Potjer TP, et al. Variation in precursor lesions of pancreatic cancer among high-risk groups

Statement of translational relevance

Individuals with a genetic predisposition to develop pancreatic ductal adenocarcinoma (PDAC) may benefit from pancreatic surveillance by detection of precursor lesions or early PDAC. Previous studies suggest differences in frequency of PDAC and type of precursor lesions in different high risk groups. In the present study, we performed a detailed analysis of the outcome of surveillance in two high-risk groups, i.e. individuals from familial pancreatic cancer (FPC) families and individuals with a p16-Leiden germline mutation. Radiologically detected cystic lesions and histologically confirmed IPMN lesions were more common in the FPC cohort, whereas the frequency of PDAC in the p16-Leiden cohort was ten times higher than in the FPC cohort. Precursor lesions in this group appear to have a higher malignant potential. Therefore, a more intensive surveillance program should be considered in p16-Leiden mutation carriers.
Variation in precursor lesions of pancreatic cancer among high-risk groups

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Running title: Precursor lesions of PC in high-risk groups

Keywords: Pancreatic ductal adenocarcinoma; surveillance; CDKN2A-gene; familial pancreatic carcinoma, precursor lesions

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Abstract

Purpose: Pancreatic ductal adenocarcinoma (PDAC) surveillance programs are currently offered to high-risk individuals aiming to detect precursor lesions or PDAC at an early stage. We assessed differences in frequency and behaviour of precursor lesions and PDAC between two high-risk groups.

Experimental Design: Individuals with a p16-Leiden germline mutation (N = 116; median age 54 years) and individuals from familial pancreatic cancer (FPC) families (N = 125; median age 47 years) were offered annual surveillance by magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) with or without endoscopic ultrasound (EUS) for a median surveillance period of 34 months (0-127 months) or 36 months (3-110 months), respectively. Detailed information was collected on pancreatic cystic lesions detected on MRCP and precursor lesions in surgical specimens of patients who underwent pancreatic surgery.

Results: Cystic lesions were more common in the FPC cohort (42% versus 16% in p16-Leiden cohort), while PDAC was more common in the p16-Leiden cohort (7% versus 0.8% in FPC cohort). Intraductal papillary mucinous neoplasm (IPMN) was a common finding in surgical specimens of FPC-individuals, and was only found in two patients of the p16-Leiden cohort. In the p16-Leiden cohort, a substantial proportion of cystic lesions showed growth or malignant transformation during follow-up whereas in FPC-individuals most cystic lesions remain stable.

Conclusion: In p16-Leiden mutation carriers, cystic lesions have a higher malignant potential than in FPC-individuals. Based on these findings, a more intensive surveillance program may be considered in this high risk group.
Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death in the western world. It is one of the most lethal cancers with an incidence rate almost equaling the mortality rate and an overall 5-year survival of approximately 5%.\[1, 2\] There has been no improvement in prognosis in the last decades. However, longer survival has been reported for patients with early stage tumors.\[3\] Probably, the only way to detect PDAC at an early stage and to improve the prognosis is by surveillance of asymptomatic individuals. Such a surveillance program should ideally focus on the detection of known precursor lesions, that is, intraductal papillary mucinous neoplasms (IPMNs) and pancreatic intraepithelial neoplasias (PanINs).\[4, 5\] Because of the low incidence rate of PDAC, surveillance for this cancer would not be appropriate in the general population. However, in high-risk groups, i.e. individuals with an inherited predisposition to PDAC, screening could be valuable in improving the prognosis.

Approximately 3-5\%\[6, 7\] of PDAC cases are associated with an inherited predisposition. Individuals with certain tumor syndromes, such as familial atypical multiple mole melanoma (FAMMM), Peutz-Jeghers syndrome (PJS) and hereditary breast cancer (BRCA2 mutation carriers), have a marked increase in risk of developing PDAC.\[8\] In FAMMM syndrome, which is associated with a mutation in the CDKN2A (or p16) gene, individuals are at increased risk of developing melanoma of the skin. FAMMM members with the Dutch founder mutation, a 19-base pair deletion of exon 2 of the CDKN2A gene (p16-\textit{Leiden}), have a 15-20\% lifetime risk of developing PDAC.\[8, 9\]

When there is no proven tumor syndrome, but apparent familial clustering of PDAC, the condition is referred to as familial pancreatic cancer (FPC), which represents...
the largest proportion of hereditary PDAC. By definition, there should be at least two first
degree relatives with PDAC to fulfill the criteria for FPC. The risk of developing PDAC
increases with the number of family members affected. Individuals with two affected first
degree relatives have a 6.4-fold increased risk, and the risk increases to 32-fold in case of
three or more first degree relatives affected.[10]

Several studies on screening for PDAC in high-risk individuals, predominantly
FPC, have been published during the last decade.[11-22] Various screening modalities
have been used in these studies, but the optimal strategy for surveillance in high-risk
groups remains undetermined. Endoscopic ultrasonography (EUS) is able to detect small
solid tumors, but it is an invasive procedure. Magnetic resonance imaging (MRI) and
magnetic resonance cholangiopancreatography (MRCP) are appropriate for detecting
small cystic lesions, but are less sensitive in detecting small solid tumors.[23, 24]

In studies focusing on FPC, a high frequency of precursor lesions have been
described, but an overall low rate of PDAC.[11-14, 17-21] On the other hand, screened
individuals with the p16-Leiden mutation are reported to have a much lower frequency of
precursor lesions but a high rate of PDAC.[22] Therefore, the question arises whether
there is a different role of precursor lesions in the development of PDAC in the various
high-risk groups.

In the present study, we evaluated screening data from a large p16-Leiden cohort
and a large FPC cohort from the Leiden University Medical Center and the German
FaPaCa registry, respectively. The aims were to compare the frequency of precursor
lesions and PDAC between these two cohorts, to compare the features and natural course
of precursor lesions, and to discuss possible implications for the surveillance protocol.
Patients and Methods

Surveillance Group

Individuals at risk (IAR) from two different registries were included in this study. The current study is a retrospective analysis of two ongoing prospective surveillance studies. A subset of these have been published earlier and were updated for this study.[17, 22] Individuals with a p16-Leiden germline mutation were referred from the Clinical Genetics Department to the Department of Gastroenterology and Hepatology of the Leiden University Medical Center in The Netherlands to participate in a surveillance program. Individuals from FPC families were recruited via the FaPaCa registry, a German national case collection for FPC families which is coordinated by the Philipps-University of Marburg in Germany. The diagnosis of FPC was based on the presence of two or more first degree relatives with a confirmed diagnosis of PDAC. Also, individuals with a BRCA2 or a PALB2 mutation and familial clustering of PDAC (primary tumor burden in family) were included in the FPC cohort. Individuals with two first degree relatives with PDAC were classified as moderate risk (5- to 10-fold), individuals with three or more first degree relatives with PDAC or with a BRCA2 or PALB2 mutation were classified as high risk (>10-fold). Both inclusion procedures and criteria were previously described for the two cohorts.[17, 22] The ongoing surveillance studies in Leiden and Marburg were approved by the Ethics Committee of the Leiden University Medical Center and the Phillips-University of Marburg, respectively. For the current study, evaluation was from January 2000 to August 2011 at Leiden University Medical Center and from June 2002 to December 2011 at the FaPaCa registry.
Screening modality

The surveillance program that was used for the FaPaCa FPC-families consisted of both MRI/MRCP and EUS. In the p16-Leiden families, MRI/MRCP and optionally EUS was performed. However, for this study, only the results of the MRI/MRCP were used for comparison. IARs without any MRI/MRCP accomplished were excluded. MRI/MRCP was performed yearly in both centers. In case of an abnormal finding, either close follow-up with MRI/MRCP and EUS or surgery was advised by a multidisciplinary team. Detailed information regarding follow-up and MRI-technique were previously described for both groups.[17, 22] MRIs were evaluated by specialized radiologists at the centers in Marburg and Leiden. All abnormal MRIs from the p16-Leiden cohort were revised by the radiologist from Marburg (J.T.H.).

Cystic lesions

Cystic lesions were defined as radiologically detected cystic lesions including those originating from the pancreatic ducts. For the current study, cystic lesions were subdivided into (1) main duct type (MD) lesions, (2) branch duct type (BD) lesions with a clear connection to the main duct on imaging and (3) other cystic lesions with uncertain connection to pancreatic ducts. Cystic lesions were further classified as multicystic single lesions consisting of multiple small cysts, single or multiple unicystic lesions.

Indication for surgery
In the event of a pathological finding in the pancreas by the imaging modalities, the findings were reviewed by an interdisciplinary board consisting of geneticists, psychooncologists, surgeons and gastroenterologists at both sides. Criteria to recommend surgery included cystic lesions >3 cm, cystic lesions of any size with a substantial solid component, cystic lesions with irregular boundaries in IAR with a strong family history (e.g. three or more affected first degree relatives), significant change in size and morphology during follow up, positive or highly-suspicious EUS fine needle aspiration cytology or patients preference.

Histology

For both cohorts, pancreatic surgical specimens were investigated by pathologists at each centre and reassessed by a single experienced pathologist (G. K), with a special expertise in pancreatic pathology. All available sections were reviewed and particular attention was given to the slides showing tumorous/cystic alterations and duct changes (average number per specimen/case: 4 (range 3–6). In the sections (range 3–4) containing nontumorous/nocystic tissue all PanINs were recorded and their numbers listed in tables 4-6. PanINs were classified by their grade of dysplasia in low (1) moderate (2) or high (3). IPMNs were subtyped as gastric, intestinal, oncocytic or pancreatobiliary type with low grade, moderate or high grade dysplasia. [4, 25, 26]

Statistical analysis

Descriptive statistics were compiled for both groups. Categorical features were compared using \( \chi^2 \) analysis. Continues variables were compared using the independent samples t
test or, when indicated, the Mann-Whitney test. A $P$ value of $<0.05$ was considered significant. Statistical analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL).

## Results

### Patient Characteristics

A total of 116 IAR with a p16-Leiden germline mutation and 125 IAR from FPC families were available for evaluation and included in this study (table 1). In the FPC cohort, 66 individuals were classified as moderate risk and 59 individuals as high risk. In the high-risk group, 9 individuals (7%) had a known mutation (6x PALB2, 3x BRCA2). Median age at start screening was 54 years for the p16-Leiden cohort (range 38-72 years) and 47 years for the FPC cohort (range 27-73 years). The median time under surveillance was 34 months for the p16-Leiden cohort (range 0-127 months) and 36 months for the FPC cohort (range 0-110 months). A total of 507 MRIs were performed in the p16-Leiden cohort (mean 4.4 per individual) and 457 in the FPC cohort (mean 3.7 per individual). All abnormal MRI's from both cohorts were confirmed by one experienced radiologist (J.T.H.).

### Cystic lesions and PDAC detected by MRI.

Cystic lesions were present in 18 of 116 individuals with the p16-Leiden germline mutation (16%). In the FPC cohort, 52 of 125 individuals had cystic lesions (42%, $p<0.001$) (table 2). In the p16-Leiden cohort, PDAC was diagnosed in 8 of 116 individuals (7%). In the FPC cohort, only 1 of 125 individuals was diagnosed with PDAC (0.8%, $p=0.013$).
Four of the eight PDAC cases (50%) in the p16-*Leiden* cohort were prevalent cases (detected at the first screening round) and the other 4 were incident cases (detected during follow-up). The patient with PDAC in the FPC cohort was a high-risk FPC-patient and PDAC was detected during follow-up.

**Features and natural course of cystic lesions**

IAR with cystic lesions in the FPC cohort were significantly younger than in the p16-*Leiden* cohort (54 vs. 60 years, p=0.026) (table 3). In both cohorts, most IAR had cystic lesions not located in the main duct (89% in p16-*Leiden*, 98% in FPC), but in the p16-*Leiden* cohort, significantly more cystic lesions were located in the main duct compared to the FPC cohort (p=0.020). In both cohorts, most individuals had single unicystic or multiple unicystic lesions, only a few had multicystic lesions. All lesions were comparable in size between the two cohorts. Unicystic lesions were mostly small (mean size 3-6mm). In the FPC cohort, one high-risk individual had a relatively large unicystic lesion (31mm) at baseline screening, which was located in the main duct (the only main duct ectasia in the FPC cohort). This patient is scheduled for resection as recommended by the consensus guidelines due to the high risk of malignancy inherent to main duct lesions.[27] The distribution of cystic lesions over the pancreas in the two cohorts is shown in Table 3. Cystic lesions were significantly more often located in the corpus of the pancreas in the p16-*Leiden* mutation carriers than in the FPC-cohort. In the FPC cohort, only three of 52 (6%) individuals had a cystic lesion detected after the first screening round (incident), which was significantly less than in the p16-*Leiden* cohort (56%, p<0.001).
In the p16-Leiden cohort, thirteen of 18 (72%) individuals had follow-up of their cystic lesions (mean duration of follow-up: 2.5 years). Three individuals (23%) with follow-up MRIs showed progression, i.e. growth of a cystic lesion or PDAC-development. The individual with growth of the cystic lesion had a multicystic lesion with a diameter of 15mm. During six years of follow-up there was no change in size, but one year later the diameter of the lesion increased to 17mm. The two other individuals with progression at follow-up developed PDAC at the site of the cystic lesion. One of these individuals had two multicystic lesions (14.2mm and 12mm) and developed a 20mm cancer detected by MRI one year later. The second patient had a small solitary lesion and irregular duct and developed a 10mm cancer detected by MRI five months later. The two other incident cases of PDAC in the p16-Leiden cohort did not have a cystic lesion detected on previous MRI. One individual developed a 15mm cancer 12 months after a normal MRI; the other individual developed a 40mm cancer 28 months after a normal MRI. Thus, of the four incident PDAC cases, two had one or more cystic lesions detected on previous MRI.

A comparable number of individuals in the FPC cohort had follow-up of their cystic lesions (33/52=63%, p=0.500). Mean follow-up of these lesions was however significantly longer (mean duration of follow-up: 3.8 years, Mann-Whitney test: p=0.027). Only four individuals had progression of their cystic lesions (12%). The MRIs of three individuals showed growth of a lesion, of which one was a multicystic lesion and two were unicystic lesions. Growth was slow in all three cases. One individual developed PDAC in the pancreatic head two years after the first and only MRI. This MRI showed multiple tiny unicystic lesions in the whole pancreas, the largest located in the head with
a diameter of 5mm. The proportion of individuals with progression of their cystic lesions was higher in the p16-Leiden cohort (23%) than in the FPC cohort (12%).

**Histological findings in surgical specimens**

In the p16-Leiden cohort, seven cases underwent surgery, of which six had PDACs (table 4). Three of these cases had single low grade PanIN lesions (PanIN1 and 2) adjacent to the carcinoma. One case (table 4, case A), with the smallest PDAC of the series, showed a small gastric type BD-IPMN with low to high grade dysplasia, and another case (table 4, case G) showed multifocal PanIN 1 and 2 disease combined with peripheral foci of lobular fibrosis and small gastric-type BD-IPMNs in the subtotal pancreatectomy specimen. The surgical specimens of four additional PDACs from symptomatic patients with a p16-Leiden germline mutation diagnosed in the same time period at the Leiden University Medical Center, were histologically reviewed (table 5). In two cases, the PDAC was accompanied by few low grade PanIN lesions. One of the two cases had in addition a PanIN3 lesion. IPMNs were not found in these cases. In total, five of the 10 operated PDAC cases (50%) (table 4 and table 5) revealed PanIN lesions and 1 of 10 had IPMNs in the surrounding tissue. Only one case (table 4, case G) in the screened p16-Leiden cohort was operated because of growth of a cystic lesion on MRI. This patient who was already previously mentioned showed multifocal PanIN-disease but no infiltrating PDAC (see above).

In the FPC cohort, one of the twelve cases that underwent pancreatic resection had PDAC (table 6). Five cases had small BD-IPMN lesions. Three cases had one or more PanIN3 lesions as highest grade, of which two were found in combination with a
BD-IPMN. Two cases had one or more PanIN2 lesions as highest grade, of which again one occurred in association with a BD-IPMN. One case had only PanIN1 lesions, one case had in addition to a PanIN1 lesion a serous cystadenoma (SCA) and two cases only had a SCA.

Discussion

In this study we compared a FPC cohort with a p16-Leiden cohort to evaluate the role of precursor lesions in the early detection of PDAC in these two high-risk groups. We demonstrated a significant difference in recognition of precursor lesions and PDAC between the two groups. Cystic lesions were more common in the FPC cohort (42% vs. 16%), while the incidence of PDAC was ten times higher in the p16-Leiden cohort (7% vs. 0.8%). Interestingly, on histological examination of resected pancreas specimens, the FPC cohort showed both PanIN lesions as well as IPMN lesions, whereas patients in the p16-Leiden cohort revealed only a few low-grade PanIN lesions. In the p16-Leiden cohort, a substantial proportion of cystic lesions showed growth or malignant transformation during follow-up whereas in the FPC cohort most cystic lesions were stable. These findings suggest a high malignant potential of cystic lesions occurring in p16-Leiden mutation carriers.

To date, a number of studies focused on screening for PDAC has been published, predominantly concerning individuals from FPC families.[11-14, 17-21] Overall, in these studies both PanIN lesions and IPMN lesions were detected in FPC-individuals, but there was an overall low incidence of PDAC (<1%). To date, there is only one screening study[22] that solely looked at a large FAMMM/p16-Leiden cohort. It showed a high
incidence of PDAC (9%) and revealed no confirmed IPMN lesions. Other studies that included FAMMM patients in their screening program also did not report confirmed IPMN lesions. IPMNs were lacking in the pancreas of genetically engineered mice with K-RAS and p16 germline mutations. Taken together these data show that the results of the current study are in line with previous screening investigations on FPC and p16-heritage.

What is the role of cystic lesions in the development of PDAC? De Jong et al studied the prevalence of cystic lesions in the pancreas in the general population and demonstrated that 2.4% of almost 3000 asymptomatic individuals who had a screening abdominal MRI had a pancreatic cyst of any kind, but only 8% of these cysts (0.2% of total) communicated with the pancreatic duct, which can be considered a cystic duct lesion. Our current study demonstrated a frequency of cystic lesions in the FPC and p16-heritage cohort of 42% and 16%, respectively, of which the majority probably originate from pancreatic ducts. Thus, the rate of cystic lesions in high-risk groups compared to the general population is much higher, which suggests an association between these lesions and the development of PDAC. However, in the study by De Jong et al, no MRCP was performed and the MRI was not directed to imaging of the pancreas, so the difference could be overestimated.

In the development of PDAC, usually only PanIN2-3 or IPMN are considered relevant lesions. Andea et al compared tumor free pancreatic tissue from pancreas specimens with PDAC with that of entirely nonneoplastic pancreatic tissue. A substantial proportion (28%) of normal pancreas specimens harbored low-grade PanIN (PanIN 1 and 2) lesions but no PanIN 3 lesions whereas the latter lesions were detected in more than
half (58%) of pancreas specimens with PDAC, an observation which suggests the pathological significance of these lesions. Shi et al[31] found, in their comparison of specimens from FPC associated PDACs with sporadic PDACs, that IPMNs are common lesions in FPC-individuals. In the FPC series, 33% of the individuals had IPMNs (20% high grade), whereas the surrounding tissue of sporadic PDACs only harbored IPMNs in 6% of cases (none of high grade).

In our p16-Leiden cohort, including the four PDAC cases not under surveillance, three of 10 PDAC cases (30%) had a few associated PanIN1 lesions, whereas in the FPC cohort, six of 12 patients (50%) had PanIN2-3 lesions that were not associated with a PDAC. In the FPC cohort, five of the 12 patients (42%) had BD-IPMNs of gastric type. These lesions were only seen twice in our p16-Leiden cohort, but in both patients the findings resembled the precursor pattern observed in FPC cohort. These results suggest that PanINs and BD-IPMNs of gastric type play an important role in the FPC phenotype, but have much less significance for the p16-Leiden phenotype. Our study also showed that in the p16-Leiden cohort some PDACs developed without evidence for the presence of precursor lesions.

A common finding in our FPC cohort was serous cystadenoma (SCA), confirmed in three cases. SCAs were not observed in p16-families. The screening studies in FPC families by Canto et al[13] and Ludwig et al[19] also reported serous cystadenomas and a serous microcystic adenoma, all variants of serous cystic neoplasms (SCN), which are considered rare benign lesions.[32] The relatively high frequency of SCAs in FPC might be explained by selection bias as FPC patients underwent surgery because of suspicion of an IPMN.
Overall, our findings and the findings reported in the literature suggest an important role of precursor lesions in the carcinogenesis of PDAC in different high-risk groups which justifies the goal of screening, i.e. to identify these precursor lesions.

The current study has some limitations. First of all it is a *retrospective* analysis of the presence of precursor lesions and PDAC in two high risk groups. However, the data were retrieved from two ongoing *prospective* surveillance studies.

Secondly, there are some differences between the two cohorts that might have influenced the results. The mean age of the FPC group at the start of surveillance is seven years younger than the age of the p16-*Leiden* group. Because the frequency of cystic lesions was higher in the FPC group, we would expect that the differences would be even larger if the age distribution in the two groups was similar. However, because the mean age at diagnosis of PDAC in FPC is in the mid-60s and the mean age at the start of the surveillance of the FPC cohort was only 47 years, it is likely that the incidence of PDAC will increase over the coming decades. The difference in frequency of PDACs might thus become smaller, although the incidence of PDAC in other cohorts consisting of participants that enrolled in their mid-50s was also low (<1%).

In the present study we compared only the outcome of the MRI/MRCP between the two cohorts. A possible source of bias is the fact that in the FPC cohort also EUS was used in the surveillance protocol whereas only MRI/MRCP was applied in the p16-*Leiden* cohort. The use of EUS in the FPC-cohort could have increased the detection of cystic lesions. However, because the sensitivity of MRCP for detection of such lesions is higher compared to EUS, we don’t think that adding EUS to the FPC-protocol had a major effect on the results.
The results of our current study could have implications for the current screening protocol. In FPC, the incidence of PDAC is low (0.8%) and almost all lesions (88%) detected by screening are stable at follow-up (or only slowly growing). This would suggest a relatively low malignant potential of precursor lesions in the setting of FPC. Because of these findings, it could be argued that it is safe to screen young FPC-individuals (e.g. <55 years) without evidence of precursor lesions with larger intervals between examinations, for instance once every two years and those with lesions at shorter intervals.

In p16-Leiden, however, we demonstrated a high incidence of PDAC and a probably high malignant potential of precursor lesions. A more intensive surveillance program with MRI/MRCP as well as EUS is probably needed for the timely detection of early stage tumors or precursor lesions.

Grant support: Deutsche Krebshilfe (no. 109126 to DKB) for the FaPaCa project; ZonMW, an independent organisation supported by the government, for the p16-Leiden cohort.

**Literature**


### Table 1. Patient characteristics of the two cohorts

<table>
<thead>
<tr>
<th></th>
<th>Median age at start screening (range)</th>
<th>Gender m:f</th>
<th>Median time under surveillance [months] (range)</th>
<th>Total MRI (pp)</th>
</tr>
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<tbody>
<tr>
<td>♦ FPC (n=125)</td>
<td>47 (27-73)</td>
<td>54:71</td>
<td>36 (0-110)</td>
<td>457 (3.7)</td>
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<tr>
<td>♦ p16-Leiden (n=116)</td>
<td>54 (38-72)</td>
<td>50:66</td>
<td>34 (0-127)</td>
<td>507 (4.4)</td>
</tr>
</tbody>
</table>

FPC = familial pancreatic cancer, pp = per person (mean), n = number

### Table 2. Frequency of radiologically detected cystic lesions and of PDAC

<table>
<thead>
<tr>
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<th>Cystic lesions (%)*</th>
<th>PDAC (%)</th>
<th>Operation (%)</th>
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<tbody>
<tr>
<td>♦ FPC (n=125)</td>
<td>52 (42)</td>
<td>1 (0.8)</td>
<td>12 (10)</td>
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<tr>
<td>♦ p16-Leiden (n=116)</td>
<td>18 (16)</td>
<td>8 (7)</td>
<td>7 (6)</td>
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</table>

FPC = familial pancreatic cancer, PDAC = pancreatic ductal adenocarcinoma, n = number

* Numbers represent the number of individuals with one or more radiologically detected cystic lesions of the pancreas
Table 3. Features and course of cystic lesions on radiology

<table>
<thead>
<tr>
<th></th>
<th>p16-Leiden N Patients (%)</th>
<th>FPC N Patients (%)</th>
<th>p-value</th>
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<tr>
<td>Mean age at detection (range)</td>
<td>60 (50-72)</td>
<td>54 (31-71)</td>
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<tr>
<th>Localization</th>
<th>Main duct</th>
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<th>Appearance</th>
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<th>Multiple unicystic</th>
<th>Single unicystic</th>
<th>FPC</th>
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<th>Mean size (range)</th>
<th>Multicystic</th>
<th>Multiple unicystic</th>
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<td>14mm (11-18)</td>
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<th>Site of pancreas</th>
<th>Head</th>
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<th>Proc. Uncinatus</th>
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<tr>
<th>Follow-up</th>
<th>N patients</th>
<th>Mean follow-up (range)</th>
<th>Growth of lesion</th>
<th>Development of PDAC†</th>
<th>FPC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13</td>
<td>2.5 years (0.25-8)</td>
<td>1</td>
<td>2</td>
<td>33</td>
<td>ns</td>
</tr>
</tbody>
</table>

Numbers represent the number of individuals. Since an individual is able to have more than one lesion, overlap may exist.
N= number, FPC = familial pancreatic cancer, PDAC = pancreatic ductal adenocarcinoma, ns = not significant.
* includes branch duct cystic lesions with clear connection to the main duct and cystic lesion with uncertain connection to pancreatic ducts.
† at the same site of the cystic lesion(s).
**Table 4.** p16-*Leiden* cohort: Histological findings in surgical specimens

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor diagnosis</th>
<th>Precursor lesions in the peritumorous tissue (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>62 Ductal adenocarcinoma G1</td>
<td>BD-IPMN; PanIN1 (1)</td>
</tr>
<tr>
<td>B</td>
<td>49 Ductal adenocarcinoma G1</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>47 Ductal adenocarcinoma G3</td>
<td>Few PanIN1-2 (2)</td>
</tr>
<tr>
<td>D</td>
<td>72 Ductal adenocarcinoma G1</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>58 Ductal adenocarcinoma G1</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td>57 Ductal adenocarcinoma G1</td>
<td>Few PanIN1 (3)</td>
</tr>
<tr>
<td>G</td>
<td>62 No PDAC. Multifocal PanIN1-2; BD-IPMN</td>
<td>n/a</td>
</tr>
</tbody>
</table>

G = grade, PanIN = pancreatic intraepithelial neoplasia, BD-IPMN = intraductal papillary mucinous neoplasm of branch duct, n/a = not applicable, n = number of lesions
Table 5. p16-Leiden: Histological findings in surgical specimens of additional (symptomatic) PDAC cases, not screened

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor diagnosis</th>
<th>Precursor lesions in the peritumorous tissue (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 38</td>
<td>Ductal adenocarcinoma G2</td>
<td>Few PanIN1 (3)</td>
</tr>
<tr>
<td>B 58</td>
<td>Ductal adenocarcinoma G2</td>
<td>-</td>
</tr>
<tr>
<td>C 40</td>
<td>Ductal adenocarcinoma G1</td>
<td>-</td>
</tr>
<tr>
<td>D 47</td>
<td>Ductal adenocarcinoma G3</td>
<td>PanIN1, 3 (2)</td>
</tr>
</tbody>
</table>

G = grade, PanIN = pancreatic intraepithelial neoplasia, n = number of lesions
Table 6. FPC cohort: Histological findings in surgical specimens

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Risk group†</th>
<th>Histological characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>Moderate</td>
<td>PDAC PanIN1-2 (multifocal*)</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>Moderate</td>
<td>PanIN1-3 (multifocal)</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>Moderate</td>
<td>SCA</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>Moderate</td>
<td>PanIN1-3 (multifocal)</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>Moderate</td>
<td>PanIN1-2</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>High</td>
<td>PanIN1-3 (multifocal)</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>High</td>
<td>PanIN1</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>High</td>
<td>PanIN1</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>High</td>
<td>yes</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>High</td>
<td>PanIN1</td>
</tr>
<tr>
<td>11</td>
<td>69</td>
<td>High</td>
<td>PanIN1-3 (multifocal)</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>High</td>
<td>PanIN1-2 (multifocal)</td>
</tr>
</tbody>
</table>

FPC = familial pancreatic cancer, PDAC = pancreatic ductal adenocarcinoma, PanIN = pancreatic intraepithelial neoplasia, (BD-)IPMN = intraductal papillary mucinous neoplasm (of branch duct), SCA = serous cystadenoma

† Moderate risk = two first degree relatives with PDAC, High risk = three or more first degree relatives with PDAC, or with a BRCA2 or PALB2 germline mutation

* multifocal indicates > 3 PanIN lesions
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Variation in precursor lesions of pancreatic cancer among high-risk groups


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