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Early detection of pancreatic cancer in high-risk individuals

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General introduction and thesis outline



GENERAL INTRODUCTION

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PANCREATIC CANCER

Pancreatic cancer incidence and mortality are rising rapidly. Globally, the number of cases has more than doubled between 1990 to 2017 and pancreatic cancer is soon expected to be the second leading cause of cancer-related mortality.¹ As only a minority of approximately 16% of patients have a resectable tumor at time of presentation², there is an urgent need for detection and treatment of early lesions to improve outcomes. Currently, the implementation of widespread general population-based screening is not feasible due to the low overall incidence (5.7 per 100,000 person-years) and absence of accurate screening tests.^{3,4} However, it is estimated that up to 10% of cases occur in individuals with a strong family history or carriers of a germline mutation⁵, referred to as high-risk individuals, for whom pancreatic cancer surveillance in expert centers is recommended.⁶⁻⁸

HIGH-RISK INDIVIDUALS

The average lifetime risk of pancreatic cancer in the general population is approximately 1.5%.⁹ There is consensus that individuals with a lifetime risk of pancreatic cancer greater than 5%, or a 5-fold increased relative risk, are considered high-risk individuals.¹⁰ These individuals can be categorized into familial pancreatic cancer (FPC) or those with hereditary cancer syndromes, each with varying population prevalence and pancreatic cancer risk (**Table 1**).

Familial pancreatic cancer

FPC is defined as a family clustering of pancreatic cancer with at least two first-degree relatives without a known hereditary cancer syndrome (*nonsyndromic* FPC). The risk of pancreatic cancer increases with the number of affected family members.¹¹ Early onset of pancreatic cancer in the family is also associated with a higher individual risk.^{11,12}

Hereditary pancreatic cancer

Approximately 50 forms of hereditary cancer syndromes have been identified in humans.¹³ A number of these have been associated with development of pancreatic cancer. The “two-hit” hypothesis proposed by Knudson is an intriguing concept that has been demonstrated in several autosomal dominant inherited cancers.¹⁴ According to this hypothesis, the first genetic hit occurs due to a germline mutation of one allele, while the second hit involves a somatic deletion of the other allele, resulting to a condition known as loss-of-heterozygosity. This process leads to the inactivation of tumor suppressor genes, paving the way for the development of cancer. The applicability of this theory to different hereditary cancer syndromes underscores its significance in understanding the genetic basis of cancer predisposition, including in cases of pancreatic cancer.¹⁵ Cancer predisposition syndromes with the greatest risk of developing pancreatic cancer include Peutz-Jeghers syndrome (*STK11/LKB1* gene), hereditary pancreatitis (*PRSS1/SPINK1* gene) and familial atypical multiple melanoma (FAMMM) syndrome, also known as hereditary melanoma (*CDKN2A* gene).¹⁶⁻²⁵

Table 1. Epidemiology of germline mutations, associated cancer syndromes and risk of pancreatic cancer

Gene(s)	Cancer syndrome	Inheritance pattern	Prevalence general population	Associated cancers	Relative risk for PC	Lifetime risk for PC	Ref.
APC	Familial Adenomatous Polyposis (FAP)	Autosomal dominant	1/10,000	Gastrointestinal, brain, thyroid, hepatic	4.5		58, 59
ATM	Ataxia-telangiectasia (AT)	Autosomal recessive	1/40,000-1/100,000	Lymphoma, acute leukemia, breast	6.5	9.5%	60, 61
BRCA1	Hereditary Breast and Ovarian syndrome (HBOC)	Autosomal dominant	1/300-1/500	Breast, ovarian, prostate	2.3-3.0	2.2%-3.0%	62-64
BRCA2					3.5-10.0	3.0%-7.0%	
CDKN2A/p16	Hereditary melanoma, Familial Atypical Multiple Melanoma Mole (FAMMM) syndrome	Autosomal dominant	<1/1,000	Melanoma and non-melanoma skin, oropharynx, respiratory, respiratory	13-47.8	19%	25, 65, 66
STK11/LKB1	Peutz-Jeghers syndrome (PJS)	Autosomal dominant	1/50,000-1/200,000	Colorectal, breast, small bowel, gastric	132	11%-36%	16, 17, 19
MLH1/MSH2/MSH6	Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	Autosomal dominant	1/279-1/2,000	Gastrointestinal, endometrial, urological	8.6	3.68%	67-69
PALB2	-	Autosomal dominant	1/500	Breast, ovarian	2.4	4%	70, 71
TP53	Li-Fraumeni syndrome	Autosomal dominant	1/3,000-1/5,000	Breast, sarcoma, leukemia, adrenocortical, brain	7.3	-	72, 73
PRSS1/SPINK1	Hereditary pancreatitis	Autosomal dominant (PRSS1)	<1/100,000	-	69	7.2%-53.3%	21-23

Recommendations for genetic testing

Genetic testing for hereditary cancer syndromes is useful in identifying individuals at high risk of pancreatic cancer or other related cancers, who could benefit from cancer surveillance.²⁶ However, because of the large variety of cancer syndromes associated with pancreatic cancer, identification of individuals who are candidates for genetic testing is complex. Family history, in combination with a patient's personal cancer history, is key to identifying those individuals who have an inherited predisposition to malignancy. A three-generation pedigree is the gold standard for autosomal inherited disorders, which should include tumor types and ages at diagnosis. Family history of cancer in first- and second-degree relatives is most important. Factors that increase the likelihood of a hereditary component are an early age of cancer onset, multiple affected relatives within the same family, and multiple primary tumors, especially in specific organs that are associated with a particular cancer syndrome such as the breast and ovaries in context of a *BRCA1/2* germline mutation or the colon in Lynch syndrome. When obtaining family history, clinicians should be aware of any information regarding ethnicity that may be relevant to specific cancer syndromes of interest. Traditionally, guidelines have recommended genetic testing for suspected hereditary cancer syndromes, however more recent guidelines from the United States advocate for genetic testing of all individuals diagnosed with pancreatic cancer, regardless of family history.²⁷

PANCREATIC CANCER SURVEILLANCE

Whom to offer surveillance

Several guidelines have been published with recommendations for pancreatic cancer surveillance of high-risk individuals.^{6,10,26} All guidelines recommend that carriers of germline mutations in *CDKN2A* and *STK11/LKB1* – who are at highest risk of developing pancreatic cancer – are offered pancreatic surveillance regardless of family history of pancreatic cancer, starting at age 40 years, or 10 years younger than the youngest affected blood relative (**Table 2**). For carriers of germline mutations in *ATM*, *BRCA1/2*, *PALB2*, *MLH1/MSH2/MSH6*, surveillance is recommended in the presence of one or more first-degree relative with pancreatic cancer. In individuals with a familial clustering of pancreatic cancer, without a known germline mutation (FPC), international guidelines recommend surveillance in those with at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer, starting at age 50 or 10 years younger than the youngest affected blood relative. However, recent data from a large pancreatic cancer surveillance study in the Netherlands showed that the diagnostic yield of FPC was non-existent.²⁸ Therefore, whether surveillance is beneficial in these individuals remains to be proven.

Table 2. Summary of pancreatic surveillance recommendations for high-risk individuals from the International Cancer of the Pancreas Screening (CAPS) Consortium and the American Gastroenterological Association (AGA)

High-risk group	CAPS 2019 ⁶		AGA 2020 ²⁶	
	Family criteria	Starting age*	Family criteria	Starting age*
FPC	≥1 FDR who in turn also has ≥1 FDR	50 or 55†	≥2 affected relatives	50
APC	-	-	-	-
ATM	≥1 FDR	45 or 50	≥1 FDR	50
BRCA1	≥1 FDR	45 or 50	≥1 FDR	50
BRCA2	≥1 FDR	45 or 50	≥1 FDR	50
CDKN2A/p16	Regardless of family history	40	Regardless of family history	40
STK11/LKB1	Regardless of family history	40	Regardless of family history	35
MLH1/MSH2/ MSH6	≥1 FDR	45 or 50	≥1 FDR	50
PALB2	≥1 FDR	45 or 50	≥1 FDR	50
TP53	-	-	-	-
PRSS1/SPINK1	-	40 or 20 years after the first pancreatitis attack	Regardless of family history	40

Abbreviations: FDR, first-degree relative. FPC, familial pancreatic cancer.

*Or 10 years younger than the initial age of onset in the family.

†Consensus as to when to start surveillance was not reached for FPC.

How to perform surveillance

Currently, pancreatic cancer surveillance is performed using imaging with magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), or a combination of both.^{6, 26, 29} While EUS appears to be more sensitive in detecting small solid lesions, MRI is superior in detecting and characterizing cystic lesions.³⁰ Therefore, it is recommended that both modalities are used complementary rather than interchangeable.⁶ EUS offers the advantage of performing tissue sampling through fine-needle aspiration or biopsy, but it also comes with potential interobserver variability and risks associated with the procedure and sedation.^{31, 32} Computed tomography is useful for staging and assessing resectability but has limitations in detecting small lesions and carries radiation exposure, which is undesirable for long-term surveillance. Reliable biomarkers for surveillance are currently not yet available. Although CA19-9 has proven useful for monitoring treatment response and detecting disease recurrence³³, its performance in detecting early-stage disease has been shown to be inadequate, and false-positive results are common.³⁴ As a result, surveillance remains currently limited to MRI and EUS. In the case of a normal pancreas or non-concerning abnormalities, follow-up imaging should be performed after 12 months. If worrisome features are found that do not warrant immediate surgery, the surveillance interval should be shortened to 6 months for intermediate (e.g., cystic lesions ≥ 3 cm) and within 3 months for high-risk lesions (e.g., solid lesion < 5 mm). Further characterization by EUS-guided tissue sampling is recommended for indeterminate or high-risk lesions. In cases with high suspicion of malignancy (e.g., solid lesions ≥ 10 mm or cystic lesions with

an enhancing solid component), surgical resection should be performed.^{6,26} Overall, surveillance and management decisions should be made by dedicated multidisciplinary teams in expert centers.

Targets for surveillance

Small, early-stage tumors and high-grade precursors are considered ideal target lesions for pancreatic surveillance. These lesions are usually resectable and have by far the most favorable prognosis.^{35,36} Therefore, the goal of surveillance is to detect and treat stage I pancreatic cancer that is confined to the pancreas, resected with negative margins, and pancreatic cancer precursor lesions with high-grade dysplasia. The most relevant precursor lesions are pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCN).

The majority of PDAC are thought to arise from PanINs and therefore considered the most important precursor lesions for pancreatic malignancy. PanINs are defined as microscopic (<5 mm) papillary or flat, noninvasive epithelial lesions in the pancreatic duct.³⁷ They are characterized by columnar-to-cuboidal cells with variable amounts of mucin and varying degrees of cytological and architectural atypia. PanINs are part of a multistep tumor progression model, in which genetic events are observed in *KRAS*, *CDKN2A*, *TP53* and *SMAD4* are observed during progression from low-grade to high-grade dysplasia (**Figure 1**).³⁸ Low-grade PanIN previously encompassed three older definitions: PanIN-1A (flat), PanIN-1B (papillary), and PanIN-2, representing low- and intermediate-grade lesions, respectively. Thus, the term high-grade dysplasia is now used only for most advanced dysplasia, characterized by severe cytologic and architectural atypia.³⁹ Although PanIN are microscopic lesions and are typically diagnosed on histopathologic evaluation, they may be surrounded by multifocal lobular atrophy, which may serve as an indirect marker of neoplasia on imaging.⁴⁰ PanIN lesions are common in the pancreas. A histopathologic review of resected pancreata without PDAC identified PanIN in 26% of patients, including 8% with high-grade dysplasia. In contrast, high-grade PanIN was found in 40% of patients with PDAC.⁴¹ Only a very small proportion of low-grade PanIN is expected to progress to PDAC, therefore only resection of high-grade PanIN is considered a success of surveillance.

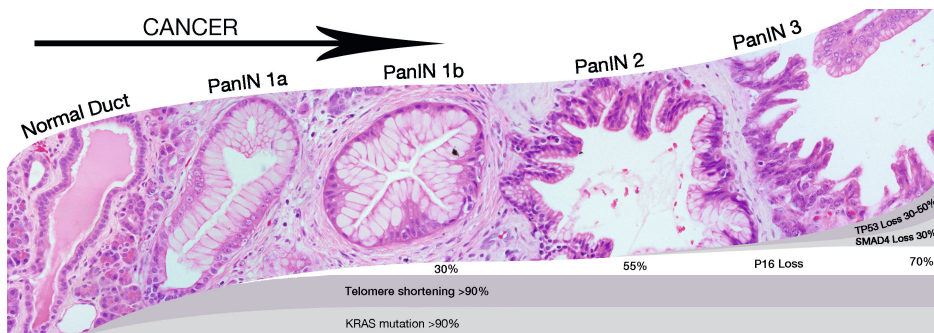


Figure 1. Progression model for pancreatic cancer. The PanIN progression model shown here shows that accumulation of genetic and epigenetic alterations drives neoplastic progression in these precursor lesions from low-grade dysplasia (PanIN-1 and PanIN-2) to high-grade dysplasia (PanIN-3) to eventually invasive cancer. Progressive telomere shortening creates genetic instability that facilitates tumor development. Reprinted with permission from Hackeng et al. *Diagn Pathol*. 2016.³⁸

IPMN are grossly visible (>5 mm), noninvasive, epithelial neoplasms that are composed of mucin-producing columnar cells. They are usually found in the pancreatic head, but can be found throughout the entire length of the pancreas. Similar to PanIN, IPMN can harbor different grades of dysplasia, including low-grade, high-grade and invasive carcinoma. Morphologically, IPMNs can be classified as originating from the main pancreatic duct (MD-IPMN), one of the side branches (SB-IPMN), but can also involve both the main duct and side branches (mixed type; MT-IPMN). MD-IPMN have a much higher risk of progression to malignancy (61.6%), compared to SB-IPMN (25.5%).⁴² Up to 40% of MD-IPMN are multifocal, but this has not been shown to increase the risk of malignancy.⁴³ IPMN can become symptomatic and cause pancreatitis-like symptoms, such as abdominal pain, jaundice and weight loss. Several international, European and American guidelines have been developed regarding the prediction of malignancy, surveillance, and management of IPMNs. Factors that require immediate surgery ("high-risk stigmata") include obstructive jaundice, an enhancing mural nodule ≥ 5 mm, and main pancreatic duct dilatation ≥ 10 mm. "Worrisome features" – which are relative indications for surgery – are cysts ≥ 3 cm, an enhancing mural nodule < 5 mm, thickened/enhancing cyst walls, a main duct size of 5–9 mm, an abrupt change in pancreatic duct caliber with distal atrophy, lymphadenopathy, an elevated serum CA19-9, and a cyst growth rate > 5 mm in 2 years.⁴⁴

MCNs are typically large mucin-producing cysts found predominantly in women. Most MCNs are found in the body or tail of the pancreas, and unlike IPMN usually do not communicate with the pancreatic duct. Malignant transformation of MCNs is comparable with the multistep tumor progression model as observed in PanIN.⁴⁵ Up to 34% of all resected MCNs are malignant, however in asymptomatic lesions < 40 mm with no worrisome features, the rate of malignant progression is less than 0.10%.^{46,47} Therefore, European guidelines advocate surveillance for small MCNs.⁴⁸ Larger cysts (≥ 40 mm) or those with worrisome features such as mural nodules or enhancing walls should be considered for surgery due to the high malignant potential.⁴⁹

Although pancreatic cancer is notorious for its high metastatic potential, it is estimated that it takes many years for precursor lesions to progress to a malignant clone.⁵⁰ This is encouraging from an early detection perspective as it would in potential provide a large window for surveillance programs to detect malignant precursor lesions and early stage cancer.

Outcomes of surveillance

Over the past two decades, multiple centers have reported their findings from surveillance programs in various high-risk populations, yielding mixed results.^{24, 28, 36, 51–53} More recent evaluations have shown promise in detecting early-stage cancer with improved survival rates, mostly in carriers of germline mutations.^{24, 36} However, the benefit of surveillance for FPC remains questionable, with a low success rate in detecting target lesions and a higher risk of unnecessary surgical procedures.^{28, 54} The variation in outcomes from these programs emphasize that continuous evaluation is essential. A key limitation in assessing the survival benefit of pancreatic surveillance programs is the use of observational data in which lead time represents a potential source of bias. Lead-time bias arises when cancer is detected by screening earlier than that it would have been diagnosed based on symptoms, without affecting the disease course, leading to an apparent increase in survival time. Only randomized controlled trials can completely control for this source of bias. It is however unlikely

that such a trial will be conducted, because this would require a large number of participants and a long follow-up duration to accurately assess differences in survival. Moreover, there are ethical concerns in withholding high-risk individuals from surveillance in a trial setting. Besides, individuals will be unlikely to participate when informed about potential risks and benefits. As effects of lead-time are most prominent in short term survival, long-term (> 10-year) follow-up studies are most likely to give a reliable appraisal of a true survival benefit of surveillance participation.

Harms of surveillance

Individuals undergoing surveillance programs should be informed about the potential harms of screening before starting the program. Some risks are directly related to some of the limitations of imaging-based surveillance, including the lacking discriminative capabilities to distinguish low-grade from high-grade precursor lesions, and incidental findings, which may result in surgical resection of benign lesions.⁵⁵ Overtreatment is particularly troublesome as pancreatic resection is associated with considerable perioperative morbidity, exocrine and endocrine dysfunction. Moreover, there is a risk treatment of malignancies diagnosed at an advanced stage, where the potential for survival benefit is limited or absent. Another important consideration is the psychological impact on individuals with hereditary cancer syndromes, who may experience increased distress and a lower quality of life compared to the general population.⁵⁶ However, current literature does not clearly indicate that surveillance participation itself significantly increases cancer-specific anxiety or general distress, as cancer worries may even decrease over time.⁵⁷

SUMMARY

Approximately 10% of PDAC cases are observed in high-risk individuals with a strong family history or germline mutations. Pancreatic surveillance is recommended for these individuals, and genetic testing plays a critical role in identifying those who may benefit from such screening. Combining family history with a patient's personal cancer history is essential in identifying individuals with an inherited predisposition to malignancy. There is a wide variation in the lifetime risk of PDAC between different cancer syndromes and the number of affected relatives in FPC, which determines the starting age and family criteria for participation in surveillance. Surveillance aims to detect early-stage pancreatic cancer and high-grade precursor lesions, of which the two most relevant are PanIN and IPMN. Although PanINs are considered the most important precursors, they are microscopic lesions and therefore extremely difficult to detect with conventional imaging. Surveillance should be performed by multidisciplinary teams in expert centers, with most programs using MRI and/or EUS. Several studies have demonstrated a potential survival benefit of surveillance, although this benefit is less certain in FPC. Potential harms of surveillance include the risk of false-positive findings and overtreatment, detection and treatment of lesions at advanced stages, with a minimal survival benefit, and psychological distress.

THESIS OUTLINE AND AIMS

The overall aim of the studies conducted in this thesis is to improve surveillance of individuals at high risk of developing pancreatic cancer, with a specific focus on carriers of a germline *CDKN2A* mutation. In Part I, we evaluate the effectiveness of pancreatic cancer surveillance by reporting on the long-term yield and outcomes of pancreatic surveillance conducted in germline *CDKN2A* mutation carriers (**Chapter 2**) and comparing these outcomes with a control group while correcting for potential lead-time bias (**Chapter 3**). The second part focuses on various aspects to improve pancreatic cancer surveillance programs. In **Chapter 4** we explore the psychosocial aspects associated with carriership of a germline *CDKN2A* mutation. Next, **Chapter 5** describes the study of longitudinal changes in serum protein *N*-glycans as a biomarker for early detection. In **Chapter 6** we assess whether risk stratification can help to identify which individuals with a germline *CDKN2A* mutation participating in surveillance are at highest risk of developing pancreatic cancer. The final part of this thesis examines and evaluates strategies to identify high-risk individuals who may be eligible for participation in surveillance. **Chapter 7** describes the identification of individuals at high risk for pancreatic cancer using a tool that focuses on family history and development of new-onset diabetes. The use and outcomes of multigene panel testing in patients with PDAC to identify a hereditary predisposition are evaluated in **Chapter 8**. In **Chapter 9**, we investigate the prediagnostic changes occurring in body composition and metabolic markers prior to diagnosis of PDAC in a large cohort of patients. Finally, in **Chapter 10**, the main findings of this thesis and future perspectives are summarized and discussed.

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