Variation in Precursor Lesions of Pancreatic Cancer among High-Risk Groups

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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 behavior 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 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 (0–110 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% vs. 16% in p16-Leiden cohort), whereas PDAC was more common in the p16-Leiden cohort (7% vs. 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. On the basis of these findings, a more intensive surveillance program may be considered in this high-risk group. Clin Cancer Res; 19(2); 442–9. ©2012 AACR.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related 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, intra ductal papillary mucinous neoplasms (IPMN) and pancreatic intraepithelial neoplasias (PanIN; refs. 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, that is, individuals with an inherited predisposition to PDAC, screening could be valuable in improving the prognosis.

Approximately 3% to 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.
Precursor Lesions of Pancreatic Cancer in High-Risk Groups

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 conducted a detailed analysis of the outcome of surveillance in two high-risk groups, that is, individuals from familial pancreatic cancer (FPC) families and individuals with a p16-Leiden germline mutation. Radiologically detected cystic lesions and histologically confirmed intraductal papillary mucinous neoplasm (IPMN) lesions were more common in the FPC cohort, whereas the frequency of PDAC in the p16-Leiden cohort was 10 times higher than in the FPC cohort. Precursor lesions in this group seem to have a higher malignant potential. Therefore, a more intensive surveillance program should be considered in p16-Leiden mutation carriers.

FAMMM members with the Dutch founder mutation, a 19-base pair deletion of exon 2 of the CDKN2A gene (p16-Leiden), have a 15% to 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 2 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 2 affected first-degree relatives have a 6.4-fold increased risk, and the risk increases to 32-fold in case of 3 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 (23, 24). Magnetic resonance cholangiopancreatography (MRCP) is the standard modality for the detection of PDAC in FPC families, MRI/MRCP and optionally EUS was carried out. 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 carried out 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 about follow-up and MRI-technique were previously described for both groups (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 carried out. 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 carried out 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 about 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 and Leiden. All abnormal MRIs from the p16-Leiden cohort were revised by the radiologist from Marburg and Leiden.

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 pathologic finding in the pancreas by the imaging modalities, the findings were reviewed by an interdisciplinary board consisting of geneticists, psychono- 
ocologists, surgeons, and gastroenterologists at both sides. Criteria to recommend surgery included cystic lesions more than 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., 3 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. Klöppel), 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/noncystic 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. Continuous variables were compared using the independent samples t test or, when indicated, the Mann–Whitney test. A $P$-value of less than 0.05 was considered significant. Statistical analyses were conducted using SPSS 17.0 (SPSS Inc).

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### Table 1. Patient characteristics of the 2 cohorts

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

$pp$ = per person (mean), $n$ = number.
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 2 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 3 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, 13 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, that is, growth of a cystic lesion or PDAC-development. The individual with growth of the cystic lesion had a multicystic lesion with a diameter of 15 mm. During 6 years of follow-up there was no change in size, but 1 year later the diameter of the lesion increased to 17 mm. The 2 other individuals with progression at follow-up developed PDAC at the site of the cystic lesion. One of these individuals had 2 multicystic lesions (14.2 and 12 mm) and developed a 20 mm cancer detected by MRI 1 year later. The second patient had a small solitary lesion and irregular duct and developed a 10 mm cancer detected by MRI 5 months later. The 2 other incident cases of PDAC in the p16-Leiden cohort did not have a cystic lesion detected on previous MRI. One individual developed a 15 mm cancer 12 months after a normal MRI; the other individual developed a 40 mm cancer 28 months after a normal MRI. Thus, of the 4 incident PDAC cases, 2 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 4 individuals

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

\( n \) = number.

\(^*\)Numbers represent the number of individuals with one or more radiologically detected cystic lesions of the pancreas.

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

<table>
<thead>
<tr>
<th></th>
<th>p16-Leiden</th>
<th>FPC</th>
<th>( P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N ) Patients (%)</td>
<td>18 (16)</td>
<td>52 (42)</td>
<td>0.026</td>
</tr>
<tr>
<td>Mean age at detection (range)</td>
<td>60 (50–72)</td>
<td>54 (31–71)</td>
<td></td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main duct</td>
<td>3</td>
<td>1</td>
<td>0.020</td>
</tr>
<tr>
<td>Other than main duct(^*)</td>
<td>16</td>
<td>51</td>
<td>Ns</td>
</tr>
<tr>
<td>Detection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalent</td>
<td>9</td>
<td>49</td>
<td>Ns</td>
</tr>
<tr>
<td>Incident</td>
<td>10</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Appearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicystic</td>
<td>5</td>
<td>7</td>
<td>ns</td>
</tr>
<tr>
<td>Multiple unicystic</td>
<td>9</td>
<td>21</td>
<td>ns</td>
</tr>
<tr>
<td>Single unicystic</td>
<td>7</td>
<td>26</td>
<td>ns</td>
</tr>
<tr>
<td>Mean size (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicystic</td>
<td>14 mm (11–18)</td>
<td>11 mm (6–18)</td>
<td>ns</td>
</tr>
<tr>
<td>Multiple unicystic</td>
<td>4 mm (2–14)</td>
<td>5 mm (1–10)</td>
<td>ns</td>
</tr>
<tr>
<td>Single unicystic</td>
<td>3 mm (2–4)</td>
<td>6 mm (2–31)</td>
<td>ns</td>
</tr>
<tr>
<td>Site of pancreas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>10</td>
<td>18</td>
<td>ns</td>
</tr>
<tr>
<td>Corpus</td>
<td>13</td>
<td>23</td>
<td>0.041</td>
</tr>
<tr>
<td>Tail</td>
<td>9</td>
<td>27</td>
<td>ns</td>
</tr>
<tr>
<td>Proc. Uncinatus</td>
<td>1</td>
<td>–</td>
<td>ns</td>
</tr>
<tr>
<td>( N ) patients</td>
<td>13</td>
<td>33</td>
<td>ns</td>
</tr>
<tr>
<td>Mean follow-up (range)</td>
<td>2.5 years (0.25–8)</td>
<td>3.8 years (1–7)</td>
<td>0.027</td>
</tr>
<tr>
<td>Growth of lesion</td>
<td>1</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Development of PDAC(^*)</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

**NOTE:** Numbers represent the number of individuals. As an individual is able to have more than one lesion, overlap may exist. \( N \) = number, ns = not significant.

\(^*\)Includes branch duct cystic lesions with clear connection to the main duct and cystic lesion with uncertain connection to pancreatic ducts.

\(^{\text{At the same site of the cystic lesion(s).}}\)
had progression of their cystic lesions (12%). The MRIs of 3 individuals showed growth of a lesion, of which one was a multicystic lesion and 2 were unicystic lesions. Growth was slow in all 3 cases. One individual developed PDAC in the pancreatic head 2 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 5 mm. The proportion of individuals with progression of their cystic lesions was higher in the p16-Leiden cohort (23%) than in the FPC cohort (12%).

**Histologic findings in surgical specimens**

In the p16-Leiden cohort, 7 cases underwent surgery, of which 6 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 IPMN of branch duct (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 4 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 2 cases, the PDAC was accompanied by few low-grade PanIN lesions. One of 2 cases had in addition a PanIN3 lesion. IPMNs were not found in these cases. In total, 5 of 10 operated PDAC cases (50%; Tables 4 and 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 (as discussed earlier).

In the FPC cohort, one of the 12 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 2 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 2 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 2 high-risk groups. We have shown a significant difference in recognition of PanIN lesions and IPMNs between the 2 cohorts. The proportion of individuals with progression of their cystic lesions was higher in the p16-Leiden cohort (23%) than in the FPC cohort (12%).
precursor lesions and PDAC between the 2 groups. Cystic lesions were more common in the FPC cohort (42% vs. 16%), whereas the incidence of PDAC was 10 times higher in the p16-Leiden cohort (7% vs. 0.8%). Interestingly, on histologic 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 mainly 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 about 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 patients with FAMMM in their screening program also did not report confirmed IPMN lesions (15, 16, 20). IPMNs were lacking in the pancreas of genetically engineered mice with K-RAS and p16 germline mutations (28). Taken together these data show that the results of the current study are in line with previous screening investigations on FPC and p16-Leiden mutation carriers.

What is the role of cystic lesions in the development of PDAC? de Jong and colleagues (29) studied the prevalence of cystic lesions in the pancreas in the general population and have shown that 2.4% of almost 3,000 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 has shown a frequency of cystic lesions in the FPC and p16-Leiden 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 with 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 and colleagues, no MRCP was carried out 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 and colleagues (30) 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) and revealed 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 pathologic significance of these lesions. Shi and colleagues (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 4 PDAC cases not under surveillance, 3 of 10 PDAC cases (30%) had a few associated PanIN1 lesions, whereas in the FPC cohort, 6 of 12 patients (50%) had PanIN2-3 lesions that were not associated with a PDAC. In the FPC cohort, 5 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 3 cases. SCAs were not observed in p16-families. The screening studies in FPC families by Canto and colleagues (13) and Ludwig and colleagues (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 patients with FPC 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, that is, 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 2 high-risk groups. However, the data were retrieved from 2 ongoing prospective surveillance studies. Second, there are some differences between the 2 cohorts that might have influenced the results. The mean age of the FPC group at the start of surveillance is 7 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 2 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 2 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 with 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 2 years and those with lesions at shorter intervals.

In p16-Leiden, however, we have shown 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.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Writing, review, and/or revision of the manuscript: T.P. Potjer, I. Schot, P. Langer, J.T. Heatherhagen, E.P. Slater, G. Kloppel, W.H. Nederveen Cappel, M. Bargello, T.M. Gresen, H.F.A. Vasen, D.K. Bartsch
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): I. Schot, W.H. Nederveen Cappel, T.M. Gress, D.K. Bartsch
Study supervision: I. Schot, H.F.A. Vasen, D.K. Bartsch

Grant Support
Deutsche Krebshilfe (no. 109126 to D.K. Bartsch) for the FaPaCa project; ZonMW, an independent organization supported by the government, for the p16-Leiden cohort.

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Received August 20, 2012; revised October 26, 2012; accepted November 12, 2012; published OnlineFirst November 21, 2012.

References
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