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# Surveillance for familial and hereditary pancreatic ductal adenocarcinoma

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CHAPTER 1

# Introduction

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is considered one of the most lethal forms of cancer, with a 5-year survival rate of less than 10%. Over the years, the incidence of PDAC in the US increased from 11.42 per 100.000 people in 2017 to 12.91 per 100.000 people in 2020 (1, 2). The risk in men is higher compared to women, 14.70 versus 11.31 per 100.000, respectively (2).
Three percent of all new cancer cases are associated with PDAC, which makes it the 12$^{th}$ on the list of most common cancers in the general US population. The median age at diagnosis is 70 years, with 30% of all cases being diagnosed between the age of 65 and 74 years (2). Currently, PDAC is the third leading cause of cancer death, with a yearly mortality almost as high as the incidence (1, 3). The high mortality is explained by the fact that PDAC becomes symptomatic at a late stage, and only 15% of the tumors are resectable at diagnosis. The only way to improve prognosis is through early detection by screening. However, the risk of PDAC in the general population is too low to justify screening but surveillance of high risk groups might be more attractive.

Familial and hereditary PDAC

In 5% of all cases of pancreatic cancer, hereditary factors play a role in its development (4). These cases are subdivided into two groups: (1) familial and (2) hereditary PDAC. Familial PDAC is the largest group and is usually defined by the presence of at least two first-degree relatives with this cancer in a family (5). The risk of PDAC depends of the number of relatives with the tumor and varies from 8% for individuals with two relatives with PDAC to 30% for those with three relatives with this cancer (4). Hereditary PDAC, 5-10% of all PDAC cases, is defined by the presence of an underlying gene defect. Such gene defects can be identified in 3-5% of (apparently) sporadic PDAC and 3-10% of familial PDAC(6). Table 1 provides an overview of the most frequent underlying gene defects that predispose to PDAC including clinical features and estimated cancer risks (4). The highest risk is observed in individuals with a pathogenic variant in the SSTK-gene (Peutz-Jeghers syndrome) and in the p16 gene (Familial melanoma). Surveillance for PDAC is currently recommended by the International Cancer of the Pancreas Screening (CAPS) consortium if the risk exceeds 5% (5).

Table 1. Gene defects PDAC with clinical features

| Gene defect | Risk PDAC until 70 years | Clinical features |
|---|---|---|
| CDKN2A (FAMMM) | 15-20% | Atypical naevi, malignant melanomas |
| STK11 (Peutz-Jeghers syndrome) | >20% | Mucocutaneous pigmentation, hamartomatous polyps |
| BRCA1/2 (HBOC) | 3-8% | Breast-, ovarian-, prostate cancer |
| TP53 (Li-Fraumeni syndrome) | <5% | Sarcoma, breast, leukemia, adrenal gland cancer |
| PRSS1 (Hereditary Pancreatitis) | 40% | Acute recurrent or chronic pancreatitis |
| Familial Pancreatic Cancer (FPC) | 2 First Degree Relatives: 8-12%<br>>3 First Degree Relatives: 16-38% | NA |
| Lynch Syndrome | <5% | Colorectal, endometrial, urinary tract, stomach, small bowel cancer |

Abbreviations: FAMMM: Familial Atypical Multiple Mole Melanoma; HBOC: Hereditary Breast- and Ovarian cancer ; PDAC, pancreatic ductal adenocarcinoma.

Surveillance for Pancreatic Ductal Adenocarcinoma (PDAC)

One of the requirements that should be met before implementing a surveillance program is thorough knowledge of the natural history of PDAC. Several studies have suggested that PDAC originates from precursor lesions including intraductal papillary mucinous neoplasms (IPMN) and pancreatic intraepithelial neoplasia (PanIN) lesions (7-10). IPMNs are epithelial pancreatic cystic tumors of mucin-producing cells that arise from the pancreatic ducts. If an IPMN originates from the main duct, it is referred to as main branch IPMN and if the lesion arises from side branches it is called side-branch IPMN.

PanIN lesions are composed of columnar to cuboidal cells with varying amounts of mucin and varying degrees of cytological and architectural atypia. They are classified into three grades: PanIN-IA (flat) and PanIN-IB (papillary) are low grade lesions with minimal cytological and architectural atypia. PanIN-2 lesions show mild to moderate cytological and architectural atypia. High grade PanINs (PanIN-3) are characterized by severe cytological and architectural atypia.

Both IPMN as well as PanIN-lesions may progress into cancer. The histological progression is paralleled by the accumulation of genetic changes. The early detection and treatment of these precursor lesions may prevent the development of PDAC.

Theresa Brentnall, gastroenterologist in Seattle, US, was the first who reported in 1999 the outcome of surveillance of fourteen individuals from three kindreds with familial PDAC(11). Surveillance using EUS, CT-scanning, ERCP and tumormarkers suggested the presence of dysplasia in seven patients who subsequently underwent total pancreatectomy. All patients had histological evidence of dysplasia in the surgical specimens. The authors concluded that thorough screening of individuals with a family history of PDAC is feasible and that clinical data and imaging studies including EUS and ERCP can be used to identify individuals with dysplasia. Since then, many surveillance studies have been published(12-19).

Hereditary and Familial Melanoma

Familial melanoma is usually defined by the presence of 2 or 3 close relatives with invasive melanoma with or without multipele melanoma in a kindred. In the 1980s, a large number of such families, previously referred to as families with Familial Atypical Multiple Mole Melanoma (FAMMM), were identified in the region of Leiden, The Netherlands, by Professor Wilma Bergman, dermatologist at the Leiden University Medical Centre. Subsequent genetic research by Nelleke Gruis et al. led to the identification of a founder mutation (the Leiden-p16-gene mutation) in the CDKN2A-gene which was responsible for the high frequency of these families with FAMMM in the region (20). All these families were offered surveillance of the skin for the early detection of melanoma (21, 22). By thorough research of a large series of families, Bergman et al. discovered a high frequency of PDAC in FAMMM families. In collaboration with Henry Lynch and Patrice Watson et al., she identified 18 cases of PDAC in twelve families with FAMMM (22). In 1999, we calculated that the life time risk of developing PDAC in P16-Leiden associated families was 15-20% by the age of 70 years which was later confirmed by Snoo & Bishop et al. (23, 24). These high risks and the above-mentioned succesfull study by Brentnall et al. inspired us to start in 2000 a surveillance program for PDAC in families with a confirmed P16-Leiden mutation at the Department of

Gastroenterology & Hepatology of the Leiden University Medical Centre in Leiden, The Netherlands.

Aims of our studies included in this thesis

The aims of our studies were, first, to investigate the outcome of longterm surveillance of P16 carriers and to compare the results of surveillance of P16-families with the surveillance outcome of familial PDAC. (Chapter 2). For this study, we collaborated with the German Familial Pancreatic Carcinoma Registry established by Professor Detlef Bartsch at the University of Marburg in 1999 and the Spanish National Registry in Madrid established in 2009 by Professor Alfredo Carrato. The second aim was to evaluate the natural history and role of precursor lesions including IPMN and PanIN lesions in families associated with a P16-Leiden mutation (Chapter 3). It is common knowledge that hereditary cancer is associated with the development of multiple tumors due to the fact that all body cells carry the inherited mutation. The third aim, therefore, was to evaluate the risk of multiple PDAC in carriers of a P16-Leiden founder mutation (Chapter 4). The fourth aim was to evaluate the cost-effectiveness of surveillance (Chapter 5); this study was performed in collaboration with Dr W. van den Hout, Department of Medical Decision Making at the LUMC.
During our surveillance study, the program unexpectedly detected also other types of cancer than PDAC including benign lesions (incidentaloma). The fifth aim was to evaluate what type of cancers and benign lesions were detected and whether surveillance and early detection offered any benefit (Chapter 6). This study was also performed in collaboration with the German Familial PDAC Registry and the Registry in Madrid.
The final aim was to describe the dilemmas in the management of screen-detected lesions that we experienced during our surveillance program (Chapter 7).

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