Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers

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ABSTRACT

Purpose
Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis. Hereditary factors play a role in the development of PDAC in 3% to 5% of all patients. Surveillance of high-risk groups may facilitate detection of PDAC at an early stage. The aim of this study was to assess whether surveillance aids in the detection of early-stage PDAC or precursor lesions (PRLs) and improves the prognosis.

Patients and Methods
Screening outcomes were collected from three European centers that conduct prospective screening in high-risk groups including families with clustering of PDAC (familial pancreatic cancer [FPC]) or families with a gene defect that predisposes to PDAC. The surveillance program consisted of annual magnetic resonance imaging, magnetic resonance cholangiopancreatography, and/or endoscopic ultrasound.

Results
Four hundred eleven asymptomatic individuals participated in the surveillance programs, including 178 CDKN2A mutation carriers, 214 individuals with FPC, and 19 BRCA1/2 or PALB2 mutation carriers. PDAC was detected in 13 (7.3%) of 178 CDKN2A mutation carriers. The resection rate was 75%, and the 5-year survival rate was 74%. Two CDKN2A mutation carriers (1%) underwent surgical resection for low-risk PRL. Two individuals (0.9%) in the FPC cohort had a pancreatic tumor, including one advanced PDAC and one early grade 2 neuroendocrine tumor. Thirteen individuals with FPC (6.1%) underwent surgical resection for a suspected PRL, but only four (1.9%) had high-risk lesions (ie, high-grade intraductal papillary mucinous neoplasms or grade 3 pancreatic intraepithelial neoplasms). One BRCA2 mutation carrier was found to have PDAC, and another BRCA2 mutation carrier and a PALB2 mutation carrier underwent surgery and were found to have low-risk PRL. No serious complications occurred as consequence of the program.

Conclusion
Survveillance of CDKN2A mutation carriers is relatively successful, detecting most PDACs at a resectable stage. The benefit of surveillance in families with FPC is less evident.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, with a 5-year survival rate of only 5%. Despite progress in our understanding of PDAC development and improvements in surgical techniques, the survival rate has not substantially changed since the introduction of pancreaticoduodenectomy 80 years ago. Currently, surgical resection is the only potentially curative treatment for PDAC, but in approximately 80% of symptomatic patients, the tumor is already unresectable at the time of diagnosis. Improvement in the resectability of tumors requires detection of PDAC at an earlier stage. Selective screening of individuals at high risk for PDAC might be one way to reach this goal.

Hereditary factors play a role in the development of PDAC in 3% to 5% of all patients, and
individuals at increased risk of developing PDAC can be subdivided into those with an underlying gene defect such as CDKN2A, BRCA1/2, PALB2, and STK11 mutations and those individuals with a significant family history of PDAC (familial pancreatic cancer [FPC]). The risk of PDAC varies from 5% to 36% depending on the underlying gene defect. Disease risk in FPC depends on the number of relatives with PDAC and varies from 8% (two relatives) to 30% (three relatives).

Surveillance of individuals at high risk for PDAC complies with most of these requirements. The target group (ie, individuals with a substantial risk of PDAC) is well defined. Although the natural history of the disease is not completely known, studies have reported that patients with FPC as well as carriers of a CDKN2A mutation frequently develop PRLs including pancreatic intraepithelial neoplasms (PanINs) and intraductal papillary mucinous neoplasms (IPMNs).

Surveillance tools (magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography [MRCP], and endoscopic ultrasound [EUS]) that are able to detect small PRLs are available. Surveillance of individuals at high risk for PDAC uses these types of screening tools to detect early-stage PDAC or to the detection of relevant PRLs and to evaluate whether the program leads to improvements in prognosis.

### Study Design

The current study was made possible through the collaboration of three tertiary referral centers: the Department of Surgery at Philipps University in Marburg, the Department of Medical Oncology at Ramon y Cajal University Hospital in Madrid, and the Department of Gastroenterology at Leiden University Medical Center in Leiden. The study design was a retrospective evaluation of an ongoing prospective follow-up study. The three centers have conducted screening programs for IARs for PDAC over the past 4 to 15 years. The number of high-risk individuals and the type of hereditary PDAC or type of familial PDAC (ie, families with two first-degree relatives with PDAC [FPC2] or families with at least three first-degree relatives with PDAC [FPC3]) in the three centers are listed in Table 1. Only asymptomatic individuals were offered surveillance.

A detailed description of patient selection has been published previously. At Leiden University Medical Center, individuals with the Dutch founder mutation, a 19-base pair deletion of exon 2 of the CDKN2A gene p16-Leiden, were referred to the Department of Gastroenterology by a clinical geneticist. Only patients with a proven CDKN2A mutation or individuals diagnosed with a personal history of melanoma and a known mutation in the family were selected for the program. At Philipps University, a national registry for families with familial PDAC was established in 1999. Individuals from families with two or three first-degree relatives with PDAC were offered surveillance. Members of FPC families were also recruited through physician referral, the counseling office of the Deutsche Krebshilfe, or the FaPaCa Web site. In Madrid, patients were selected through a case-control study of patients with newly diagnosed pancreatic cancer and through 17 familial cancer units set up in Spain.

### Table 1. Distribution of Individuals at High Risk for PDAC Under Surveillance at the Three Expert Centers

<table>
<thead>
<tr>
<th>Factor</th>
<th>Marburg, Germany</th>
<th>Leiden, the Netherlands</th>
<th>Madrid, Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year surveillance program began</td>
<td>2002</td>
<td>2000</td>
<td>2010</td>
</tr>
<tr>
<td>Current surveillance recommendation</td>
<td>From 2002-2011 annual MRI, MRCP, and EUS; from 2011 to present annual MRI and MRCP, EUS ever 3 years or in case of suspicious MRI</td>
<td>Annual MRI; since 2012 option for EUS</td>
<td>Annual MRI and EUS</td>
</tr>
<tr>
<td>No. of high-risk individuals per group at January 1, 2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPC2</td>
<td>114</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>FPC3</td>
<td>70</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>CDKN2A/p16-Leiden</td>
<td></td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>BRCA2/PALB2</td>
<td>12</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Sex, No. of individuals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>81</td>
<td>72</td>
<td>24</td>
</tr>
<tr>
<td>Female</td>
<td>115</td>
<td>106</td>
<td>11</td>
</tr>
<tr>
<td>Total No. of MRI surveillance examinations at January 1, 2015</td>
<td>622</td>
<td>866</td>
<td>45</td>
</tr>
<tr>
<td>Total No. of surveillance EUSs at January 1, 2015</td>
<td>363</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average age at start of surveillance, years (range)</td>
<td>45.5 (25-73)</td>
<td>56 (37-75)</td>
<td>46.6 (29-81)</td>
</tr>
<tr>
<td>Average follow-up time, years (range)</td>
<td>3.4 (0.0-10.8)</td>
<td>4.4 (0.0-14.1)</td>
<td>1.3 (0.0-3.3)</td>
</tr>
</tbody>
</table>

Abbreviations: EUS, endoscopic ultrasound; FPC2, families with two first-degree relatives with familial pancreatic cancer; FPC3, families with at least three first-degree relatives with familial pancreatic cancer; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma.
In Leiden, surveillance started at the age of 45 years. In Marburg and Madrid, surveillance started at age 40 or 10 years earlier than the youngest age at diagnosis in the family.

The current study is an update of the outcome of surveillance that was published previously. All participants were fully informed of the age at diagnosis in the family.

**Surveillance Protocol**

The CDKN2A/p16-Leiden mutation carriers in Leiden were invited for an annual MRI/MRCP. Beginning in 2012, EUS was also offered as an option in addition to annual MRI. In the event of a small lesion, MRI was repeated 3 to 6 months later. In cases where there was serious suspicion of PDAC, additional EUS and CT scanning was performed. The surveillance program in Marburg included annual screening by MRI with MRCP and EUS between 2002 and 2010. Since 2011, follow-up imaging consisted of annual MRI with MRCP and EUS every third year or in case of suspicious MRI findings. If there was suspicion for a significant abnormality, IARs underwent repeated imaging after 4 weeks supplemented with EUS-guided fine-needle aspiration (FNA) in some individuals. The surveillance program in Madrid included annual EUS and MRI. All patients with confirmed suspicious lesions at the three centers were discussed within a multidisciplinary team, and a decision was made regarding the need of surgery. The criteria that were generally used to propose surgery were as follows: multiple cystic lesions greater than 10 mm, in particular, cystic lesions that showed significant growth or a solid component; solitary cystic lesions greater than 30 mm; solid lesions greater than 5 mm confirmed by MRI, EUS, and CT scanning, especially those that increase in size; a dilated main pancreatic duct (> 10 mm); and positive results of a biopsy.

The surveillance protocols used at the three centers are listed in Table 1. The data collected include number of IARs with a PRL or PDAC, age at diagnosis and surgery, site of the PRL and cancer, type of surgery, complications, histologic type of PRL, stage of PDAC, and survival rate of patients with PDAC. The observation time was from the start of the screening programs until January 1, 2015. In the evaluation of the surveillance program, we consider the program a success if a high-risk PRL (PanIN grade 3 lesions or IPMN with high-grade dysplasia) was detected and treated or an early PDAC (T1N0M0 with negative resection margins) was resected.

**Statistical Analysis**

Age-specific cumulative incidence of PDAC in the CDKN2A/p16-Leiden mutation carriers and the PDAC survival were calculated using Kaplan-Meier survival analysis. Analysis of the data was conducted using the SPSS version 23.0 (SPSS, Chicago, IL).

**RESULTS**

**CDKN2A/p16-Leiden Mutation Carriers**

**Patient characteristics.** One hundred seventy-eight CDKN2A mutation carriers comprising 177 p16-Leiden mutation carriers and one carrier of a CDKN2A (c.67G>C, G23R) mutation were included in the study; 106 of these patients (59.6%) were women, and 72 (40.4%) were men. The mean age at the start of the program was 56 years (range, 37 to 75 years), and the mean follow-up time was 53 months (range, 0 to 169 months). Seventeen patients (9.6%) were lost to follow-up. A total of 866 MRIs and 106 EUSs were performed.

**Surveillance outcomes: Pancreatic cancer.** PDAC was detected in 13 (7.3%) of the 178 mutation carriers, including eight women and five men. The mean age at diagnosis was 58 years (range, 39 to 74 years). The cumulative incidence of PDAC was 14% by the age of 70 years (Fig 1). Five tumors were diagnosed at first screening, and eight were detected during follow-up. Four tumors were located in the head of the pancreas, five in the tail, three in the body, and one in the transition area from head to body (Table 2). Nine patients underwent surgery, including three who underwent a distal pancreatectomy, two a Whipple procedure, one a subtotal pancreatectomy, one a resection of the body and a distal pancreatectomy, and two a distal pancreatectomy including splenectomy. In five (56%) of the nine patients, the lymph nodes were free of tumor, and in seven (78%) of nine patients, the resection margin was free of tumor. Of the four patients who did not undergo surgery, two patients had distant metastasis of PDAC, and a third...
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)/Sex</th>
<th>MRI Findings</th>
<th>Interval From Previous MRI to Cancer Diagnosis (months)</th>
<th>Findings at Previous MRI</th>
<th>Management</th>
<th>Histology</th>
<th>TNM Staging</th>
<th>Outcome</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72/F</td>
<td>22-mm tumor in head-body</td>
<td>11.3</td>
<td>Two duct ectasias</td>
<td>Subtotal pancreatectomy (excluding duodenum)</td>
<td>Well-differentiated ductal adenocarcinoma, resection margin positive; one of two nodes positive</td>
<td>T4N1M0</td>
<td>Died 4.5 months after diagnosis</td>
<td>PDAC</td>
</tr>
<tr>
<td>2</td>
<td>57/F</td>
<td>CT scan: 48-mm tumor in tail</td>
<td>4</td>
<td>In retrospect, there was a 1-cm lesion visible</td>
<td>No surgery because of liver metastases</td>
<td>—</td>
<td>T3NxM1</td>
<td>Died 15 months after diagnosis</td>
<td>PDAC metastases</td>
</tr>
<tr>
<td>3</td>
<td>58/M</td>
<td>10-mm tumor in body</td>
<td>5.1</td>
<td>Slightly irregular pancreatic duct</td>
<td>No surgery because of pulmonary metastases of melanoma</td>
<td>—</td>
<td>T1N0M0</td>
<td>Died 10 months after diagnosis</td>
<td>Melanoma metastases</td>
</tr>
<tr>
<td>4</td>
<td>58/M</td>
<td>30-mm tumor in tail</td>
<td>12.2</td>
<td>Normal</td>
<td>Distal pancreatectomy</td>
<td>Moderately differentiated ductal adenocarcinoma, resection margin positive; four of four nodes positive</td>
<td>T4N1M0</td>
<td>Died 22 months after diagnosis</td>
<td>PDAC</td>
</tr>
<tr>
<td>5</td>
<td>63/F</td>
<td>20-mm tumor in head</td>
<td>12.0</td>
<td>Normal</td>
<td>Unresectable</td>
<td>Adenocarcinoma distant metastases with positive nodes in transverse mesocolon</td>
<td>T2N3M1</td>
<td>Died 8 months after diagnosis</td>
<td>PDAC metastases</td>
</tr>
<tr>
<td>6</td>
<td>56/F</td>
<td>9-mm tumor in tail</td>
<td>12.3</td>
<td>Normal</td>
<td>Distal pancreatectomy</td>
<td>Moderately differentiated ductal adenocarcinoma, resection margin free; zero of 10 nodes positive</td>
<td>T1N0M0</td>
<td>Alive 25 months after diagnosis</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>57/F</td>
<td>36-mm tumor in tail</td>
<td>28.3</td>
<td>Normal</td>
<td>Distal pancreatectomy including splenectomy</td>
<td>Ductal adenocarcinoma, resection margin free</td>
<td>T2N0M0</td>
<td>Died 21 months after diagnosis</td>
<td>PDAC metastases</td>
</tr>
<tr>
<td>8</td>
<td>58/M</td>
<td>CT scan: 35-mm tumor in head</td>
<td>9.6</td>
<td>Normal</td>
<td>Unresectable</td>
<td>—</td>
<td>T4N0M0</td>
<td>Alive 6 months after diagnosis</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>62/F</td>
<td>5-mm tumor in head-body</td>
<td>Not applicable</td>
<td>—</td>
<td>Whipple</td>
<td>Well-differentiated ductal adenocarcinoma, resection margin free; zero of seven nodes positive</td>
<td>T1N0M0</td>
<td>Alive 73 months after diagnosis</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>49/M</td>
<td>37-mm tumor in tail</td>
<td>Not applicable</td>
<td>—</td>
<td>Distal pancreatectomy including splenectomy</td>
<td>Moderately differentiated ductal adenocarcinoma, resection margin free; zero of 13 nodes positive</td>
<td>T3N0M0</td>
<td>Died 35 months after diagnosis</td>
<td>PDAC metastases</td>
</tr>
<tr>
<td>11</td>
<td>74/F</td>
<td>15-mm tumor in tail</td>
<td>12.2</td>
<td>Stenosis pancreatic duct</td>
<td>Distal pancreatectomy</td>
<td>Moderately differentiated ductal adenocarcinoma, resection margin free; zero of 15 nodes positive</td>
<td>T1N0M0</td>
<td>Alive 6 months after diagnosis</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>47/F</td>
<td>57-mm tumor in body</td>
<td>Not applicable</td>
<td>—</td>
<td>Resection of pancreatic body and distal pancreatectomy</td>
<td>Moderately differentiated ductal adenocarcinoma, resection margin free; four of 15 nodes positive</td>
<td>T3N1M0</td>
<td>Died 18 months after diagnosis</td>
<td>PDAC</td>
</tr>
<tr>
<td>13</td>
<td>39/M</td>
<td>23-mm tumor in head</td>
<td>Not applicable</td>
<td>—</td>
<td>Whipple</td>
<td>Moderately differentiated ductal adenocarcinoma, resection margin free; four of 24 nodes positive</td>
<td>T2N1M0</td>
<td>Alive 36 months after diagnosis</td>
<td>—</td>
</tr>
</tbody>
</table>

(continued on following page)
Table 2. Detailed Information on CDKN2A Mutation Carriers Who Underwent Pancreatic Resection Under Surveillance (continued)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)/Sex</th>
<th>MRI Findings</th>
<th>Interval From Previous MRI to Cancer Diagnosis (months)</th>
<th>Findings at Previous MRI</th>
<th>Management</th>
<th>Histology</th>
<th>TNM Staging</th>
<th>Outcome</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>63/F</td>
<td>17-mm cystic lesion in body</td>
<td>3.9</td>
<td>15-mm cystic lesion in body</td>
<td>Distal pancreatectomy</td>
<td>Multifocal PanIN grade 1-2, BD-IPMN and severe multifocal fibrosis</td>
<td>—</td>
<td>Alive 87 months after diagnosis</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>67/F</td>
<td>15-mm solid lesion in head</td>
<td>Not applicable</td>
<td>—</td>
<td>Whipple</td>
<td>IPMN gastric-type LGD</td>
<td>—</td>
<td>Alive 17 months after diagnosis</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE. Patients 1, 3 to 8, 11, and 14 had an incident pancreatic ductal adenocarcinoma (PDAC) or precursor lesions (PRLs); patients 2, 9, 10, 12, 13, and 15 had a prevalent PDAC or PRLs. Patient 2 underwent CT scanning because of abdominal symptoms 4 months after a normal MRI scan and was found to have an unresectable tumor. In retrospect, a 10-mm lesion was found. Patient 8 presented with jaundice 9.6 months after a normal MRI scan. He was found to have an unresectable tumor in the head of the pancreas. Patient 5 developed abdominal symptoms 12 months after a normal MRI and was found to have a 20-mm solid lesion in the head of the pancreas with distant metastases.

Abbreviations: BD, branch duct; CT, computed tomography; F, female; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; M, male; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasm.
patient had extensive local disease. The fourth patient was found to have a small resectable pancreatic lesion but did not undergo surgical resection as a result of extensive pulmonary metastasis of a melanoma. The MRI images suggested that the pancreatic mass was a PDAC and not a melanoma metastasis. The overall resection rate was 75%.

One patient developed a second PDAC 54 months after a Whipple procedure of the primary tumor and underwent a distal pancreatectomy.²⁶ Eight of the 13 patients died; seven patients died as a result of PDAC, and one patient died as a result of melanoma metastasis. The overall 5-year survival rate was 24% (Fig 2). In terms of screening efficiency, 14 patients needed to be screened to detect one PDAC, and a total of 67 MRIs were needed to detect one PDAC.

Surveillance outcomes: PRLs. In 26 (14.6%) of 178 CDKN2A/p16-Leiden mutation carriers, a cystic lesion was found. Two individuals (1%), both women, underwent surgery (Table 2). In the first patient, the initial MRI/MRCP (2001) at the age of 63 years showed multiple ductectasia in side branches in the body of the pancreas with a diameter of 15 mm. In 2008, there was slight growth of the lesion, and an extended distal pancreatectomy was subsequently performed. Histologic examination revealed multifocal PanIN grade 1 to 2 lesions with branch duct (BD) IPMN and severe multifocal lobulocentric fibrosis. The patient is currently doing well 7.2 years later.

The second patient underwent a Whipple procedure at the age of 67 years as a result of a 15-mm solid lesion in the uncinate process detected at the first MRI. Histologic examination revealed a ductal adenocarcinoma pT3N1 (nine positive lymph nodes out of 22) M0 with tumor-free resection margins. The patient died 38 months after surgery as a result of metastatic disease.

The third individual was a member of an FPC2 family. EUS at the age of 48 revealed a 5-mm solid lesion in the tail of the pancreas. FNA biopsy showed a grade 2 neuroendocrine tumor. After distal pancreatectomy, the surgical specimen showed a T1 grade 2 neuroendocrine tumor, with tumor-free lymph nodes and resection margins. The patient is alive 2 years after surgery.

Surveillance outcomes: PRLs. Cystic lesions were detected in 112 (52%) of 214 IARs. A total of 13 patients (6.1%) underwent surgical resection because of suspicious lesions. The average age at surgery was 56 years (range, 42 to 69 years). Six IARs belonged to FPC2 families, and seven IARs belonged to FPC3 families.

Suspicious lesions were diagnosed at the first examination in five IARs (38.5%) and during follow-up in eight IARs (61.5%). The

![Fig 2. Overall survival of CDKN2A/p16 mutation carriers with pancreatic ductal adenocarcinoma (PDAC) detected during surveillance.](image-url)
lesions were mainly located in the pancreatic body and tail of IARs (n = 11); two IARs had suspicious lesions in the pancreatic head (Table 3).

Seven patients underwent a distal pancreatectomy, five patients a total pancreatectomy, and one patient a Whipple procedure. One additional patient underwent surgical exploration because of a suspicious lesion, but no abnormalities were found.

High-risk PRLs, including grade 3 PanIN (n = 3) and IPMN gastric type with high-grade dysplasia (n = 1), were detected on histopathologic analysis in four (1.9% of all screened cases)  

<table>
<thead>
<tr>
<th>No.*</th>
<th>Age (years)/ Sex</th>
<th>Disorder</th>
<th>MRI Findings</th>
<th>Incident or Prevalent</th>
<th>Management</th>
<th>Histology</th>
<th>Outcome</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>52/M</td>
<td>FPC2</td>
<td>Dilated main pancreatic duct with stenosis, head</td>
<td>Prevalent</td>
<td>Whipple</td>
<td>Main duct IPMN HGD</td>
<td>Alive 30 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 2</td>
<td>58/F</td>
<td>FPC2</td>
<td>Multiple (2-8 mm) cystic lesions, body and tail</td>
<td>Incident</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, BD-IPMN LGD, AFL</td>
<td>Died 22 months after surgery</td>
<td>Klatskin tumor</td>
</tr>
<tr>
<td>Patient 3</td>
<td>52/F</td>
<td>FPC3</td>
<td>Two ductectomies (5 and 7 mm)</td>
<td>Incident</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, PanIN grade 3, BD-IPMN LGD, AFL</td>
<td>Alive 55 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 4</td>
<td>64/F</td>
<td>FPC2</td>
<td>Multiple (2-13 mm) cystic lesions, body and tail</td>
<td>Incident</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, PanIN grade 3, BD-IPMN LGD, AFL</td>
<td>Alive 49 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 5</td>
<td>69/F</td>
<td>FPC3</td>
<td>Multiple (3-10 mm) ductectomies, body and tail</td>
<td>Prevalent</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, PanIN grade 3</td>
<td>Alive 16 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 6</td>
<td>47/M</td>
<td>FPC3</td>
<td>10-mm cystic lesion, head</td>
<td>Incident</td>
<td>Whipple</td>
<td>Multifocal PanIN grade 2, BD-IPMN LGD</td>
<td>Alive 29 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 7</td>
<td>54/F</td>
<td>FPC3</td>
<td>Multiple cystic lesions (3-10 mm), body and tail</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>Multifocal PanIN grade 2, BD-IPMN LGD, AFL</td>
<td>Alive 3 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 8</td>
<td>53/F</td>
<td>FPC3</td>
<td>8-mm hypointense lesion, tail</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>PanIN grade 2, BD-IPMN LGD</td>
<td>Alive 88 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 9</td>
<td>55/M</td>
<td>FPC3</td>
<td>6-mm hypointensive lesion, tail</td>
<td>Prevalent</td>
<td>Distal pancreatectomy</td>
<td>Lobular fibrosis with PanIN grade 1 lesion</td>
<td>Alive 94 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 10</td>
<td>60/M</td>
<td>FPC2</td>
<td>7-mm hypointense lesion, tail</td>
<td>Prevalent</td>
<td>Distal pancreatectomy</td>
<td>Focal fibrosis with PanIN grade 1 lesion</td>
<td>Alive 120 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 11</td>
<td>61/F</td>
<td>FPC3</td>
<td>Cystic lesions (14 and 22 mm), head and tail</td>
<td>Prevalent</td>
<td>Distal pancreatectomy</td>
<td>Serous cystadenoma</td>
<td>Alive 132 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 12</td>
<td>42/F</td>
<td>FPC2</td>
<td>Lobulated 32-mm macrocystic lesion, tail</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>Serous cystadenoma</td>
<td>Alive 98 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 13</td>
<td>61/F</td>
<td>FPC2</td>
<td>Normal (EUS 6-mm hypoechoic lesion, body)</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>Serous cystadenoma</td>
<td>Alive 86 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 14</td>
<td>53/F</td>
<td>FPC3</td>
<td>24-mm solid lesion, head; small cystic lesions, body and tail</td>
<td>Incident</td>
<td>Total pancreatectomy</td>
<td>Ductal adenocarcinoma; 9 of 22 nodes positive, pT3N1M0</td>
<td>Died 38 months after surgery</td>
<td>PDAC metastases</td>
</tr>
<tr>
<td>Patient 15</td>
<td>47/F</td>
<td>FPC3</td>
<td>10-mm cystic lesion</td>
<td>Prevalent</td>
<td>Distal pancreatectomy including splenectomy</td>
<td>FNA biopsy: malignant cells; surgical specimen: serous cystadenoma, no (residual) cancer</td>
<td>Alive 13 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>Patient 16</td>
<td>48/F</td>
<td>FPC2</td>
<td>Normal (EUS 5-mm solid lesion in body)</td>
<td>Prevalent</td>
<td>Distal pancreatectomy</td>
<td>T1 grade 2 neuroendocrine tumor, resection margins free; no positive nodes</td>
<td>Alive 28 months after surgery</td>
<td>—</td>
</tr>
</tbody>
</table>

**Table 3.** Detailed Information on Individuals at Risk for FPC Who Underwent Pancreatic Resection

<table>
<thead>
<tr>
<th>Patient No.*</th>
<th>Age (years)/ Sex</th>
<th>Disorder</th>
<th>MRI Findings</th>
<th>Incident or Prevalent</th>
<th>Management</th>
<th>Histology</th>
<th>Outcome</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52/M</td>
<td>FPC2</td>
<td>Dilated main pancreatic duct with stenosis, head</td>
<td>Prevalent</td>
<td>Whipple</td>
<td>Main duct IPMN HGD</td>
<td>Alive 30 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>58/F</td>
<td>FPC2</td>
<td>Multiple (2-8 mm) cystic lesions, body and tail</td>
<td>Incident</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, BD-IPMN LGD, AFL</td>
<td>Died 22 months after surgery</td>
<td>Klatskin tumor</td>
</tr>
<tr>
<td>3</td>
<td>52/F</td>
<td>FPC3</td>
<td>Two ductectomies (5 and 7 mm)</td>
<td>Incident</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, PanIN grade 3, BD-IPMN LGD, AFL</td>
<td>Alive 55 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>64/F</td>
<td>FPC2</td>
<td>Multiple (2-13 mm) cystic lesions, body and tail</td>
<td>Incident</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, PanIN grade 3, BD-IPMN LGD, AFL</td>
<td>Alive 49 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>69/F</td>
<td>FPC3</td>
<td>Multiple (3-10 mm) ductectomies, body and tail</td>
<td>Prevalent</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, PanIN grade 3</td>
<td>Alive 16 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>47/M</td>
<td>FPC3</td>
<td>10-mm cystic lesion, head</td>
<td>Incident</td>
<td>Whipple</td>
<td>Multifocal PanIN grade 2, BD-IPMN LGD</td>
<td>Alive 29 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>54/F</td>
<td>FPC3</td>
<td>Multiple cystic lesions (3-10 mm), body and tail</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>Multifocal PanIN grade 2, BD-IPMN LGD, AFL</td>
<td>Alive 3 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>53/F</td>
<td>FPC3</td>
<td>8-mm hypointense lesion, tail</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>PanIN grade 2, BD-IPMN LGD</td>
<td>Alive 88 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>55/M</td>
<td>FPC3</td>
<td>6-mm hypointensive lesion, tail</td>
<td>Prevalent</td>
<td>Distal pancreatectomy</td>
<td>Lobular fibrosis with PanIN grade 1 lesion</td>
<td>Alive 94 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>60/M</td>
<td>FPC2</td>
<td>7-mm hypointense lesion, tail</td>
<td>Prevalent</td>
<td>Distal pancreatectomy</td>
<td>Focal fibrosis with PanIN grade 1 lesion</td>
<td>Alive 120 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>61/F</td>
<td>FPC3</td>
<td>Cystic lesions (14 and 22 mm), head and tail</td>
<td>Prevalent</td>
<td>Distal pancreatectomy</td>
<td>Serous cystadenoma</td>
<td>Alive 132 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>42/F</td>
<td>FPC2</td>
<td>Lobulated 32-mm macrocystic lesion, tail</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>Serous cystadenoma</td>
<td>Alive 98 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>61/F</td>
<td>FPC2</td>
<td>Normal (EUS 6-mm hypoechoic lesion, body)</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>Serous cystadenoma</td>
<td>Alive 86 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>53/F</td>
<td>FPC3</td>
<td>24-mm solid lesion, head; small cystic lesions, body and tail</td>
<td>Incident</td>
<td>Total pancreatectomy</td>
<td>Ductal adenocarcinoma; 9 of 22 nodes positive, pT3N1M0</td>
<td>Died 38 months after surgery</td>
<td>PDAC metastases</td>
</tr>
<tr>
<td>15</td>
<td>47/F</td>
<td>FPC3</td>
<td>10-mm cystic lesion</td>
<td>Prevalent</td>
<td>Distal pancreatectomy including splenectomy</td>
<td>FNA biopsy: malignant cells; surgical specimen: serous cystadenoma, no (residual) cancer</td>
<td>Alive 13 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>48/F</td>
<td>FPC2</td>
<td>Normal (EUS 5-mm solid lesion in body)</td>
<td>Prevalent</td>
<td>Distal pancreatectomy</td>
<td>T1 grade 2 neuroendocrine tumor, resection margins free; no positive nodes</td>
<td>Alive 28 months after surgery</td>
<td>—</td>
</tr>
</tbody>
</table>

**Abbreviations:** AFL, atypical flat lesion; BD, branch duct; EUS, endoscopic ultrasound; F, female; FNA, fine-needle aspiration; FPC, familial pancreatic cancer; FPC2, families with two first-degree relatives with familial pancreatic cancer; FPC3, families with at least three first-degree relatives with familial pancreatic cancer; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; M, male; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasm; PDAC, pancreatic ductal adenocarcinoma.

*Patient 15 underwent surgery in Madrid, Spain; all other patients underwent surgery in Marburg, Germany.*
The patient is in good health 10 months after surgery. The second patient was a 67-year-old woman with a BRCA2 mutation. Multiple cystic lesions (3 to 8 mm) were detected on the first MRI. She demanded to undergo a total pancreatectomy. Histology showed multifocal grade 2 PanIN and atypical flat lesions. The patient is in good health 10 months after surgery.

The current study demonstrated that the resection rate of screen-detected PDAC in CDKN2A/p16-Leiden mutation carriers (75%) was much higher than reported for sporadic PDAC patients (15% to 20%) and for historical controls of CDKN2A/p16-Leiden mutation carriers with symptomatic PDAC (15%).23 The 5-year survival rate was substantially higher (24%) than the survival rate reported for patients with symptomatic sporadic PDAC (4% to 7%).28

PRLs were much more frequent in patients with FPC than in CDKN2A/p16-Leiden mutation carriers. Surgical resection was performed in 13 patients (6.1%) with FPC. According to the definition of high-risk lesions proposed by the expert group,29 only four lesions (1.9% of all screened patients) were high-risk lesions (grade 3 PanIN or high-grade gastric-type IPMN). However, another four IARs showed multifocal grade 2 PanIN lesions in combination with low-grade gastric-type BD-IPMNs and/or atypical flat lesions. Thus, the question arises of whether multifocal grade 2 PanIN lesions and low-grade IPMNs are also relevant PRLs for PDAC in the setting of FPC. In a large autopsy study, grade 2 PanIN lesions (previously referred to as atypical hyperplasia or low-grade dysplasia) were reported in 29% of patients with PDAC and only 0.7% of individuals without PDAC, suggesting that grade 2 PanIN lesions are also strongly associated with PDAC development.30 Although the time interval and rate at which grade 2 PanIN lesions progress to invasive cancer is unknown, one can hypothesize that multifocal grade 2 PanIN lesions and atypical flat lesions are biologically relevant in the setting of FPC.27

The strengths of the current study were the design as a prospective long-term follow-up study and the inclusion of a large series of high-risk individuals. In addition, family history in

Table 4. Detailed Information on BRCA2 and PALB2 Mutation Carriers Who Underwent Pancreatic Resection

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)/Sex</th>
<th>Disorder</th>
<th>MRI Findings</th>
<th>Incident or Prevalent</th>
<th>Management</th>
<th>Histology</th>
<th>Outcome</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68/F</td>
<td>BRCA2</td>
<td>Solid lesion (17 × 12 mm) in the tail</td>
<td>Incident</td>
<td>Distal pancreatectomy</td>
<td>Ductal adenocarcinoma; resection margins free; zero of 16 lymph nodes positive</td>
<td>Died 17 months after surgery</td>
<td>PDAC metastases</td>
</tr>
<tr>
<td>2</td>
<td>71/F</td>
<td>PALB2</td>
<td>Multiple cystic lesions (3-7 mm) in head</td>
<td>Prevalent</td>
<td>Whipple</td>
<td>Multifocal PanIN grade 2, BD-IPMN LGD</td>
<td>Alive 21 months after surgery</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>67/F</td>
<td>BRCA2</td>
<td>Multiple cystic lesions (3-8 mm) in body and tail</td>
<td>Prevalent</td>
<td>Total pancreatectomy</td>
<td>Multifocal PanIN grade 2, AFL</td>
<td>Alive 10 months after surgery</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: AFL, atypical flat lesion; BD, branch duct; F, female; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasm; PDAC, pancreatic ductal adenocarcinoma.

*All patients underwent surgery in Marburg, Germany.

of 13 IARs. Another four IARs revealed multifocal grade 2 PanIN lesions in combination with BD-IPMNs of the gastric type and/or atypical flat lesions,27 whereas three IARs showed serous cystadenomas and two IARs showed focal fibrosis with grade 1B PanIN lesions. Thus, five IARs (2.3%) were overtreated.

Four of 13 IARs developed postoperative complications, including three who developed a pancreatic fistula and one who had had a postoperative bleeding after Whipple resection at the pancreaticogastrostomy, which could be managed endoscopically. Twelve IARs are alive without evidence of relevant pancreatic lesions after a median follow-up of 52 months. One female patient developed an adenocarcinoma of the biliary tract 22 months after surgery and died as a result of liver failure.

BRCA1/2 or PALB2 Mutation Carriers

Patient characteristics. Nineteen individuals carried a BRCA1/2 or PALB2 mutation, including seven men and 12 women. One individual had a BRCA1 mutation, 12 individuals had a BRCA2 mutation, and six individuals had a PALB2 mutation. Average age at start of the program was 52.6 years (range, 25 to 70 years), and the average follow-up time was 32.7 months (range, 1 to 119 months).

Surveillance outcomes. In this cohort, only one individual (3.8%), a woman with a BRCA2 mutation, developed PDAC (Table 4). The lesion was detected at age 68 years. The previous MRI 1 year before revealed a small side BD-IPMN at the transition from head to body. The patient underwent a distal pancreatectomy that showed a 19-mm lesion in the tail; resection margins were free, and all lymph nodes were negative (zero of 16 nodes). Seventeen months after surgery, the patient died as a result of liver metastasis.

Two individuals underwent surgery for cystic lesions. The first patient was a 71-year-old woman with a PALB2 mutation. She underwent a Whipple procedure after finding a 12-mm lesion on the first MRI and EUS. Histology showed multifocal grade 2 PanIN lesions and BD-IPMNs with low-grade dysplasia. The patient is in good condition 21 months after surgery. The second
patients with FPC was verified by medical and pathology reports in greater than 95% of all patients. Furthermore, all participants in the Leiden series were found to have either a CDKN2A mutation or a personal history of melanoma and a close relative with a CDKN2A mutation. A weakness of the study was the lack of a control group.

One of the most important criteria defined by Wilson and Jungner was that surveillance should improve prognosis. Without a control group, it is difficult to determine with certainty the effects of the surveillance program on PDAC outcome. However, in view of the high resection rate and the better survival compared with the survival rates reported for patients with sporadic PDAC, surveillance of CDKN2A/p16-Leiden carriers complies with this requirement.

However, whether surveillance of FPC families meets this criterion is still questionable. The yield of PDAC is low (0.9%), and most screen-detected PDACs reported in the literature were advanced cancers. Likewise, the yield in terms of detection of relevant PRLs (grade 3 PanIN and high-grade IPMN) was low (1.0%). However, if surgical removal of multifocal grade 2 PanIN and multifocal BD-IPMNs is regarded as beneficial, the diagnostic yield increases to 3.7% (eight of 214 patients), and surveillance of FPC might also be considered effective.

In summary, surveillance of CDKN2A mutation carriers was relatively successful, detecting most PDACs at a resectable stage. The value of surveillance of FPC is still not clear, and the main effect seems to be prevention of PDAC by removal of PRLs.

REFERENCES


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Disclosures provided by the authors are available with this article at www.jco.org.

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28. Integraal Kankercentrum Nederland: Dutch Cancer Registry. www.cijfersoverkanker.nl


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Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers

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