasia and PanIN-3 lesions (n=13)
C. Stage I and II PDACs (n=16)
D. Stage III and IV PDACs (n=8)

DISCUSSION

In this multicenter international retrospective study, high-risk neoplastic lesions or PDAC were present in 45% of the HRI that underwent surgery while participating in PDAC-surveillance. Survival between HRI with no or low-risk neoplastic lesions versus HRI with

HRN did not differ significantly. However, PDAC had a significantly higher overall mortality and poorer survival as compared to HRI with no or low-risk neoplastic lesions.

As surveillance has the potential to improve the poor survival of PDAC, it is increasingly being performed worldwide and already a sizeable number of HRI are being screened and surveilled. In 2010, the CAPS Consortium was formed to help organize global pancreatic surveillance. By pooling data from all participating centers into a worldwide registry, important research questions pertaining to pancreatic surveillance can be assessed much more readily and reliably. In a step-by-step approach of gathering worldwide data, we now report the pooled data of HRI for whom surveillance led to the detection of advanced disease or the detection of a lesion for which pancreatic surgery was performed.

Goals of surveillance previously described by the CAPS Consortium [17] were early invasive cancers (T1N0M0), PanIN-3, MD-IPMNs and BD-IPMNs with high-grade dysplasia. We also defined PanNETs ≥ 2 cm as a goal of surveillance, however, no such large PanNETs were detected in our cohort. Timing of intervention is an important issue. In this series, 55% of the resection specimens harbored no HRN or PDAC, but did harbor, for example, low-risk PanIN lesions (PanIN-1 or 2) or small PanNETs. Although not the primary intent of the surgery, long-term follow-up may show that patients with resected low-risk lesions might have a reduced risk for developing PDAC. Obviously, all-cause mortality and morbidity including quality of life after surgery, should be taken into consideration to genuinely assess the effects of surgery in individuals with low-risk neoplasia. In other individuals, surgical resection was performed too late, as only 3 of the 19 PDAC-cases were T1. The main challenge in any surveillance program for PDAC is how to rightfully distinguish between those individuals that can be safely monitored and those who require surgery to resect an (early) neoplastic lesion. Based on the complexity to diagnose and differentiate these early lesions, we currently do not advocate expanding surveillance programs outside expert centers. Instead, surveillance for pancreatic cancer should only be done within the framework of a collaborative study consortium, in order to continuously monitor, analyze and optimize performance.

In this study, 55% of lesions that prompted surgery were detected at baseline visit. This could raise the question whether one-time screening of HRI at a given age is also effective. Nevertheless, in some individuals in whom an advanced lesion was found at the index investigation, it could be argued that this lesion would have been detected at an earlier stage with potentially a better outcome if that subject had entered the surveillance protocol at an earlier age. We also observed newly developed or detected high-risk lesions in several patients who missed their follow-up visit by only a few months. Therefore, based on current observations, we believe that it is appropriate to adhere to an annual surveil-

lance protocol, until more data are available from large prospective cohort series to define the optimal management strategy per risk group.

Although not all cases with main-duct IPMN progress to cancer, the overall 10-year risk is estimated at approximately 25% which is the rationale why these lesions are regarded high risk [21]. Interestingly, only 2 patients in our study cohort were identified with main-duct IPMN (dilated pancreatic duct) prior to surgery. After pathological evaluation of the resection specimen 4 cystic lesions were re-classified as main-duct IPMN. A discrepancy between imaging report and pathology report is not an uncommon finding [22] and it would be very interesting to compare imaging characterization of a lesion and duct diameter on imaging to pathology reports, however this is beyond the scope of this study.

To improve selection of HRI for surgery, we also looked for risk factors that can easily be assessed preoperatively for association with HRN or PDAC in the resection specimens. Multivariate analyses showed age ≥ 65, female gender, carriage of a gene mutation and location of a lesion in the head/uncinate region of the pancreas to be associated with the detection of HRN or PDAC in the resection specimen. Therefore, particularly in female carriers of a gene mutation aged above 65 with a lesion suspicious for malignancy in the head/uncinate region of the pancreas, one should carefully weigh the option of pancreatic surgery versus continuing surveillance.

In our risk factor analyses, we examined the potential effect of time on the prevalence of neoplasia in resection specimen because criteria for surgery might be confounded by increased clinical experience and accumulating data. Surgery in more recent years (after 2011) did not yield significantly more HRN or PDAC in the resection specimens as compared to prior years when surveillance was just being implemented, however, there was a trend towards more HRN or PDAC in recent years ('the learning curve'). Also, when disregarding index cases (detection of the indication for surgery at baseline visit, no statistically significant difference over the years was found.

Our survival analysis confirmed that overall mortality and survival rates strongly depend on the stage of disease at diagnosis [23]. Importantly, we found that the survival of HRI with HRN in their resection specimen was equal to the HRI with no or low-risk neoplastic lesions, which emphasizes the need to reliably identify these HRN lesions, more so than detecting early cancers. Our study results support the intent and pursuit of pancreatic cancer surveillance programs to detect and resect advanced neoplastic lesions before they have developed into PDAC.

The strength of this study is the worldwide pooling of data on PDAC-surveillance programs. This yielded a unique and sizeable cohort of HRI participating in PDAC-surveillance programs in whom either a suspicious lesion was detected for which they underwent surgery, or in whom an inoperable pancreatic cancer developed. The main limitations of this study are its retrospective design and potential lead-time and length bias [24]. Another limitation of this retrospective study is that differences between protocols of screening centers worldwide existed, in particular for the period before publication of consensus statements of the Cancer of the Pancreas Screening (CAPS) Consortium in 2013 [17]. Furthermore, even though this is the largest cohort ever described, its sample size is still too limited to assess differences in survival between R0 and R1 resections. Another limitation of our study due to the retrospective design is the lack of detailed information of all 1700 HRI that underwent surveillance. We specifically focused our attention and efforts to the high selected group of HRI who either developed advanced neoplasia or underwent pancreatic surgery. The aim of this particular manuscript was not to assess the overall performance of screening, simply because we lack reliable (retrospective) data to do such an analysis and make any claim on that regard. We do believe however that with the current manuscript and methodology, despite its retrospective nature, we add new, interesting and valuable data to the literature that provides some rationale to screening individuals at high risk for pancreatic cancer. Furthermore, it provides a foundation to our initiative to initiate a world-wide prospective collaborative CAPS-registry to further analyze the merits of screening.

In conclusion, pooling of worldwide data on HRI in whom PDAC-surveillance led to the detection of advanced disease or the detection of a lesion for which pancreatic surgery was performed, yielded the following outcomes: 45% of pancreatic resection specimens harbored PDAC or HRN; age ≥ 65 at time of surgery, female gender, carriership of a gene mutation, and location of a lesion in the head/uncinate region were significantly associated with the detection of PDAC or HRN in the resection specimen. Importantly, survival between HRI with non-malignant or low-risk neoplastic lesions versus HRI with HRN did not differ; survival was worse among patients with (advanced) PDAC. While all screening programs carry the risk of overtreatment, our results suggest that surveillance of HRI leads to the treatment of an acceptable mix of lesions. More research is needed to better understand the risk factors for individuals at high risk of developing PDAC, and importantly to improve selection of HRI for surgery. Collaborating internationally in large worldwide prospective studies is of high importance due to the small number of interventions at any individual center.

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PART II

Psychosocial aspects of surveillance

Chapter 6

Repeated participation in pancreatic cancer surveillance by high-risk individuals imposes low psychological burden

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ABSTRACT

Background When assessing the feasibility of surveillance for pancreatic cancer (PC), it is important to address its psychological burden. The aim of this ongoing study is to evaluate the psychological burden of annual pancreatic surveillance for individuals at high risk to develop PC.

Methods This is a multicenter prospective study. High-risk individuals who undergo annual pancreatic surveillance with magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) were invited to complete questionnaires to assess motivations for participating in surveillance, experiences with participation, perceived PC risk, topics of concern, and psychological distress. Questionnaires were sent after intake for participation (T1), after the first MRI and EUS (T2), and after the MRI and EUS 1 (T3), 2 (T4) and 3 years (T5) after first surveillance.

Results In total, 140 out of 152 individuals returned one or more of the questionnaires (response 92%); 477 questionnaires were analyzed. The most frequently reported motivation for participating in surveillance was the possible early detection of (a precursor stage of) cancer (95-100%). Only a minority of respondents experienced MRI and EUS as uncomfortable (10% and 11%, respectively) and respondents dreaded their next EUS investigation less as surveillance progressed. Respondents' cancer worries decreased significantly over time, and both their anxiety and depression scores remained stable and low over the 3-year period of follow-up.

Conclusions The psychological burden of pancreatic surveillance is low at all assessments. Therefore, from a psychological point of view, participation of high-risk individuals in an annual pancreatic surveillance program is feasible.

BACKGROUND

Pancreatic cancer (PC) is one of the most fatal human malignancies with a 5-year survival of only 5% [1]. Survival rates strongly depend on the stage of PC. Therefore, there is great interest in surveillance to detect PC, or more preferably precursor lesions, in an earlier and potentially still curable stage. Screening and surveillance of the entire population for PC, however, seem infeasible because of the relatively low incidence [2] and the lack of a non-invasive, reliable and affordable surveillance tool. Nevertheless, surveillance of well-defined high-risk groups might be effective.

Two separate groups of individuals are considered to be at an inherited high risk to develop PC: (1) mutation-carriers of PC-prone hereditary syndromes and (2) individuals without a known gene mutation but with a strong family history of PC (familial pancreatic cancer (FPC)). The risk of developing PC in these high-risk individuals can be increased up to 75-fold [3-10].

Multiple studies on surveillance for PC in high-risk individuals have provided results on the efficacy of the detection of precursor lesions and asymptomatic cancers [6, 11-20]. Importantly, when assessing the successfulness of a surveillance program, one should not only focus on clinical results, but also on the psychological aspects of repeated participation in such a program; if eligible patients do not start participation or quit prematurely because of perceived psychological burden, this program will not be successful.

Only three studies have assessed the feasibility of PC surveillance from a psychological point of view [21-23], with a maximum follow-up of only 12 months. All three conclude that participation in surveillance does not lead to increased psychological distress. However, as surveillance entails long-term participation and repeated exposure to investigations, longer follow-up studies are required to clarify whether the psychological burden remains acceptable as surveillance progresses. The aim of this prospective, sizeable, and ongoing multicenter study was therefore to evaluate the long-term psychological burden of repeated pancreatic surveillance.

METHODS

Patients

All participants of an ongoing Dutch PC surveillance study (FPC study) are invited to participate in a psychological questionnaire study. The Dutch FPC study is a multicenter prospective study investigating the effectiveness of PC surveillance in high-risk individuals.

Eligible individuals are: (1) all ***CDKN2A*** mutation carriers and all Peutz-Jeghers syndrome patients, (2) ***BRCA 1/BRCA 2*** or ***p53*** mutation carriers or Lynch syndrome patients, all with at least two family members affected by PC, and (3) all first-degree relatives (FDR) of an FPC case. FPC was defined as families affected by PC in at least (1) two FDR, (2) three relatives in which the affected cases are FDR or second-degree relatives of each other, or (3) two second-degree relatives of whom at least one relative was aged <50 years at the time of diagnosis.

All participants are evaluated and counseled by a clinical geneticist prior to inclusion and are informed that the effectiveness of surveillance for PC in reducing morbidity and mortality is not yet proven.

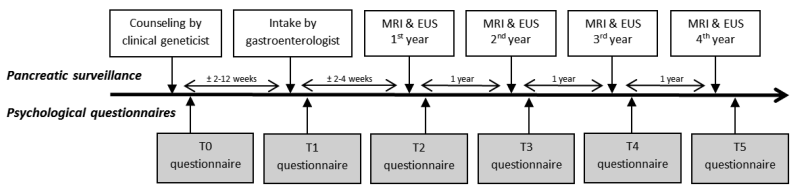
Clinical study procedures

The PC surveillance study consists of annual endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI). EUS is performed under conscious (midazolam/fentanyl) or propofol sedation.

Questionnaire study

All participants of the ongoing PC surveillance study are invited to participate in the psychological questionnaire study. Participants receive a first questionnaire on background data after having undergone counseling by the clinical geneticist (T0), a second questionnaire after having received the explanation of study procedures by the gastroenterologist (T1), and thereafter annually after having received their surveillance results (T2 and further) (Figure 1). We report the results of a 3-year period here. Participants receive their questionnaires 1- 4 weeks after counseling/intake or surveillance results. Because this questionnaire-study was added after the first inclusion period of the original clinical study protocol, some participants had already had their first investigations and therefore started their questionnaires at T2.

Figure 1. Overview of both the clinical part of the pancreatic cancer surveillance study and timing of psychological questionnaires.



MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography

Measurements

Socio-demographic and clinical data: Data were obtained on age, sex, marital status, children, level of education, personal and family history of cancer, genetic background, and surveillance results, using medical records and questionnaires.

Motivations for participating in pancreatic cancer surveillance: Participants were asked to select their motive(s) from a checklist as used in our previous study [22]; for the items on this checklist, see Table 1.

Attitudes towards and experiences with participation in pancreatic cancer surveillance: A 16-item questionnaire comprising four subscales was used, assessing communication, reassurance, nervous anticipation and specific perceived advantages [24]. The Cronbach's alpha on internal consistency of the subscales in this study was moderate to low (between 0.03 and 0.34), for which we do not have an obvious explanation but which led us to the decision of showing the results on item level and not on subscale level (see items in Table 2). Experiences with each of the surveillance tests (EUS and MRI) were assessed with questions having four response options (i.e., not uncomfortable, slightly uncomfortable, rather uncomfortable or very uncomfortable).

Perceived risk: Participants were asked to report their perceived risk of developing PC when compared with the risk of an average similar-aged person in the Dutch population (lower, equal, slightly elevated, moderately elevated, or strongly elevated risk - item adapted from Lerman ***et al.*** [25]). They were also asked to scale their perceived risk between 0 and 100, with and without undergoing annual surveillance.

Cancer worries: Cancer-related worries were assessed with the eight-item Cancer Worry Scale (CWS) [26, 27]. The total score ranges from 8 to 32, with higher scores indicating more frequent worries about cancer. The Cronbach's alpha on internal consistency in this study was high (0.85-0.90).

Anxiety and depression: Generalized anxiety and depression were measured with two seven-item subscales of the Hospital Anxiety and Depression Scale (HADS) [28, 29]: HADS-A and HADS-D. The total score for each subscale ranges from 0 to 21; a score >10 reflects a high level of anxiety or depression and is considered clinically significant. The Cronbach's alpha in this study was high on both the anxiety and the depression subscale (0.79-0.88, and 0.82-0.87, respectively).

Topics of concern and need for additional psychosocial support: Participants were asked to select the importance of their level of concern on a list of 22 possible topics

(not important, slightly important, rather important, or very important). For each of the concerns, participants were asked to report their need for professional psychosocial support (developed by Bleiker and Hahn, unpublished (a copy of the Dutch questionnaire is available upon request by emailing the corresponding author)).

Data analysis

Questionnaires were analyzed using descriptive statistics. Intra-individual changes over time were assessed, with mixed-effect models for longitudinal data (growth curve models) having a maximum likelihood estimator and unstructured covariance matrix, and with repeated measures generalized estimated equations having binomial distribution for ordinal outcomes. The numbers in the tables of this paper refer to average percentages (proportional analyses); the superscript lowercase letters in the tables refer to intra-individual changes over time (non-proportional analyses). β, ***P***-values, standard errors (SE), and confidence intervals (CI) are shown in Supporting Information Table S1. To correct for multiple testing, we only report ***P***-values of <0.01 as statistically significant. For all statistical analyses, the Statistical Package for the Social Sciences was used (version 21.0, SPSS Institute, Chicago, IL, USA).

Both the clinical study procedures as well as the questionnaire study were approved by the Ethical Review Committees of the participating hospitals.

RESULTS

Response

Of the 152 individuals who have been participating in the FPC study since its start in 2008, 140 individuals (92%) returned one or multiple completed questionnaires. In total, 477 questionnaires have been received and analyzed: 36 (out of 38 sent) T0 questionnaires, 69 (out of 74 sent) T1 questionnaires, 127 (out of 136 sent) T2 questionnaires, 109 (out of 116 sent) T3 questionnaires, 85 (out of 93 sent) T4 questionnaires, and 51 (out of 54 sent) T5 questionnaires. The mean number of questionnaires returned per respondent was 3.4 (range 1-6).

Sociodemographic and clinical data

Patient characteristics of both respondents (***n*** = 140) and non-respondents (***n*** = 12) are shown in Table 1; there were no differences.

In total, 368 clinical surveillance investigations were performed. Seven participants were referred to surgery as a result of surveillance. Eight patients (6%) withdrew from the sur-

Table 1. Patient characteristics

	Ever-respondents (returned at least one questionnaire) (n = 140) N (%)	Never-respondents (n = 12) N (%)	P-value
Gender, male	59 (42%)	7 (58%)	0.28
Age at inclusion, mean (range, SD)	51 (19-73, 9.3)	47 (32-65, 10.0)	0.15
Genetic background of individuals			
FPC	71 (51%)	4 (33%)	
Syndromic PC	69 (49%)	8 (67%)	0.25
Syndromic PC individuals			
CDKN2A mutation carriers	38 (27%)	5 (42%)	
BRCA 1 mutation carriers	2 (1%)	2 (17%)	
BRCA 2 mutation carriers	19 (14%)	1 (8%)	
LKB1 / STK 11 mutation carriers	7 (5%)	0	
p53 mutation carriers	3 (2%)	0	0.07
Number of relatives with PC, mean (range, SD)	2.3 (0-7, 1.3)	2.9 (0-4, 1.1)	0.12
Marital status			
Married/cohabiting/living apart together relationship	114 (81%)		
Single/divorced/widowed	15 (11%)		
No data	11 (8%)	12 (100%)	N/A
Children			
Yes	122 (87%)	7 (58%)	
No	15 (11%)	1 (8%)	
No data	3 (2%)	4 (33%)	1.00
Level of education			
Primary school	3 (2%)		
High school	39 (28%)		
College / university	96 (69%)		
No data	2 (1%)	12 (100%)	N/A
Ever treated for any type of cancer	42 (30%)	4 (33%)	0.76
Underwent surveillance with:			
EUS and MRI	135 (96%)	12 (100%)	
EUS only	2 (1%)	0	
MRI only	3 (2%)	0	0.80
Motivations for participating in PC surveillance (more than one answer could be checked on the checklist)			
Cancer, or a precursor stage, might be detected early and might still be treatable	98%		
I will be contributing to scientific research	71%		
Reduces my fear of cancer	22%		
Gives me a sense of control over my body	22%		
A physician referred me to undergo surveillance	11%	N/A	N/A
A family member asked me to undergo surveillance	9%		

SD, standard deviation, FPC, familial pancreatic cancer; PC, pancreatic cancer; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; N/A, not applicable

veillance program: one for financial reasons, one because of the psychological burden of repeated participation, and six did not provide a reason. The available questionnaires from these individuals were included in our analyses.

Motivations for participating in pancreatic cancer surveillance

The results of the checklist for motivations for participating in PC surveillance are shown in Table 1. The most frequently reported motivations were that cancer might be detected early (checked in an average of 98% of all instances) and that by participating, they would be contributing to scientific research (71%).

Attitudes towards and experiences with participation in pancreatic cancer surveillance

The results of the 16-item questionnaire assessing attitudes towards surveillance are shown in Table 2. For as much as 87% of respondents, the advantages of surveillance outweigh the disadvantages, and the majority of respondents (79%) feel reassured after their follow-up visit. Only a minority of respondents are nervous before their follow-up visit or dread the visit (14% and 13%, respectively). Only 8% of respondents perceive the investigations as burdensome. Compared with the first assessment of attitudes and experiences (T2), respondents felt that they could ask fewer questions during follow-up at T3 (β = -1.29, SE 0.46, CI -2.47 to -0.10, ***P*** = 0.005); that the advantages outweighed the disadvantages less at T3 (β = -0.99, SE 0.28, CI -1.71 to -0.27, ***P*** <0.001), T4 (β = -0.95, SE 0.34, CI -1.83 to -0.08, ***P*** = 0.005) and T5 (β = -1.05, SE 0.40, CI -2.09 to -0.01, ***P*** = 0.009); and that the follow-up visits at T4 (β = -0.82, SE 0.31, CI -1.61 to -0.03, ***P*** = 0.007) and T5 (β = -1.07, SE 0.33, CI -1.91 to -0.23, ***P*** = 0.001) conveyed less sense of security.

The experiences of respondents with MRI and EUS are summarized in Supporting Information Table S2. Both MRI and EUS are experienced as uncomfortable by only the minority of respondents (10% and 11%, respectively). Only 3% of respondents dread their first MRI versus 34% of respondents dreading their first EUS. However, once experienced, the percentage of respondents dreading their next EUS dropped significantly (***P*** <0.001) to the same level as that of the MRI (6-9% and 0-8%, respectively).

Perceived risk

The majority of respondents perceived the risk of their developing PC as elevated when compared with the risk of an average similar-aged person: 0-6% reported their perceived risk as 'lower', 6-22% as 'equal', 29-42% as 'slightly elevated', 18-31% as 'moderately elevated', and 19-28% as 'strongly elevated'.

Table 2. Attitudes towards surveillance for pancreatic cancer

To what extent…	% 'rather' / 'very' T2 (%)	T3 (%)	T4 (%)	T5 (%)	Average (%)
Communication					
… do people in the hospital pay attention to what you say?	95	85	88	88	90%
… do the physicians have enough time for you?	67	74	75	75	79%
… can you ask about things at a follow-up visit?	77	72[a]	71	76	74%
… can you discuss with your doctor matters that are of concern to you or about which you worry at a follow-up visit?	76	65	60	55	66%
Reassurance					
… do the advantages of follow-up outweigh the disadvantages?	85	87[a]	91[a]	86[a]	87%
… are you reassured after the follow-up visit?	77	81	82	78	79%
… do the follow-up visits convey a sense of security to you?	63	70	67[a]	77[a]	68%
… would you worry more about your disease if there was no follow-up?	66	66	69	71	67%
Nervous anticipation					
… are you nervous before a follow-up visit?	16	14	15	8	14%
… do you dread the follow-up visits?	16	13	9	14	13%
… do you sleep worse in the week before your follow-up visit?	11	5	7	4	7%
… do you postpone plans until after the follow-up visit?	4	8	6	2	5%
… would you rather have follow-up visits less often?	5	2	2	8	4%
Perceived disadvantages					
… would you prefer, if possible, to have follow-up visits in a hospital closer by?	26	19	19	16	21%
… does the follow-up visit remind you each time of your disease, while you would rather think less often about it?	20	15	16	16	17%
… do you experience the investigations at follow-up visits to be burdensome?	12	7	5	2	8%

[a] Significant intra-individual decrease over time (in comparison with first assessment (T2)), non-proportional analysis, P <0.01

Respondents scaled their risk (scale 0-100) significantly higher when they would not undergo annual surveillance (mean 44.3, SD 28.1) than when they would undergo annual surveillance (mean 29.4, SD 24.7, P <0.001) (Supporting Information Table S3). This difference in risk perception reflects respondents' belief that the surveillance program is effective in early detection.

Cancer worries

The mean CWS score of respondents was low at 13.0 (SD 3.6) (Supporting Information Table S3). The mean CWS score from baseline (14.4, SD 4.3) decreased significantly by 0.5

point each year (β = -0.53, SE 0.09, CI -0.78 to -0.28, ***P*** <0.001), indicating fewer cancer worries as surveillance progressed.

Anxiety and depression

Anxiety and depression levels of respondents were low with a mean HADS-A score of 4.5 (SD 3.7) and a mean HADS-D score of 2.8 (SD 3.2) (Supporting Information Table S3). Only a few respondents showed scores indicative of clinically significant anxiety or depression disorder (score >10; 7% and 5%, respectively). No significant intra-individual changes over time were noted for either anxiety or depression levels.

Topics of concern

The results of the questionnaire on possible topics of concern are shown in Table 3. The most important concern was that of cancer risk in children and family (rather important or very important for 83% of respondents). Moreover, bereavement of family losses (67%) scored high on importance of concern. Interestingly, the risk of getting cancer scored lower on importance (rather or very important for 46% of respondents). In addition, feelings of guilt towards their children or family scored low on importance (for 37% of respondents rather or very important). The most frequent topics of concern that respondents would like to discuss with a psychosocial worker were 'consequences of (preventive) resection', 'dealing with cancer', and 'cancer-risk in children and family' (20%, 19%, and 19% of respondents, respectively).

Eleven different topics showed an intra-individual decrease over time (i.e., fewer worries about these topics as surveillance progressed): cancer risk in children and family, communication with the clinician, genetic testing, bereavement of family losses, informing children or family, consequences of (preventive) resection, choice of medical treatment, complications after medical treatment, physical complaints, body image, and sexual functioning. However, three topics showed an intra-individual increase over time (i.e., more worries on these topics as surveillance progressed): former psychological problems, fear about frequent medical checkups, and desire for children.

Table 3. Topics of concern and wishes to discuss with a psychosocial worker

Topics of concern	% 'rather important' / 'very important'							
	T0 (%)	T1 (%)	T2 (%)	T3 (%)	T4 (%)	T5 (%)	Average (%)	Wish to discuss topic (%)
Cancer risk in children and family	80	83[a]	83	82[a]	78	92	83%	19%
Communication with clinician	66	67	74	69[a]	61[a]	80	70%	12%
Genetic testing	56	63[a]	68[a]	70	67[a]	80	69%	14%
Bereavement of family losses	65	67	66[a]	70[a]	68[a]	68[a]	67%	14%
Informing children or family	65	60	73[a]	67	63[a]	67[a]	67%	14%
Consequences of (preventive) resection	70	67	67[a]	60	64	73[a]	66%	20%
Choice of medical treatment	71	70	68	62	65[a]	80	65%	18%
Complications after medical treatment	60	60	62	59[a]	61	73	62%	18%
Physical complaints (such as pain)	58	63	54	57[a]	60	62	58%	12%
Fatigue	42	57	52	45	55	60	52%	12%
Relationship problems	52	47	47	48	52	52	49%	10%
Dealing with cancer	50	48	45	51	41	49	47%	19%
Chances of getting cancer	38	59	45	49	43	50	46%	14%
Body image	52	40[a]	43	44	49	42	45%	8%
Mood swings/depressive feelings	49	37	48	39	43	48	44%	14%
Questions concerning life and death	42	36	45	41	51	40	44%	11%
Consequences for work, study, and social activities	30	31	41	38	49	44	41%	10%
Sexual functioning	50	33	40[a]	41	41	36	40%	8%
Feelings of guilt towards children or family	44	32	34	42	33	36	37%	12%
Former psychological problems	16	14[b]	23[b]	18[b]	23[b]	22[b]	21%	9%
Fear about frequent medical checkups	26	17[b]	22[b]	21[b]	16[b]	18[b]	20%	9%
Desire for children	13	7	11[b]	10[b]	8[b]	9[b]	10%	3%

[a] Significant intra-individual decrease over time (in comparison with first assessment (T0)), non-proportional analysis, P <0.01

[b] Significant intra-individual increase over time (in comparison with first assessment (T0)), non-proportional analysis, P <0.01

DISCUSSION

This study shows that PC surveillance is well feasible from a psychological point of view, as the repeatedly assessed psychological burden of participation in a PC surveillance program is low, which is also supported by a low clinical drop-out rate (6%).

Multiple studies have assessed the clinical effectiveness of surveillance for PC in high-risk individuals [6, 11-20]. It is, however, important to also take into account the psychological aspects of ongoing participation and repeated investigations because this will have an important effect on adherence to surveillance. To date, there are no prospective studies with more than 12 months of follow-up assessing the feasibility of PC surveillance from a psychological point of view. Hart ***et al.*** [23] found that cancer-related distress and worries did not increase over the course of 1 year. From our cohort, we previously published the results of 69 individuals who completed a one-time questionnaire, concluding that PC surveillance by EUS and MRI was feasible from a psychological point of view [22]. Because surveillance for PC in high-risk individuals will entail a lifelong program with repetitive investigations, it is pivotal to investigate the psychological burden in a prospective design with a longer follow-up period.

In our unique prospective and large cohort of high-risk individuals, we have now acquired follow-up data up to 3 years including six assessments pertaining to psychological burden with a high overall response rate of 92%. We found that respondents experienced annual EUS and MRI investigations as 'not' uncomfortable or only 'slightly' uncomfortable and dread their next EUS investigations less as surveillance progressed while having decreasing worries about cancer and having normal and stable levels of anxiety and depression. These results are in line with the psychological burden of surveillance for other inherited forms of cancer [30-39].

A total of 34% of respondents dreaded their first EUS in contrast to only 3% of respondents dreading their first MRI. However, on follow-up questionnaires, the percentage of respondents dreading their next EUS dropped significantly to 6-9%, comparable with the percentage level of respondents dreading their next MRI (0-8%). This indicates that once respondents had experienced EUS, it proved to be very tolerable. This assumption is supported by our finding that only 11% of respondents experienced EUS as uncomfortable, which is comparable with the percentage of respondents experiencing MRI as uncomfortable (10%). In this regard, it is important to emphasize that all EUS investigations were performed under sedation.

Interestingly, we found that the individual worries about cancer decreased significantly each year. One might have expected an increase in cancer worries due to the reminder of their increased risk at follow-up visits. However, only 17% of respondents answered 'rather' or 'very much' to the question as to what extent the follow-up visits reminded them of their risk of developing PC. Because a high percentage of respondents (79%) are reassured after their follow-up visit, this might explain the decrease in their worries about developing cancer. Moreover, respondents scaled their risk of developing PC significantly

lower when they undergo annual surveillance than when they would not; this might also explain the decreasing worries. These are interesting findings because all participants were informed that the effectiveness of PC surveillance in reducing morbidity and mortality is not yet proven.

Many topics of concern showed an intra-individual change over time. These changes cannot all readily be explained. The decrease in concerns about genetic testing and informing of children or family might be explained by the fact that genetic testing, and therefore informing children and family members, was almost always completed after questionnaire T0 and that, therefore, as time progressed, fewer and fewer concerns on these topics were present. However, the increase in concerns about the desire for children cannot be explained and is contra-intuitive to what one might expect because participants are mostly beyond child-bearing age.

In our cohort, we found an average of 7% of respondents having clinically significant anxiety scores and an average of 5% with clinically significant depression scores. This prevalence of clinically significant scores is low, stable over our 3-year follow-up period, and comparable with the scores of the general European population [40].

A particular strength of this multicenter study is its prospective design with long-term follow-up. In addition, a response rate of 92% is very high. Our cohort consists of true high-risk individuals for developing PC, based on strict inclusion criteria and extensive genetic evaluation prior to inclusion in this study.

A limitation of our study is that we were only able to send questionnaires to individuals actively participating in the surveillance study and not to those who decided against participation after counseling by the geneticist. Previously, we reported that only a small proportion of high-risk individuals, 14%, declined participation in surveillance [22]; thus, we expect that our current data are not severely biased. Another limitation of our study is that the majority of the respondents were highly educated and that we therefore cannot estimate the psychological burden in a less educated population. A final limitation of this study is multiple testing and possible power issues. This was corrected for by only reporting *P*-values <0.01 as statistically significant and showing CIs to facilitate the determination of the adequacy of the sample size.

In conclusion, the psychological burden of repeated investigations in pancreatic surveillance is low with only few respondents experiencing annual MRI and EUS as uncomfortable. Few respondents experience worries about cancer, and the mean level of worries decreases even further each year of participation. For the vast majority of respondents,

the advantages of surveillance outweigh the disadvantages. The percentage of individuals with clinical relevant levels of anxiety and depression is low and stable over a 3-year period. Therefore, from a psychological point of view, repeated participation of high-risk individuals in an annual PC surveillance program is well feasible.

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Supporting Information Table S1. Results of the analyses on intra-individual change over time (assessed with mixed effect models and generalized estimated equations) showing β / estimate, *P*-values and standard errors (SE) per assessed item.

Assessed items	Measurement in time	β / estimate	Standard error	99% Confidence interval of estimate		P-value
ATTITUDES TOWARDS SURVEILLANCE FOR PANCREATIC CANCER				Lower	Upper	
To what extent do people in the hospital pay attention to what you say?	T2	0	.	.	.	.
	T3	-0.15	0.25	-0.79	0.50	0.563
	T4	-0.07	0.30	-0.84	0.70	0.823
	T5	-0.84	0.49	-2.12	0.43	0.089
To what extent do the physicians at follow-up in the hospital have enough time for you?	T2	0	.	.	.	.
	T3	-0.34	0.22	-0.92	0.23	0.126
	T4	-0.39	0.30	-1.16	0.39	0.199
	T5	-0.28	0.31	-1.09	0.53	0.375
To what extent can you ask about things at follow-up?	T2	0	.	.	.	.
	T3	-1.29	0.46	-2.47	-0.10	0.005
	T4	-1.06	0.54	-2.44	0.32	0.048
	T5	-1.18	0.57	-2.65	0.29	0.039
To what extent at follow-up, can you discuss with your doctor matters that are of concern to you or about which you worry?	T2	0	.	.	.	.
	T3	-0.12	0.30	-0.90	0.67	0.705
	T4	-0.57	0.35	-1.47	0.34	0.106
	T5	-0.34	0.46	-1.53	0.86	0.469
To what extent do the advantages of follow-up outweigh the disadvantages?	T2	0	.	.	.	.
	T3	-0.99	0.28	-1.71	-0.27	<0.001
	T4	-0.95	0.34	-1.83	-0.08	0.005
	T5	-1.05	0.40	-2.09	-0.01	0.009
To what extent are you reassured after the follow-up visit?	T2	0	.	.	.	.
	T3	-0.48	0.32	-1.29	0.34	0.132
	T4	-1.03	0.48	-2.28	0.21	0.033
	T5	-1.60	0.67	-3.33	0.13	0.017
To what extent do the follow-up visits convey you a sense of security?	T2	0	.	.	.	.
	T3	-0.61	0.26	-1.28	0.06	0.020
	T4	-0.82	0.31	-1.61	-0.03	0.007
	T5	-1.07	0.33	-1.91	-0.23	0.001
To what extent would you worry more about your disease if there was no follow-up?	T2	0	.	.	.	.
	T3	0.27	0.19	-0.21	0.74	0.149
	T4	0.23	0.23	-0.35	0.82	0.309
	T5	0.39	0.28	-0.32	1.11	0.156
To what extent are you nervous before a follow-up visit?	T2	0	.	.	.	.
	T3	0.74	0.49	-0.53	2.01	0.135
	T4	0.20	0.69	-1.59	1.99	0.775
	T5	-0.55	0.68	-2.30	1.21	0.424
To what extent do you normally dread the follow-up visits?	T2	0	.	.	.	.
	T3	0.24	0.28	-0.49	0.98	0.391
	T4	0.45	0.31	-0.35	1.25	0.147
	T5	0.12	0.39	-0.88	1.12	0.761

Supporting Information Table S1. *(continued)* Results of the analyses on intra-individual change over time (assessed with mixed effect models and generalized estimated equations) showing β / estimate, ***P***-values and standard errors (SE) per assessed item.

Assessed items	Measurement in time	β / estimate	Standard error	99% Confidence interval of estimate		P-value
To what extent do you sleep worse in the week before follow-up?	T2	0	.	.	.	.
	T3	-0.43	0.26	-0.72	0.63	0.869
	T4	0.25	0.19	-0.25	0.75	0.198
	T5	-0.18	0.38	-1.15	0.79	0.633
To what extent do you postpone plans till after the follow-up visit?	T2	0	.	.	.	.
	T3	-0.26	0.28	-0.97	0.46	0.354
	T4	-0.17	0.31	-0.96	0.62	0.585
	T5	-0.44	0.49	-1.70	0.83	0.375
To what extent would you rather have follow-up visits less frequently?	T2	0	.	.	.	.
	T3	-0.31	0.23	-0.90	0.29	0.187
	T4	-0.25	0.28	-0.98	0.49	0.386
	T5	-0.53	0.37	-1.48	0.43	0.154
To what extent would you prefer, if possible, to have follow-up visits in a hospital closer by?	T2	0	.	.	.	.
	T3	-0.02	0.21	-0.55	0.52	0.942
	T4	0.07	0.21	-0.46	0.60	0.746
	T5	0.18	0.27	-0.52	0.87	0.511
To what extent does the follow-up remind you each time of your disease, while you would rather think less often about it?	T2	0	.	.	.	.
	T3	-0.92	0.45	-2.07	0.24	0.041
	T4	-0.54	0.38	-1.53	0.45	0.163
	T5	-1.24	0.64	-2.90	0.42	0.054
To what extent do you think the investigations at follow-up burdensome?	T2	0	.	.	.	.
	T3	-1.16	0.77	-3.13	0.82	0.131
	T4	-1.02	0.88	-3.29	1.24	0.245
	T5	0.39	0.48	-0.86	1.64	0.418
EXPERIENCES OF RESPONDENTS WITH ENDOSCOPIC ULTRASOUND (EUS) AND MAGNETIC RESONANCE IMAGING (MRI)						
How uncomfortable was your experience with MRI?	T2	0	.	.	.	.
	T3	-0.70	0.38	-1.68	0.28	0.066
	T4	-0.57	0.37	-1.52	0.38	0.121
	T5	-1.26	0.76	-3.22	0.70	0.098
To what extent do you dread your next MRI?	T1	0	.	.	.	.
	T2	0.45	0.77	-1.53	2.42	0.560
	T3	0.06	0.79	-1.99	2.10	0.945
	T4	-0.75	1.01	-3.36	1.86	0.459
	T5	-0.19	1.12	-3.08	2.70	0.865
How uncomfortable was your experience with EUS?	T2	0	.	.	.	.
	T3	-0.59	0.31	-1.38	0.21	0.059
	T4	-1.05	0.51	-2.37	0.27	0.040
	T5	-0.34	0.52	-1.69	1.02	0.523

Supporting Information Table S1. *(continued)* Results of the analyses on intra-individual change over time (assessed with mixed effect models and generalized estimated equations) showing β / estimate, ***P***-values and standard errors (SE) per assessed item.

Assessed items	Measurement in time	β / estimate	Standard error	99% Confidence interval of estimate		P-value
To what extent do you dread your next EUS?	T1	0	.	.	.	.
	T2	-1.37	0.40	-2.39	-0.35	0.001
	T3	-1.76	0.47	-2.98	-0.54	<0.001
	T4	-2.30	0.65	-3.98	-0.63	<0.001
	T5	-0.54	0.41	-1.60	0.52	0.192
PERCEIVED RISK						
Perceived risk of developing PC without surveillance	T0-T5	0.45	0.72	-1.43	2.33	0.533
Perceived risk of developing PC with surveillance	T0-T5	0.97	0.70	-0.87	2.82	0.170
CANCER WORRY SCALE SCORE						
Cancer Worry Scale score	T0-T5	-0.53	0.09	-0.78	-0.28	<0.001
HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS) SCORE						
HADS-anxiety score	T0-T5	-0.12	0.10	-0.37	0.14	0.242
HADS-depression score	T0-T5	0.04	0.09	-0.19	0.26	0.667
TOPICS OF CONCERN						
Cancer risk in children and family	T0	0	.	.	.	.
	T1	-2.25	0.68	-4.00	-0.50	0.001
	T2	-0.04	0.43	-1.13	1.06	0.935
	T3	-1.38	0.41	-2.45	-0.32	0.001
	T4	-0.66	0.44	-1.78	0.46	0.129
	T5	-0.24	0.50	-1.53	1.05	0.633
Communication with clinician	T0	0	.	.	.	.
	T1	-0.35	0.43	-1.46	0.76	0.415
	T2	0.51	0.43	-0.59	1.61	0.233
	T3	-1.51	0.38	-2.50	-0.51	<0.001
	T4	-1.90	0.42	-2.98	-0.82	<0.001
	T5	1.36	0.61	-0.20	2.92	0.025
Genetic testing	T0	0	.	.	.	.
	T1	-1.33	0.34	-2.21	-0.45	<0.001
	T2	-1.89	0.34	-2.75	-1.02	<0.001
	T3	0.08	0.30	-0.69	0.85	0.787
	T4	-2.30	0.38	-3.29	-1.31	<0.001
	T5	0.29	0.40	-0.75	1.33	0.470
Bereavement of family losses	T0	0	.	.	.	.
	T1	-0.12	0.19	-0.61	0.37	0.536
	T2	-1.05	0.30	-1.83	-0.26	0.001
	T3	-1.29	0.31	-2.09	-0.49	<0.001
	T4	-0.90	0.33	-1.75	-0.05	0.006
	T5	-3.18	0.59	-4.70	-1.65	<0.001

Supporting Information Table S1. *(continued)* Results of the analyses on intra-individual change over time (assessed with mixed effect models and generalized estimated equations) showing β / estimate, ***P***-values and standard errors (SE) per assessed item.

Assessed items	Measurement in time	β / estimate	Standard error	99% Confidence interval of estimate		P-value
Informing children or family members	T0	0	.	.	.	.
	T1	-0.06	0.39	-1.07	0.95	0.873
	T2	-2.92	0.42	-4.01	-1.84	<0.001
	T3	-0.01	0.35	-0.92	0.89	0.967
	T4	-3.33	0.54	-4.71	-1.95	<0.001
	T5	-2.45	0.49	-3.71	-1.19	<0.001
Consequences of (preventive) resection	T0	0	.	.	.	.
	T1	0.10	0.52	-1.24	1.43	0.850
	T2	-2.33	0.37	-3.29	-1.38	<0.001
	T3	-0.32	0.34	-1.20	0.56	0.352
	T4	0.21	0.33	-0.64	1.06	0.523
	T5	-2.46	0.45	-3.63	-1.30	<0.001
Choice of medical treatment	T0	0	.	.	.	.
	T1	-1.02	0.43	-2.12	0.08	0.017
	T2	-0.87	0.37	-1.83	0.09	0.020
	T3	-0.63	0.36	-1.56	0.29	0.076
	T4	-2.30	0.41	-3.35	-1.26	<0.001
	T5	-0.66	0.43	-1.78	0.46	0.127
Complications after medical treatment	T0	0	.	.	.	.
	T1	-0.26	0.39	-1.28	0.76	0.510
	T2	-0.67	0.33	-1.53	0.19	0.044
	T3	-1.92	0.38	-2.89	-0.94	<0.001
	T4	0.04	0.33	-0.81	0.89	0.901
	T5	-0.77	0.41	-1.82	0.27	0.056
Physical complaints (such as pain)	T0	0	.	.	.	.
	T1	-0.15	0.40	-1.18	0.88	0.714
	T2	0.49	0.34	-0.39	1.36	0.152
	T3	-1.78	0.44	-2.89	-0.65	<0.001
	T4	0.31	0.35	-0.59	1.20	0.377
	T5	-0.47	0.41	-1.52	0.59	0.251
Fatigue	T0	0	.	.	.	.
	T1	-0.22	0.46	-1.40	0.96	0.626
	T2	-0.11	0.37	-1.06	0.83	0.757
	T3	-0.37	0.36	-1.31	0.57	0.313
	T4	-0.25	0.38	-1.24	0.74	0.510
	T5	-0.11	0.42	-1.19	0.97	0.797
Relationship problems	T0	0	.	.	.	.
	T1	-0.67	0.39	-1.68	0.34	0.088
	T2	-0.38	0.28	-1.10	0.34	0.173
	T3	0.01	0.25	-0.64	0.66	0.960
	T4	-0.63	0.27	-1.31	0.06	0.019
	T5	-0.70	0.34	-1.58	0.19	0.043

Supporting Information Table S1. *(continued)* Results of the analyses on intra-individual change over time (assessed with mixed effect models and generalized estimated equations) showing β / estimate, ***P***-values and standard errors (SE) per assessed item.

Assessed items	Measurement in time	β / estimate	Standard error	99% Confidence interval of estimate		P-value
Dealing with cancer	T0	0	.	.	.	.
	T1	0.45	0.44	-0.67	1.57	0.303
	T2	-0.30	0.29	-1.03	0.44	0.302
	T3	0.30	0.33	-0.57	1.16	0.378
	T4	0.16	0.29	-0.60	0.92	0.580
	T5	-0.12	0.37	-1.06	0.83	0.754
Chance on getting cancer (again)	T0	0	.	.	.	.
	T1	-0.19	0.45	-1.35	0.96	0.666
	T2	0.32	0.33	-0.54	1.18	0.334
	T3	0.60	0.36	-0.31	1.51	0.089
	T4	-0.11	0.37	-1.06	0.84	0.772
	T5	0.46	0.38	-0.50	1.43	0.217
Body image	T0	0	.	.	.	.
	T1	-2.48	0.57	-3.94	-1.02	<0.001
	T2	0.26	0.34	-0.63	1.14	0.459
	T3	-0.61	0.30	-1.38	0.15	0.039
	T4	-0.48	0.36	-1.40	0.44	0.182
	T5	0.05	0.36	-0.88	0.97	0.892
Mood swings / depressive feelings	T0	0	.	.	.	.
	T1	0.25	0.46	-0.93	1.43	0.583
	T2	0.31	0.36	-0.62	1.24	0.387
	T3	0.66	0.36	-0.26	1.58	0.063
	T4	0.21	0.37	-0.75	1.17	0.567
	T5	-0.16	0.40	-1.20	0.89	0.697
Questions concerning life and death	T0	0	.	.	.	.
	T1	-0.65	0.50	-1.95	0.65	0.198
	T2	-0.13	0.39	-1.12	0.86	0.732
	T3	0.10	0.40	-0.92	1.13	0.797
	T4	0.17	0.39	-0.84	1.18	0.671
	T5	-0.51	0.44	-1.64	0.63	0.247
Consequences for work, study, social activities	T0	0	.	.	.	.
	T1	0.25	0.48	-0.99	1.49	0.607
	T2	0.46	0.37	-0.50	1.43	0.215
	T3	0.75	0.38	-0.23	1.72	0.048
	T4	0.99	0.39	-0.02	1.99	0.011
	T5	0.36	0.46	-0.82	1.53	0.436
Sexual functioning	T0	0	.	.	.	.
	T1	0.39	0.46	-0.80	1.57	0.401
	T2	-0.97	0.34	-1.86	-0.08	0.005
	T3	-0.49	0.34	-1.65	0.38	0.148
	T4	-0.31	0.36	-1.22	0.61	0.387
	T5	-0.91	0.43	-2.03	0.21	0.036

Supporting Information Table S1. *(continued)* Results of the analyses on intra-individual change over time (assessed with mixed effect models and generalized estimated equations) showing β / estimate, ***P***-values and standard errors (SE) per assessed item.

Assessed items	Measurement in time	β / estimate	Standard error	99% Confidence interval of estimate		P-value
Feelings of guilt towards children or family	T0	0	.	.	.	.
	T1	1.00	0.68	-0.75	2.75	0.141
	T2	-0.58	0.40	-1.60	0.44	0.143
	T3	-0.49	0.38	-1.46	0.48	0.195
	T4	-0.53	0.39	-1.53	0.47	0.174
	T5	1.21	0.49	-0.06	2.47	0.014
Former psychological problems	T0	0	.	.	.	.
	T1	1.80	0.43	0.68	2.91	<0.001
	T2	2.00	0.41	0.94	3.06	<0.001
	T3	2.73	0.45	1.59	3.88	<0.001
	T4	1.82	0.42	0.74	2.90	<0.001
	T5	2.55	0.50	1.26	3.84	<0.001
Fear about frequent medical checkups	T0	0	.	.	.	.
	T1	1.19	0.46	0.01	2.37	0.009
	T2	1.60	0.38	0.61	2.58	<0.001
	T3	-1.39	0.45	-2.54	-0.24	0.002
	T4	1.30	0.38	0.32	2.29	0.001
	T5	2.06	0.45	0.91	3.22	<0.001
Desire for children	T0	0	.	.	.	.
	T1	0.21	0.63	-1.42	1.84	0.738
	T2	2.63	0.50	1.34	3.93	<0.001
	T3	1.36	0.49	0.10	2.62	0.006
	T4	2.39	0.52	1.04	3.73	<0.001
	T5	2.28	0.55	0.87	3.69	<0.001

Supporting Information Table S2. Experiences of respondents with endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI)

	% 'rather' / 'very'					
MRI	T1* (%)	T2 (%)	T3 (%)	T4 (%)	T5 (%)	Average (%)
How uncomfortable was your experience with MRI?	-	14	8	10	6	10%
To what extent do you dread your next MRI?	3	8	5	2	0	4%
EUS						
How uncomfortable was your experience with EUS?	-	14	8	7	13	11%
To what extent do you dread your next EUS?	34	9a	7a	5a	6	11%

***** T1 questionnaire was send prior to first surveillance investigations but after explanation of study procedures by a gastroenterologist

[a] Significant intra-individual decrease over time (in comparison with first assessment (T1/T2)), non-proportional analysis, $P < 0.01$

Supporting Information Table S3. Perceived risk, cancer-related worries, anxiety and depression scores

	T0	T1	T2	T3	T4	T5	Average
Perceived risk of developing PC without surveillance, mean (scale 0-100)	34	46	46	42	46	47	44.3
Perceived risk of developing PC with surveillance, mean (scale 0-100)	24	28	32	26	32	33	29.4
Cancer Worry Scale score, mean (scale 8-32)	14.4	14.0	13.3	12.4	12.5	12.1	13.0a
HADS-A score, mean (scale 0-21)	5.3	4.6	4.3	4.3	4.4	4.5	4.5
HADS-A score categories:							
- Normal level of anxiety (score <8, %)	69	81	84	75	80	78	79%
- Elevated distress (score 8-10, %)	14	13	9	19	14	12	14%
- Significant distress (score >10, %)	17	6	7	6	6	10	7%
HADS-D score, mean (scale 0-21)	2.5	2.4	2.6	2.9	3.2	2.8	2.8
HADS-D score categories:							
- Normal level of anxiety (score <8, %)	91	90	93	92	87	90	91%
- Elevated distress (score 8-10, %)	3	6	4	4	6	6	5%
- Significant distress (score >10, %)	6	4	3	4	7	4	5%

[a] Significant intra-individual decrease over time (in comparison with first assessment (T0)), non-proportional analysis, $P < 0.01$

PC, pancreatic cancer; HADS-A, Hospital Anxiety and Depression Scale, 7-item subscale for anxiety; HADS-D, Hospital Anxiety and Depression Scale, 7-item subscale for depression

Chapter 7

FACTORS ASSOCIATED WITH CANCER WORRIES IN INDIVIDUALS PARTICIPATING IN ANNUAL PANCREATIC CANCER SURVEILLANCE

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On behalf of the Dutch research group on pancreatic cancer surveillance in high-risk individuals

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ABSTRACT

Objectives It is important to adequately and timely identify individuals with cancer worries amongst participants in a pancreatic ductal adenocarcinoma (PDAC) surveillance program, because they could benefit from psychosocial support to decrease distress. Therefore, the aim of this study was to assess both psychosocial and clinical factors associated with cancer worries.

Methods High-risk individuals participating in PDAC-surveillance were invited to annually complete a cancer worry scale (CWS) questionnaire which was sent after counseling by the clinical geneticist (T0), after intake for participation in PDAC-surveillance (T1), and then annually after every MRI and endoscopic ultrasonography (EUS) (T2 and further). Analyses were performed to identify factors associated with cancer worries in the second year of surveillance (T3).

Results We found a significant intra-individual decrease in cancer worries (β = -0.84, P <0.001), nevertheless, 33% of individuals had a CWS-score ≥14 at T3. We found one factor significantly associated with cancer worries at T3: having a family member affected by PDAC <50 years of age (β = 0.22, P = 0.03). The detection of a cystic lesion, a shortened surveillance interval, or undergoing pancreatic surgery did not lead to more cancer worries (P = 0.163, P = 0.33, and P = 0.53, respectively).

Conclusions In conclusion, this study identified 'a family history of PDAC <50 years of age' as the only predictor of cancer worries experienced after 2 years of surveillance in individuals at high risk of developing PDAC. This knowledge could help clinicians to timely identify individuals 'at risk' for high levels of cancer worries who would likely benefit from psychosocial support.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease: despite its relatively low incidence of 10-12 new cases per 100,000 persons per year [1-3], PDAC is ranked among the top five causes of cancer-related deaths [4, 5]. Its 5-year survival rate has not significantly improved over the past decades and is less than 6% [4, 5]. Since survival rates strongly depend on the stage of PDAC when detected, there is globally an increasing interest in surveillance to detect PDAC or its precursor high-grade dysplastic lesions at an early stage. Although screening of the entire population for PDAC is unlikely to be feasible because of the lack of a non-invasive, reliable and affordable surveillance tool, surveillance of well-defined high-risk groups for PDAC might be effective.

Two specific groups of individuals are considered to be at high risk of developing PDAC: (1) mutation carriers of hereditary syndromes that increase the risk of developing PDAC (i.e. carriers of mutations in the ***CDKN2A***, ***BRCA1, BRCA2*** or ***TP53*** gene, and individuals with Peutz-Jeghers or Lynch syndrome), and (2) individuals without a known gene mutation but who have a strong family history of PDAC (familial pancreatic cancer (FPC)). In these individuals, the risk of developing PDAC can be up to 75-fold higher than in the general population [6-13].

Over the past decades, multiple studies into the effectiveness of surveillance for PDAC in high-risk individuals have been performed [14-25]. Importantly, however, when assessing the effectiveness of a surveillance program, one should also take into account the psychological aspects of repeated participation in such a surveillance program. We previously reported that repeated participation in annual surveillance imposed low psychological burden on individuals at high risk for PDAC. However, we did find that a third of the participants had moderate to high cancer worries [26].

As individuals with high levels of cancer worries might benefit from psychosocial support to decrease the levels of psychological distress, it could be essential to adequately and timely identify these individuals. Therefore, the aim of this study was (1) to evaluate the course of cancer worries over a 2-year period of PDAC-surveillance, (2) to identify psychosocial factors associated with cancer worries, and (3) to assess the impact of pancreatic cystic lesion detection, a recommended shortened surveillance interval, and undergoing pancreatic surgery on cancer worries in high-risk individuals participating in annual PDAC-surveillance.

METHODS

Participants

All participants of an ongoing Dutch pancreatic cancer surveillance study (FPC-study) were invited to participate in a psychological questionnaire study as previously described [26]. The FPC-study is an ongoing multicenter prospective study investigating the effectiveness of PDAC-surveillance in high-risk individuals. Eligible for inclusion in this study are asymptomatic individuals with an estimated familial or hereditary life-time risk of developing PDAC ≥ 10% (see inclusion criteria in Table 1). The minimal age for inclusion between 2008 and 2013 was 45 years of age (or 30 years in case of Peutz-Jeghers syndrome) or 10 years younger than the age of the youngest relative with PDAC, whichever age occurred first. Since 2013, the minimal age for inclusion is 50 years or 10 years younger than the age of the youngest relative with PDAC. Surveillance ends at the age of 75. All potential candidates are evaluated by a clinical geneticist prior to inclusion. They are informed that the effectiveness of PDAC surveillance in reducing morbidity and mortality is not yet proven.

Table 1. Inclusion criteria for the pancreatic cancer surveillance study

Carriers of CDKN2A gene mutations, regardless of the family history of PDAC
Peutz-Jeghers syndrome patients (diagnosis based on a proven LKB1/STK11 gene mutation or clinical signs), regardless of the family history of PDAC
Carriers of gene mutations in BRCA1, BRCA2, TP53, or Mismatch Repair genes with a family history of PDAC in ≥ 2 family members
Individuals with ≥ 2 relatives affected by pancreatic cancer who were related in the first degree to each other, of which at least one was related in the first-degree to the eligible individual
Individuals with ≥ 3 relatives affected by pancreatic cancer who were related in the first or second degree to each other, of which at least one was related in the first-degree to the eligible individual
Individuals with ≥ 2 relatives affected by pancreatic cancer who were related in the second degree to each other, of which at least one was related in the first-degree to the eligible individual and at least one was aged under 50 years at time of diagnosis

PDAC, pancreatic ductal adenocarcinoma

Clinical study procedures

The clinical study procedures were previously extensively described [25]. In summary, annual surveillance of the pancreas is performed using endoscopic ultrasonography (EUS), carried out by experienced endosonographers, and magnetic resonance imaging (MRI) with intravenous administration of gadobutrol. EUS is performed under conscious (midazolam/fentanyl) or propofol sedation. Some participants undergo surveillance with only MRI or EUS (see Table 2) due to contra-indications for either modality (for example claustrophobia, pacemaker or discomfort during initial EUS). Follow-up policy is based on the agreement of

an expert panel consisting of endosonographists, surgeons, radiologists and pathologists and is as follows:

1. Annual surveillance when either no pancreatic abnormalities or cystic lesions < 10 mm are detected;
2. Interval surveillance after 6 months when a novel cystic lesion is detected with a diameter of 10-30 mm without worrisome features;
3. Interval surveillance after 3 months when a lesion of unknown significance is detected for which there is no unanimous opinion amongst members of the expert panel;
4. Surgical resection in case of 1. a solid lesion which is considered suspicious for malignancy, 2. a cystic lesion ≥ 30 mm, 3. a cystic lesion with worrisome features (thickened/enhanced cyst wall and/or mural nodules), or 4. a main branch intraductal papillary mucinous neoplasm (IPMN, main pancreatic duct ≥ 10 mm).

Questionnaire study

All participants of the ongoing PDAC-surveillance study are invited to participate in the ongoing prospective multicenter psychological questionnaire study. Participants receive a first questionnaire on sociodemographic data after their counseling session with the clinical geneticist (T0), a second questionnaire after explanation of the study procedures by the gastroenterologist (T1), and then annually after receiving their surveillance results (T2 and further), see also Figure 1. Because this questionnaire study was added after the first inclusion period of the original clinical study protocol, some participants had already had their first investigations and therefore started their questionnaires at T2.

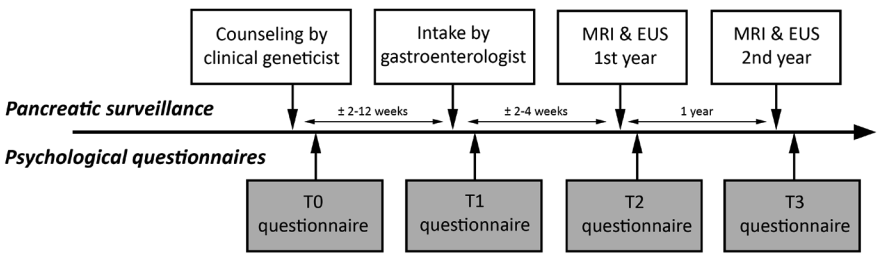


Figure 1. Overview of both the clinical part of the pancreatic cancer surveillance study and the timing of the psychological questionnaires.
MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography

All measurements used in the questionnaires were previously described [26]. We report here the results of the cancer-related worries as assessed with the eight-item cancer worry scale (CWS) [27, 28]. The items of the CWS are shown in Table 3. The total CWS-score ranges from 8 to 32, with higher scores indicating more frequent worries about cancer.

There is no clear cut-off point for the CWS-score, nevertheless, a score ≥ 14 could be indicative of moderate to high levels of cancer worries [29]. The Cronbach's alpha, a measure of internal consistency with values > 0.70 being considered acceptable, was high for the CWS in the current sample at T3 (0.86, n = 121).

The Ethical Committee of all participating centers approved the study protocol and the study was conducted in accordance with the declaration of Helsinki. All participants gave written informed consent prior to the performance of any study-related investigations.

Statistical analyses

Questionnaires were analyzed using descriptive statistics. Intra-individual change in cancer worries over time was assessed with a mixed-effect model (growth curve model) with a maximum likelihood estimator and unstructured covariance matrix. Univariate and multivariate regression analyses were performed to identify sociodemographic factors from the questionnaires T0, T1 and/or T2 that were associated with cancer worries at the second year of follow-up (T3). For these analyses, we selected all participants who returned the T3 questionnaire as well as at least a T0, T1 or T2 questionnaire. To analyze the impact on cancer worries of the detection of a pancreatic cystic lesion, a recommended shortened surveillance interval, and undergoing pancreatic surgery, we selected all participants who returned the questionnaire in the year of the event (i.e. the detection of a cyst and/or an advised shortened surveillance interval and/or undergoing pancreatic surgery; the questionnaire was sent after participants had received their surveillance results) and who returned the questionnaire 1 year before and/or 1 year after the event. A paired-samples *T* test was performed for these analyses. In all analyses, a *P*-value < 0.05 was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (version 21, SPSS Institute, Chicago, IL).

RESULTS

Participants' characteristics

In March 2015, 166 individuals participated in the questionnaire study. Baseline characteristics of all individuals are summarized in Table 2. Mean age of all 166 participants at inclusion in the clinical study was 51 years, of whom 47 (28%) were treated for cancer (predominantly for melanoma or breast cancer) prior to inclusion in the study.

Cancer worries

The scores per item on the CWS-questionnaires are shown in Table 3. The mean CWS-score was 14 at T0, 14 at T1, 13 at T2, and 12 at T3; the overall average CWS-score was 13.

Table 2. Baseline characteristics of study participants

	All individuals (n = 166) N (%)	Individuals with the T0, T1 and/or T2 AND the T3 questionnaire (n = 117) N (%)	Individuals without the T0, T1 and/or T2 NOR the T3 questionnaire (n = 49) N (%)	P-value (n = 117 vs n = 49)
Age at inclusion, mean (range, SD)	51 (19-73, 9.7)	51 (19-73, 9.5)	51 (30-72, 10.3)	0.894
Gender, male	68 (41%)	50 (43%)	18 (37%)	0.473
Genetic background				
Familial pancreatic cancer (FPC)	84 (51%)	60 (51%)	24 (49%)	
CDKN2A (FAMMM syndrome)	44 (27%)	32 (27%)	12 (25%)	
BRCA1 (HBOC)	2 (1%)	2 (2%)	0 (0%)	
BRCA2 (HBOC)	25 (15%)	17 (15%)	8 (16%)	
LKB1 (Peutz-Jeghers syndrome)	7 (4%)	4 (3%)	3 (6%)	
TP53 (Li Fraumeni syndrome)	4 (2%)	2 (2%)	2 (4%)	0.783
Number of PDAC cases in the family, mean (range, SD)	2 (0-7, 1.2)	2 (0-7, 1.2)	2 (0-5, 1.2)	0.202
Youngest family member affected by PDAC, mean (range, SD)	51 (21-89, 11.4)	51 (21-89, 11.4)	53 (40-80, 11.4)	0.357
Children				
Yes	136 (82%)	104 (89%)	32 (65%)	
No	20 (12%)	11 (9%)	9 (18%)	
No data	10 (6%)	2 (2%)	8 (16%)	**0.042**
Marital status				
Married / co-habiting / LAT relationship	129 (78%)	98 (84%)	31 (63%)	
Single / divorced / widowed	19 (11%)	11 (9%)	8 (16%)	
No data	18 (11%)	8 (7%)	10 (20%)	0.095
Level of education				
Primary school	3 (2%)	3 (3%)	0 (0%)	
High school	39 (24%)	27 (23%)	12 (25%)	
College / university	115 (69%)	85 (73%)	30 (61%)	
No data	9 (5%)	2 (2%)	7 (14%)	0.486

Table 2 (continued). Baseline characteristics of study participants

	All individuals (n = 166) N (%)	Individuals with the T0, T1 and/or T2 AND the T3 questionnaire (n = 117) N (%)	Individuals without the T0, T1 and/or T2 NOR the T3 questionnaire (n = 49) N (%)	P-value (n = 117 vs n = 49)
Smoking behavior				
Never smoker	85 (51%)	60 (51%)	25 (51%)	
Current or past smoker	67 (40%)	50 (43%)	17 (35%)	
No data	14 (8%)	7 (6%)	7 (14%)	0.580
Alcohol consuming				
Never consumer	37 (22%)	30 (26%)	7 (14%)	
Current or past consumer	114 (69%)	81 (69%)	33 (67%)	
No data	15 (9%)	6 (5%)	9 (18%)	0.230
Ever treated for cancer				
Any type of cancer	47 (28%)	35 (30%)	12 (25%)	
Melanoma	28 (17%)	20 (17%)	8 (16%)	
Breast cancer	13 (8%)	10 (9%)	3 (6%)	
Other	10 (6%)	9 (8%)	1 (2%)	0.479
Surveillance with				
EUS & MRI	159 (96%)	112 (96%)	47 (96%)	
EUS only	2 (1%)	2 (2%)	0 (0%)	
MRI only	5 (3%)	3 (3%)	2 (4%)	0.576

SD, standard deviation; FAMMM, familial atypical multiple mole melanoma; HBOC, hereditary breast and ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; LAT, living apart together; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging

Bold *P*-values are considered statistically significant

Table 3. Scores on the CWS-questionnaire, shown per item per questionnaire

Item During the last 7 days:	T0 n = 36 % often/ always worried	T1 n = 80 % often/ always worried	T2 n = 148 % often/ always worried	T3 n = 121 % often/ always worried	Average (on T0 to T3) % often/ always worried
How often have you thought about your chances of getting cancer (again)?	19	13	10	5	10
Have these thoughts affected your mood?	11	5	2	4	4
Have these thoughts interfered with your ability to do daily activities?	0	4	1	1	1
How concerned are you about the possibility of getting cancer one day?	33	26	26	19	25
How often do you worry about developing cancer?	25	11	13	7	12
How much of a problem is this worry?	11	6	5	3	5
How often do you worry about the chance of family members developing cancer?	28	25	20	12	20
How concerned are you about the possibility that you will ever need surgery (again)?	14	13	8	5	9
Mean CWS-score (range, SD)	14.4 (8-26, 4.3)	13.9 (8-26, 3.8)	13.3 (8-25, 3.4)	12.2 (8-25, 3.3)	13.2* (8-26, 3.6)

* significant (β = -0.84, ***P*** <0.001) intra-individual decrease over time (in comparison with first assessment (T0)), non-proportional analysis.
CWS, cancer worry scale; SD, standard deviation

We found a significant intra-individual decrease in the CWS-score over time (β = -0.84, ***P*** <0.001). Thirty-nine individuals (33%) had a CWS-score ≥ 14 in the second year of follow-up (T3), this was 51%, 52% and 43% at T0, T1 and T2, respectively.

Factors associated with cancer worries at the second year of follow-up

For these sub-analyses, we only included individuals with a T3 assessment, as well as at least a T0, T1 or T2 assessment. Of the 166 individuals that participated in the questionnaire study, 117 individuals returned the T3 questionnaire as well as at least a T0, T1 and/or T2 questionnaire (response 70%). Baseline characteristics for these 117 individuals selected for sub-analyses, and for the 49 individuals without the required questionnaires, are summarized in Table 2. The subgroup of 117 individuals only differed in comparison to the excluded individuals (n = 49) on having children (89% of the included individuals had children vs. 65% of excluded individuals, ***P*** = 0.04).

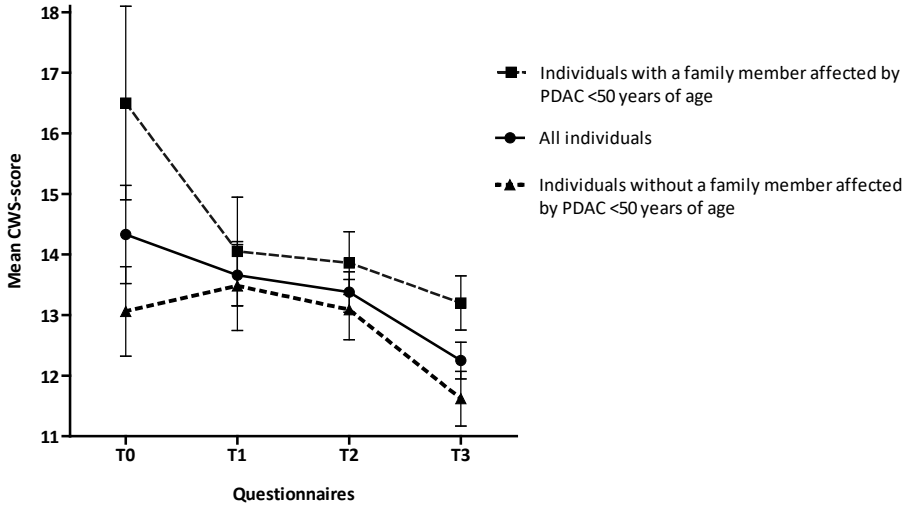
For the selection of possible predictors of cancer worries in the second year of follow-up (T3), we performed univariate regression analyses. Significant predictors were 'having a family member affected by PDAC below the age of 50' (β = 0.23, ***P*** = 0.01), and 'a perceived elevated risk of developing PDAC' (β = 0.23, ***P*** = 0.01). Not predictive were, amongst other factors, the number of PDAC-cases in the family and a personal history of cancer, see also Table 4. In the next step, the two significant predictors were included in the multivariate model, together with age, gender and genetic background. In this multivariate analysis (see Table 4), having a family member affected by PDAC below the age of 50 was associated with cancer worries in the second year of follow-up (β = 0.22, ***P*** = 0.03). Figure 2 shows the mean CWS-score per questionnaire for all individuals and for individuals with and without a family member affected by PDAC <50 years of age.

Table 4. Univariate and multivariate analysis for factors possibly associated with cancer worries in the second year of follow-up (T3)

Factors	N (%) / mean (range, SD)	Univariate analyses		Multivariate analysis	
		β	P-value	β	P-value
Age at inclusion, mean (range, SD)	51 (19-73, 9.5)	-0.142	0.126	0.010	0.924
Female gender	67 (57%)	0.140	0.133	0.119	0.215
Carriership of a gene mutation	57 (49%)	0.172	0.063	0.133	0.183
Number of PDAC cases in the family, mean (range, SD)	2 (0-7, 1.2)	0.058	0.538		
Having a family member affected by PDAC <50 years of age	45 (39%)	0.234	**0.016**	0.218	**0.031**
Having children	104 (89%)	0.033	0.723		
Being in a relationship	98 (84%)	-0.046	0.635		
Education at college/university-level	85 (73%)	-0.001	0.995		
Current or past smoker	50 (43%)	0.140	0.143		
Current or past alcohol consumer	81 (69%)	-0.031	0.744		
Personal history of any type of cancer	35 (30%)	0.048	0.610		
Body Mass Index, mean (range, SD)	25.8 (10.0-43.8, 4.6)	0.085	0.233		
Perception of moderately to strongly elevated risk of developing PDAC	69 (59%)	0.228	**0.013**	0.163	0.109
Previous psychological support	17 (15%)	0.181	0.053		
Having someone available to confide in	111 (95%)	-0.077	0.407		

SD, standard deviation; PDAC, pancreatic ductal adenocarcinoma
Bold ***P***-values are considered statistically significant

Figure 2. Mean CWS-scores at different moments in time, shown for all individuals and for individuals with and without a family member that was affected by pancreatic cancer under 50 years of age



CWS, cancer worry scale; PDAC, pancreatic ductal adenocarcinoma

Impact of the detection of a pancreatic cystic lesion on cancer worries

In 93 out of all the 166 participants (56%), a pancreatic cystic lesion was detected during surveillance. Forty of these 93 individuals (43%) returned the questionnaire the year prior to the detection of the cystic lesion (mean CWS-score 13.3, standard deviation (SD) 3.6), as well as the questionnaire in the year of the detection of the lesion (mean CWS-score 12.5, SD 3.7). The difference in mean CWS-score was not statistically significant (95% CI for the difference -0.3 to 1.9, P = 0.163). A total of 45 individuals (48%) returned the questionnaire in the year of detection (mean CWS-score 11.9, SD 3.5) as well as the questionnaire 1 year after detection (mean CWS-score 11.9, SD 3.4). Again, the difference in mean CWS-score between the 2 years was not statistically significant (95% CI for the difference -1.1 to 1.1, P = 0.97).

Impact of a recommended shortened surveillance interval on cancer worries

For 25 out of 166 individuals (15%), a shortened surveillance interval was recommended; for 16 individuals an interval of 3 months and for nine individuals an interval of 6 months. Six of these 25 individuals (24%) returned the questionnaire in the year prior to the shortened surveillance interval (mean CWS-score 14.3, SD 3.8), as well as in the year of the shortened surveillance interval (mean CWS-score 15.5, SD 4.7). The difference in mean CWS-score of 1.2 points was not significant (95% CI for the difference -3.9 to 1.6, P = 0.33). Nine individuals (36%) returned the questionnaire in the year of the shortened

surveillance interval (mean CWS-score 14.4, SD 5.2), as well as in the year after (mean CWS-score 12.2, SD 4.5). This decrease in mean CWS-score by 2.2 points was also not statistically significant (95% CI for the difference -1.0 to 5.4, ***P*** = 0.15).

Impact of pancreatic surgery on cancer worries

In 7 out of 166 individuals (4%), pancreatic surgery was performed. Two of these individuals returned both the questionnaire from the year prior to surgery (mean CWS-score 10.5, SD 3.5), as well as the post-operative questionnaire in the year of surgery (mean CWS-score 11.0, SD 0.0). The difference in mean CWS-score was not statistically significant (***P*** = 0.87). Four cases returned both the questionnaire in the year of surgery (mean CWS-score 14.0, SD 3.5), as well as the questionnaire in the year after surgery (mean CWS-score 11.8, SD 3.9). This decrease in score by 2.2 points was not statistically significant (95% CI for the difference -7.9 to 12.4, ***P*** = 0.53).

DISCUSSION

In this prospective multicenter study, we assessed the course of cancer worries over a 2-year period in high-risk individuals participating in annual PDAC-surveillance, assessed demographic baseline and psychosocial factors that could be associated with these cancer worries, as well as the impact of three clinical events on cancer worries. Independently associated with cancer worries in the second year of follow-up was having a family member that was affected by PDAC below the age of 50.

Because PDAC-surveillance is being performed more and more worldwide, it is key to take into account the psychological aspects of repeated participation. Although we previously reported a low general psychological burden of annual participation in PDAC-surveillance [26], 33% of participants did have cancer-specific worries with a CWS-score ≥ 14. While this is not a rigorously tested cut-off point and there are no norm-data on cancer worries in the general population, a score ≥ 14 is considered to be indicative of moderate to high cancer worries [29]. It is important to adequately and timely identify these individuals with cancer worries, because they would likely benefit from psychosocial support to decrease or prevent psychological distress. Psychosocial interventions, varying from psycho-education and mindfulness-training to cognitive behavioral therapy, have been proven to be effective in reducing levels of distress to such levels that patients can perform their daily activities.

Therefore, this study focused on cancer worries during PDAC-surveillance, more specifically on the course of cancer worries over time, on predictors of cancer worries, and on cancer worries during certain events. To our current knowledge, this is the first study

with a prospective design assessing these characteristics of cancer worries in individuals at inherited or familial high risk of developing PDAC over time. Although much research was done into generalized distress and levels of cancer worries, factors influencing cancer worries were hardly studied in populations at inherited high risk of developing other types of cancer [28, 30-34]. Sociodemographic and clinical variables found to be significantly associated with cancer-specific distress for familial adenomatous polyposis (FAP) were lower educational level, female gender, diagnosis of FAP (as opposed to being at risk for FAP or being a non-carrier), having a personal history of cancer, and having had surgery more than 10 years ago [28]. In individuals with Lynch syndrome, however, no difference for age, gender, level of education, actual or perceived risk of Lynch syndrome, or a personal history of cancer was found [30]. In a Von Hippel-Lindau (VHL) population, factors associated with VHL-related worries were diagnosis of, or treatment for, VHL, a high level of social constraint, a high perceived risk of developing tumors, and the loss of a close relative due to VHL during adolescence [31].

As in our previous study [26], individual cancer worries decreased over the 2-year period of surveillance in high-risk individuals for PDAC. We identified a perceived elevated risk of developing PDAC and having a family member that was affected by PDAC under 50 years of age as factors associated with cancer worries in the second year of follow-up, the latter being independently associated. Both factors resemble the findings by Lammens et al. [31], who described a high perceived risk of developing tumors and the loss of a close relative during adolescence as related to cancer-specific worries.

Surprisingly, a factor not associated with high cancer worries, was a personal history of cancer. This factor was previously described as associated with high cancer worries [28], and one might expect individuals who already had cancer in the past to be more anxious of developing cancer again, especially when being at high risk of this. Educational level was also not associated with high cancer worries at the second year of follow-up, in contrast to a previous study in FAP-individuals [28].

We also assessed three clinical events for association with increased cancer worries: the detection of a cystic lesion, a recommended shortened surveillance interval, and undergoing pancreatic surgery. For all three events, we did not find a significant change in CWS-score for the year prior to the event and/or the year after the event in comparison to the year of the event. However, the CWS-score in participants with a recommended shortened surveillance interval did differ considerably between that year and the year after the event, and so did the CWS-score in the individuals who underwent surgery. This suggests that a shortened surveillance interval and pancreatic surgery cause a decrease in CWS-score the year after, possibly due to relief at follow-up, however, our sample size for these sub-

analyses (n = 9 and n = 4) were likely too small to find a statistically significant difference, which is also demonstrated by the large 95% confidence interval for the differences in CWS-scores.

This study has several strengths. The prospective design in a large group of individuals at high risk of developing pancreatic cancer is unique and of great scientific value. However, this study also has some limitations, one of which might be the power for our sub-analyses on clinical factors. Therefore, to draw definite conclusions on these factors, a larger study sample is needed. Also, because the questionnaire study was added after the first inclusion period of the original clinical study protocol, some participants had already had their first investigations and therefore started their questionnaires at T2, which resulted in a relatively low number of available T0 questionnaires in the analyzed cohort.

In conclusion, this prospective questionnaire study identified the factor 'having a family member affected by PDAC < 50 years of age' to be associated with cancer worries in the second year of follow-up in individuals at inherited or familial high risk of developing PDAC who are participating in annual surveillance. Recognizing this factor can help clinicians to timely identify individuals 'at risk' of a high level of cancer worries whom would likely benefit from psychosocial support to decrease or prevent psychological distress.

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PART III

Summary, general discussion and appendices

Chapter 8

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

Pancreatic cancer remains one of the most fatal human malignancies. Despite improvements in surgical techniques and (neo)adjuvant therapies, survival rates have not improved during the last decades. Survival rates are strongly dependent on the stage of pancreatic cancer. These poor survival rates are at least partly due to the late onset of symptoms, leading to only 8-27% of all patients to present with localized curable disease. Because of the poor prognosis once pancreatic cancer has become symptomatic, there is great interest in the prevention of pancreatic cancer. Primary prevention strategies, such as lifestyle changes to reduce the number of risk factors (e.g. smoking, excessive alcohol consumption, obesity and dietary factors), are difficult for most people to implement and adhere to. Secondary prevention strategies (the diagnosis and treatment of advanced precursor lesions or early stage of pancreatic cancer before it causes significant morbidity), however, might contribute to the prevention of pancreatic cancer and hence improvement of pancreatic cancer survival. Currently, several studies are being performed to assess the feasibility of a pancreatic cancer surveillance program. Screening of the general population is not feasible as we currently lack a simple, reliable and inexpensive screening tool. However, evidence is starting to accumulate that screening might be worthwhile when offered to individuals at high risk of developing pancreatic cancer. High-risk individuals include mutation carriers of pancreatic cancer-prone gene mutations (e.g. *CDKN2A*, *BRCA1*, *BRCA2*, *STK11/LKB1*) and relatives of patients with familial pancreatic cancer. The risk of developing pancreatic cancer within these well-defined populations of high-risk individuals is estimated to be at least 10-fold increased compared to the general population and exceeds 76-fold in selected cases. This thesis reported on different aspects of such pancreatic cancer surveillance programs.

Part one of this thesis focused on the clinical aspects of surveillance.

Both endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) are frequently used as imaging modality in pancreatic cancer surveillance. However, hardly any study compared the diagnostic yields of both modalities in a blinded fashion and thus it is unclear whether one of both modalities would suffice or if both tests are complimentary. Therefore, in **chapter 2**, we performed a multicenter comparative blinded analysis on the yield of both EUS and MRI. We performed a blinded multicenter study in 139 Dutch high-risk individuals undergoing first-time screening of the pancreas. Participating gastroenterologists and radiologists were blinded to the baseline results of either EUS or MRI imaging. To compare both imaging test results, a percentage agreement was calculated for the detection and location of lesions, and a Spearman's rho correlation coefficient was calculated for the size of lesions.

We revealed that EUS and/or MRI detected clinically relevant pancreatic lesions in 6% of participants of surveillance (in 9 out of 139 high-risk individuals). Eleven clinically relevant lesions were detected: two solid lesions and 9 cystic lesions ≥10 mm in size. Of all 11 clinically relevant lesions, six (55%) were detected by both modalities. EUS detected a total of 8 (73%) and MRI detected a total of 9 (82%) clinically relevant lesions. Both solid lesions were detected by EUS only and proved to be a stage I pancreatic cancer and a multifocal PanIN-2. Of the 9 cysts ≥10 mm, six were detected by both imaging techniques and three were detected by MRI only. The agreement between EUS and MRI for the detection of clinically relevant lesions was only 55%. However, there was a perfect agreement between EUS and MRI for location of clinically relevant lesions and a substantial to almost perfect agreement between EUS and MRI on the size of clinically relevant lesions (Spearman's rho correlation coefficient of 0.638). This led us to conclude that both imaging modalities were complementary rather than interchangeable: contrary to EUS, MRI was found to be very sensitive for the detection of cystic lesions of any size, MRI however might have some important limitations with regard to the timely detection of solid lesions. Therefore, for future screening and surveillance we will continue to use both imaging modalities.

Frequent high-resolution imaging of the pancreas reveals frequent detection of cystic lesions, as also shown in chapter 2. Studies on pancreatic cancer surveillance show cystic lesions of the pancreas to be present in up to 42% of high-risk individuals, whereas the prevalence of pancreatic cysts in the general population is estimated to be only 0-10% depending on age. However, it is still unclear whether the prevalence and growth characteristics of cystic lesions are equal within the two distinct high-risk groups (mutation carriers versus individuals with a strong family history of pancreatic cancer (FPC individuals)). Therefore, in **chapter 3**, we evaluated the prevalence and progression of these cystic pancreatic lesions in the two distinct high-risk groups for developing pancreatic cancer. We extracted data from our ongoing pancreatic cancer surveillance study on the detected cystic lesions at diagnosis and follow-up. Cystic lesions were highly prevalent, a total of 100 (54%) of the 186 individuals included had at least one pancreatic cystic lesion. Cystic lesions ≥10 mm in size were more prevalent in FPC individuals (in 14 of 88 FPC individuals, 16%) than in mutation carriers (5 of 98 mutation carriers, 5%), even after adjusting our analysis for the statistically significant older age of the FPC individuals (***P***=0.045). Only 7 lesions showed progression during follow-up; 4 lesions grew ≥4 mm and 3 lesions developed worrisome features. Only 1 of these lesions that progressed was in a FPC individual, all 6 other progressed lesions were detected in mutation carriers. Two of these 7 lesions that progressed were found to be pancreatic cancer, both in mutation carriers.

The higher prevalence of cystic lesions in FPC individuals is unexpected. Because of the presumed autosomal dominant inheritance pattern observed in FPC families, half of the

FPC individuals probably do not carry a gene mutation and will therefore also not be at increased risk of developing pancreatic cancer. This is in contrast to our proven mutation carriers in whom an increased risk of pancreatic cancer was confirmed by genetic testing. Therefore, the higher prevalence of cystic lesions in FPC individuals might be indicative of a difference in pathophysiology or in molecular subtypes of pancreatic cancer between the 2 high-risk groups. An even more important observation, however, is the fact that almost no progression of cystic lesions was seen in FPC individuals (no single pancreatic cancer developed within the FPC cohort), whereas lesions in mutation carriers did progress in a significant proportion of individuals (pancreatic cancer incidence 2%). This difference in progression between the 2 groups eventually might have important implications for surveillance strategies, such as applying different strategies with shorter or longer surveillance intervals between groups which would not only tailor the intensity and burden of surveillance according to the actual risk, but also facilitates a cost-effective utilization of limited and costly health care resources.

Except from the frequent detection of pancreatic cystic lesions during pancreatic cancer surveillance, as shown in chapter 3, features of chronic pancreatitis are also frequently detected by EUS. The clinical significance of these features of chronic pancreatitis in asymptomatic individuals is still unclear, but research did suggest that these features might be related to emerging PanIN and IPMN lesions, both possible precursor lesions to pancreatic cancer. Therefore, in **chapter 4**, we focused our research on these features of chronic pancreatitis which we longitudinally assessed. We included all individuals that were participating in pancreatic cancer surveillance in the Erasmus University Medical Center Rotterdam for whom two EUS videos were available 3 years apart (2012 and 2015). Two highly experienced endosonographers reassessed the anonymized videos for features of chronic pancreatitis separately, after which a consensus meeting was held to discuss individuals in whom there was a difference in scored features. Forty-two videos from 21 individuals were reviewed.

Review of the EUS videos showed features of chronic pancreatitis to be highly prevalent: 86% (in 2012) and 81% (in 2015) of individuals had at least one feature of chronic pancreatitis detected by EUS. This prevalence is much higher than described in a non-high-risk cohort (17%). This causes the alleged association between (progression) of specific EUS features and presence of PanIN or IPMN lesions to bear particular interest. We performed interobserver agreement analyses, which showed an almost perfect agreement at 83%. We also performed univariate and multivariate analyses regarding possible risk factors associated with the detection of a mean of ≥4 features of chronic pancreatitis. Univariate analysis identified 'age of the youngest relative affected by pancreatic cancer' as the only risk factor (P=0.002), but it was not sustained after multivariate analysis. We also assessed

intra-individual change in the detected features of chronic pancreatitis over time. Except for hyperechoic foci without shadowing, which decreased intra-individually (β=-1.6, ***P***=0.006), the features did not change in the 3 years of follow-up. To our knowledge, this is the first study to assess intra-individual change over time in detected features of chronic pancreatitis. Although the features did not change in the 3 years of follow-up, we must keep in mind that the development and progression of precursor lesions into pancreatic cancer may take multiple years. Longer follow-up and, if available, pathological examination of pancreatic resection specimens will be essential to understanding the relationship between these features of chronic pancreatitis and development of malignancy, and whether detection of these features bears clinical relevance, for example, in setting the indication for resection or serving as a criterion of influence in determining the screening interval.

Pancreatic cancer surveillance will yield highly suspicious lesions for which surgery is performed, even in the absence of confirmatory cytology or histology. Since little is known about the surgical pathology findings of high-risk individuals who have undergone surgery, in **chapter 5**, we focused our research on the diagnostic yield and outcomes of high-risk individuals who underwent surgical resection or progressed to invasive cancer while participating in pancreatic cancer surveillance. We used data from 11 prospective surveillance programs across the world (United States of America, The Netherlands, Italy and Israel), using the CAncer of the Pancreas Screening (CAPS) collaboration which was formed in 2010 to help organize global research on pancreatic cancer surveillance. We gathered data of a total of 76 high-risk individuals of whom 71 underwent surgery and of whom 5 were diagnosed with advanced irresectable disease. High-risk neoplastic lesions (defined as PanIN-3 lesions, branch-duct IPMNs with high-grade dysplasia, main-duct IPMNs and pancreatic cancers) were present in 32 (45%) of the 71 resection specimens. We found four pre-operative factors to be associated with high-risk neoplastic lesions or pancreatic cancer: age ≥ 65 at the time of surgery, female gender, carriage of a mutation in a known pancreatic cancer susceptibility gene, and location of a lesion in the head/uncinate region of the pancreas. Survival between individuals with no or low-risk neoplastic lesions versus individuals with high-risk neoplastic lesions did not differ significantly. Survival worsened with advancing stage of pancreatic cancer. This result support the intent and pursuit of pancreatic cancer surveillance programs to detect and resect advanced neoplastic lesions before they have developed into pancreatic cancer. While all screening programs carry the risk of overtreatment, our results suggest that surveillance of high-risk individuals leads to the treatment of an acceptable mix of lesions. More research is needed to better understand the risk factors for individuals at high risk of developing pancreatic cancer, and importantly to improve selection of individuals for surgery. Collaborating internationally in large worldwide prospective studies is of high importance due to the small number of interventions at any individual center.

Part two of this thesis focused on the psychosocial aspects of surveillance.

When assessing the successfulness of a surveillance program, importantly, we should not only focus on clinical results, but also on the psychological aspects of repeated participation in such a program because it will have an important effect on the participation rate and adherence to surveillance. As surveillance entails long-term participation and repeated exposure to investigations, longer follow-up studies are required. There were no prospective studies with more than 12 months of follow-up assessing the feasibility of pancreatic cancer surveillance from a psychological point of view. Therefore, in **chapter 6**, we analyzed data from our ongoing prospective multicenter psychological questionnaire study in which participants were, at that date, followed with questionnaires for at least 3 years. Participants received a first questionnaire on background data after having undergone counseling by the clinical geneticist, a second questionnaire after having received the explanation of study procedures by the gastroenterologist, and thereafter annually after having received their surveillance results. Of the 152 individuals who have been participating in pancreatic cancer surveillance in the our study since its start in 2008, 140 individuals (92%) returned one or multiple completed questionnaires. In total, 477 questionnaires were received and analyzed. The most frequently reported motivation for participating in pancreatic cancer surveillance was that cancer might be detected early (checked in an average of 98% of all instances). For as much as 87% of respondents, the advantages of surveillance outweigh the disadvantages, and the majority of respondents (79%) feel reassured after their follow-up visit. Only a minority of respondents are nervous before their follow-up visit or dread the visit (14% and 13%, respectively). Both MRI and EUS are experienced as uncomfortable by only the minority of respondents (10% and 11%, respectively). Only 3% of respondents dread their first MRI versus 34% of respondents dreading their first EUS. However, once experienced, the percentage of respondents dreading their next EUS dropped significantly ($p < 0.001$) to the same level as that of the MRI (6–9% and 0–8%, respectively). Few respondents experience worries about cancer, and the mean level of worries decreases even further

each year of participation. The percentage of individuals with clinical relevant levels of anxiety and depression is low and stable over a 3-year period. Thus, this study shows that pancreatic cancer surveillance is well feasible from a psychological point of view, as the psychological burden of participation in a pancreatic cancer surveillance program is low.

Although we reported in chapter 6 that repeated participation in annual surveillance imposed low psychological burden, we did find that a third of the participants had moderate to high cancer worries. As individuals with high levels of cancer worries might benefit from psychosocial support, it could be essential to adequately and timely identify the

individuals with high cancer worries. Therefore, in **chapter 7**, we further investigated cancer worries using the cancer-worry-scale questionnaire. More specifically, we focused on the course of cancer worries over time, on predictors of cancers worries, and on cancer worries during certain events. We analyzed questionnaires of 166 participants. The mean cancer-worry-scale score was quite low at 14, which decreased intra-individually over the two year course of time. The detection of a pancreatic cystic lesion during surveillance did not impact on cancer worries significantly. There was a trend towards more cancer worries when a shortened surveillance interval was recommended and when surgery was recommended, however, the difference was not statistically significant which is probably due to small sample sizes. Multivariate analysis showed that having a family member affected by pancreatic cancer below the age of 50 was associated with cancer worries in the second year of follow-up. Recognizing this factor can help clinicians to timely identify individuals ´at risk´ of a high level of cancer worries whom would likely benefit from psychosocial support to decrease or prevent psychological distress.

Future perspectives

The decisive question is whether screening and surveillance programmes ultimately improve the overall survival rate of individuals at high risk for the development of pancreatic cancer. Based on present studies, it is not possible to draw a definite conclusion about the (potential) merits of surveillance to prevent pancreatic cancer death. To definitely answer this question more research is required with careful long-term follow-up of affected individuals within well-defined research programmes. Pooling of data from various (international) cohorts will be needed to acquire sufficient numbers for meaningful statistical analysis and accurate estimates of risk reduction and survival benefit.

Future research should not only focus on the use of imaging modalities, but also on the application of biomarkers. Numerous efforts have been undertaken in the last years to identify biomarkers that are reliable in diagnosing pancreatic cancer. At present, biomarkers have a limited role in diagnosing early stage pancreatic cancer, partly due to the low specificity and sensitivity of the currently available markers. Combining markers, or identifying (new) specific biomarkers from bodily secretions such as pancreatic juice obtained during endoscopic ultrasonography should be further researched. Such quest should not only focus on identifying (early) pancreatic cancer, but also on the detection of precursor lesion such as high-grade dysplastic PanIN or high-grade dysplastic IPMN as these lesions represent the ideal target for surgical resection. Sequential collection of pancreatic juice during the annual EUS investigations and following biomarker expression over time seems promising.

Future research should also be directed towards a better understanding of the risk of individuals on developing pancreatic cancer, especially in the individuals in which there is a strong family history of pancreatic cancer but no gene mutation was found. Whole genome sequencing might be able to detect additional pancreatic cancer-prone gene mutations in these individuals which could lead to a better surveillance strategy according to the actual risk, and thus could facilitate a better and more cost-effective utilization of limited health care resources.

Chapter 9

Samenvatting en discussie

SAMENVATTING EN DISCUSSIE

Pancreascarcinoom blijft één van de dodelijkste vormen van kanker. Ondanks verbeteringen in chirurgische technieken en (neo)adjuvante behandelingen is de overleving van pancreascarcinoom de laatste decennia nauwelijks verbeterd. De overleving is sterk afhankelijk van het stadium van pancreascarcinoom ten tijde van diagnose. De slechte overleving wordt dan ook deels verklaard door het laat ontstaan van symptomen waardoor slechts 8-27% van de patiënten gediagnosticeerd wordt in een stadium met beperkte lokale ziekte waarbij er nog curatieve opties bestaan. Door de slechte prognose zodra pancreascarcinoom eenmaal symptomatisch is, is er veel interesse in de preventie van pancreascarcinoom. Primaire preventie strategieën, zoals verandering van leefstijl om het aantal risicofactoren te verminderen (bv roken, excessief alcoholgebruik, obesitas en dieetfactoren), blijkt voor veel mensen lastig te implementeren en ook vol te houden. Secundaire preventie strategieën (de diagnose en behandeling van gevorderde voorloperstadia of een vroeg stadium van pancreascarcinoom voordat het significante morbiditeit geeft) kunnen wel bijdragen aan de preventie van pancreascarcinoom en daarmee de overleving van pancreascarcinoom. Onderzoek van de gehele populatie zal echter niet haalbaar zijn gezien het gebrek aan een gemakkelijke, betrouwbare en betaalbare diagnostische test. Echter, er begint zich steeds meer bewijs op te bouwen dat surveillance wel zinvol kan zijn wanneer het aangeboden wordt aan individuen met een hoog risico op het ontwikkelen van pancreascarcinoom, zoals dragers van een mutatie in een gen dat het risico op pancreascarcinoom verhoogd en verwanten van patiënten met een familiair pancreascarcinoom. **Hoofdstuk** 1 gaat dieper in op de verschillende risicogroepen, op de mogelijke testen die te gebruiken zijn voor surveillance en de doelen van surveillance. Daarna is dit proefschrift opgedeeld in twee delen.

Deel één van dit proefschrift richt zich op verschillende klinische aspecten van surveillance.

Momenteel worden endo-echografie (EUS) en MRI frequent gebruikt als beeldvormende technieken voor surveillance op pancreascarcinoom. Echter, er zijn nauwelijks geblindeerde vergelijkende studies beschikbaar welke de twee technieken met elkaar vergelijken ten aanzien van hun geschiktheid om te gebruiken in surveillance. In **hoofdstuk 2** worden de resultaten beschreven van het geblindeerd en vergelijkend onderzoek tussen EUS en MRI in 139 individuen met een verhoogd risico op het ontwikkelen van pancreascarcinoom. De deelnemers ondergingen zowel een EUS als een MRI waarbij zowel de endo-echografist als de radioloog werden geblindeerd voor de uitslag van de andere beeldvormende techniek, waarna de uitslag met elkaar werd vergeleken. De overeenkomst in de detectie van klinisch relevante laesies was slechts 55%. Daarbij bleek de MRI erg gevoelig voor het aantonen van pancreascystes, echter, werden twee solide laesies, waarvan één een pancreascarcinoom

en de ander een PanIN-2 laesie, enkel door de EUS gedetecteerd. Hieruit is te concluderen dat beide technieken elkaar aanvullen, vandaar dat ook voor toekomstige surveillance beide beeldvormende technieken gebruikt zullen blijven worden.

Frequente hoog-resolutie beeldvorming van het pancreas laat frequente detectie van cysteuze laesies zien, zoals ook in hoofdstuk 2 beschreven werd, met een veel hogere incidentie in hoog-risico individuen dan in de algemene bevolking. Echter, het is nog onduidelijk of de prevalentie en de groeikarakteristieken van deze cysteuze laesies vergelijkbaar zijn in de twee risicogroepen (mutatiedragers versus individuen met een familiaire belasting (FPC individuen)). Daarom hebben we dit in **hoofdstuk 3** verder onderzocht. Er bleek een hoge prevalentie van cysteuze laesies: 54% van de 186 deelnemers had een pancreascyste. Cystes ≥10 mm waren statistisch significant prevalenter in FPC individuen dan in mutatiedragers (16 versus 5%). Slechts 7 laesies toonden progressie: 4 laesies groeiden ≥4mm en 3 laesies ontwikkelden 'worrisome features'. Slechts 1 van deze 7 laesies werd gevonden in een FPC individu, alle andere 6 laesies die progressie vertoonden werden gevonden in mutatiedragers, waarvan 2 laesies pancreascarcinoom bleken te betreffen. Er zijn dus meer cystes in de FPC individuen echter met nauwelijks progressie, terwijl de cystes in mutatiedragers frequenter progressie vertoonden. Dit verschil tussen de beide risicogroepen kan belangrijke implicaties hebben voor de surveillance strategie, zoals bijvoorbeeld het toepassen van verschillende strategieën met kortere of langere surveillance intervallen afhankelijk van het daadwerkelijke risico op ontaarding in maligniteit.

Naast de frequente detectie van pancreascysten worden tevens frequent tekenen van chronische pancreatitis beschreven tijdens de EUS. Ook hiervan is nog onduidelijk wat de betekenis is in deze asymptomatische individuen, echter in de literatuur is eerder gesuggereerd dat deze tekenen gerelateerd kunnen zijn aan ontwikkelende PanIN en IPMN laesies, beiden mogelijke voorlopers van pancreascarcinoom. Daarom hebben we in **hoofdstuk 4** deze kenmerken van chronische pancreatitis verder onderzocht. Twee ervaren endo-echografisten hebben de 42 opgenomen video's van de EUS-onderzoeken in het Erasmus MC van 2012 en 2015 beoordeeld op kenmerken van chronische pancreatitis. Kenmerken van chronische pancreatitis bleken zeer frequent aanwezig (in 81-86% van de individuen) waarbij de interobserver agreement goed was (83%). Er was geen progressie van tekenen van chronische pancreatitis over de 3 jaar aan follow-up. Langere follow-up en, indien beschikbaar, resectiepreparaten van het pancreas zijn essentieel om verdere duidelijkheid te verkrijgen over de klinische relevantie van de bevinding van tekenen van chronische pancreatitis.

Surveillance van het pancreas brengt ook voor maligniteit verdachte laesies aan het licht waarvoor resectie wordt verricht. Er is echter nog weinig bekend over de uitkomsten na

chirurgie en de pathologische bevindingen in het resectiepreparaat in deze groep individuen. In **hoofdstuk 5** wordt er verder ingegaan op de resultaten van 76 hoog-risico individuen die werden geopereerd vanwege een voor maligniteit verdachte afwijking (n=71) of werden gediagnosticeerd met gemetastaseerd pancreascarcinoom (n=5) tijdens deelname aan surveillance. De resultaten van deze individuen werden verzameld via het CAncer of the Pancreas Screening (CAPS) samenwerkingsverband welke in 2010 werd opgericht om pancreassurveillance wereldwijd te coördineren. Hoog-risico neoplastische laesies (gedefinieerd als PanIN-3 laesies, branch-duct IPMNs met hooggradige dysplasie, main-duct IPMNs en pancreascarcinoom) bleken aanwezig in 32 (45%) van de 71 resectiepreparaten. Vier preoperatieve factoren waren gerelateerd aan deze hoog-risico neoplastische laesies, namelijk leeftijd ≥65 jaar ten tijde van chirurgie, vrouwelijk geslacht, mutatiedragerschap en locatie van de laesie in de kop/uncinatus van het pancreas. De overleving van individuen met hoog-risico neoplastische laesies verschilde niet van degenen zonder laesies of met laag-risico neoplastische laesies. De overleving verslechterde wel met vorderend stadium van pancreascarcinoom. Deze resultaten ondersteunen het streven naar detectie van voorlopers van pancreascarcinoom middels surveillance.

Deel twee van dit proefschrift richt zich op de psychosociale aspecten van surveillance.

Wanneer de haalbaarheid van een surveillance programma wordt beoordeeld, moet er niet alleen op de klinische aspecten en resultaten gelet worden, maar is ook de psychologische belasting van deelname aan surveillance erg belangrijk aangezien dit de deelname en trouw aan surveillance zal beïnvloeden. In **hoofdstuk 6** worden de resultaten van de psychosociale vragenlijststudie beschreven waarin op dat moment 3 jaar aan follow-up vragenlijsten beschikbaar was. Deelnemers kregen een vragenlijst na hun bezoek aan de klinisch geneticus, na hun bezoek aan de MDL-arts met uitleg over deelname aan pancreassurveillance in studieverband en daarna elk jaar na de jaarlijkse onderzoeken met EUS en MRI. De deelname aan de vragenlijststudie was erg hoog (92%). Voor maar liefst 87% van de participanten wogen de voordelen van surveillance op tegen de nadelen en de meerderheid (79%) van de deelnemers voelde zich elk jaar gerustgesteld na het follow-up bezoek. Een klein deel van de respondenten (13%) zag op tegen de jaarlijkse onderzoeken en slechts een klein deel ervoer de MRI en EUS als oncomfortabel (respectievelijk 10 en 11% van de deelnemers). Er waren lage scores met betrekking tot zorgen omtrent kanker en met betrekking tot depressiviteit en angst. Deze resultaten tonen dat surveillance van het pancreas vanuit psychosociaal oogpunt haalbaar lijkt.

Toch viel op dat enkele individuen vrij veel zorgen omtrent kanker hadden. Dit wordt in **hoofdstuk 7** verder onderzocht aangezien deze individuen baat zouden kunnen hebben bij psychosociale begeleiding. De cancer-worry scale vragenlijst werd geanalyseerd, waarbij

de gemiddelde score laag was en er sprake was van een intra-individuele daling over een tijd van 2 jaar aan follow-up. Daarbij leek er sprake te zijn van meer zorgen wanneer er een verkort surveillance interval werd geadviseerd en ook wanneer er een operatie werd geadviseerd, echter, de aantallen waren te klein om hier een statistisch significant verschil in aan te tonen. Multivariate analyse toonde wel dat de respondenten met een familielid bij wie op een leeftijd jonger dan 50 jaar pancreascarcinoom was vastgesteld hogere zorgen omtrent kanker hadden. Met name deze deelnemers zouden baat kunnen hebben bij psychosociale begeleiding.

In **hoofdstuk 8** worden de belangrijkste bevindingen uit dit proefschrift samengevat en aanbevelingen voor toekomstig onderzoek beschreven.

Chapter 10

Appendices

ABBREVIATIONS

5-FU	5-fluorouracil
APC	Adenomatous polyposis coli
ATM	Ataxia telangiectasia mutated
BD-IPMN	Branch-duct intraductal papillary mucinous neoplasm
BMI	Body mass index
CA 19-9	Cancer antigen 19-9
CAPS	Cancer of the pancreas screening
CEA	Carcino-embryonal antigen
CI	Confidence interval
CMM	Cutaneous malignant melanoma
CP	Chronic pancreatitis
CT	Computed tomography
CWS	Cancer worry scale
ERCP	Endoscopic retrograde cholangiopancreaticography
EUS	Endoscopic ultrasonography
EUS-FNA	Endoscopic ultrasonography-guided fine needle aspiration
F	Female
FAMMM	Familial atypical multiple mole melanoma
FAP	Familial adenomatous polyposis
FDG-PET	18F-fluorodeoxyglucose positron emission tomography
FDR	First-degree relative
FPC	Familial pancreatic cancer
FU	Follow-up
GI	Gastrointestinal
HADS	Hospital anxiety and depression scale
HBOC	Hereditary breast and ovarian cancer
HP	Hereditary pancreatitis
HRI	High-risk individual
HRN	High-risk neoplastic precursor lesion
IPMN	Intraductal papillary mucinous neoplasm
LAT	Living apart together
M	Male
MB-IPMN	Main-branch intraducatl papillary mucinous neoplasm
MCN	Mucinous cystic neoplasm
MDCT	Multi detector computed tomography
MD-IPMN	Main-duct intraductal papillary mucinous neoplasm
MMR	Mismatch repair genes
Mo	Month
MPD	Main pancreatic duct

MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
N/A	Not applicable
No	Number
OR	Odds ratio
PanIN	Pancreatic intraepithelial neoplasia
PanNET	Pancreatic neuroendocrine tumor
PC	Pancreatic cancer
PDAC	Pancreatic ductal adenocarcinoma
PET	Positron emission tomography
PJS	Peutz-Jeghers syndrome
RR	Relative risk
SB-IPMN	Side-branch intraductal papillary mucinous neoplasm
SDR	Second-degree relative
SE	Standard error
SIR	Standardized incidence ratio
SPSS	Statistical package for the social sciences
VHL	Von Hippel-Lindau
y	Year

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Surveillance voor familiair pancreascarcinoom. EUS platform, Amersfoort, The Netherlands.	2015	1.0
Higher prevalence of cystic lesions of the pancreas in first degree relatives of familial pancreatic cancer cases than in carriers of pancreatic cancer-prone gene mutations. Digestive Disease Week, Washington DC, USA.	2015	1.0
Detection and treatment of pancreatic cancer and high-grade precursor lesions in high-risk individuals undergoing surveillance: results from the international CAPS Consortium Registry. Digestive Disease Week, San Diego, USA. Awarded with the Certificate of Recognition for the Scientific Accomplishment as an Early Stage Investigator.	2016	1.0
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CURRICULUM VITAE

Ingrid Konings werd op 3 augustus 1986 geboren te Roosendaal. In 2004 behaalde zij het gymnasium diploma aan het Markland College te Oudenbosch. In datzelfde jaar begon zij met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. In 2010 behaalde zij haar artsexamen en doctoraal diploma nadat ze haar afstudeeronderzoek naar postoperatieve infecties na levertransplantatie in het Erasmus Medisch Centrum, Rotterdam, had afgerond. Aansluitend werkte zij in het Albert Schweitzer ziekenhuis te Dordrecht als ANIOS interne geneeskunde. In 2013 startte zij met het promotieonderzoek zoals in dit proefschrift beschreven op de afdeling Maag-, Darm- en Leverziekten in het Erasmus Medisch Centrum, Rotterdam, onder begeleiding van prof. dr. M.J. Bruno en dr. J.E. van Hooft. In april 2016 startte zij met de opleiding tot Maag-, Darm- en Leverarts in het Albert Schweitzer ziekenhuis te Dordrecht. Vanaf oktober 2019 zal zij haar opleiding in het Erasmus Medisch Centrum te Rotterdam vervolgen.