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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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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 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 24%. 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

Surveillance 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.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, with a 5-year survival rate of only 5%.¹ 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,² 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]).³ The risk of PDAC varies from 5% to 36% depending on the underlying gene defect.⁴⁻⁷ Disease risk in FPC depends on the number of relatives with PDAC and varies from 8% (two relatives) to 30% (three relatives).³

Surveillance of these high-risk groups may lead to early detection of PDAC or detection of precursor lesions (PRLs), allowing curative surgical treatment. However, before undertaking surveillance on a global scale, we need to first establish whether the surveillance program meets the screening criteria set out by Wilson and Jungner.⁸ 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 [$> 10\%$]) 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).⁹

Surveillance tools (magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography [MRCP], and endoscopic ultrasound [EUS]) that are able to detect small PRLs are available.¹⁰⁻¹⁴ The surveillance program does not seem to be burdensome for the patients.¹⁵ However, it is not yet known whether the surveillance program meets the most important criteria, which are the early detection of cancer or PRLs and an improved prognosis. Previous studies reported data on the yields of surveillance but did not address the benefit of programs in terms of survival.^{10-14,16-21}

In the current study, we evaluated the long-term outcome of prospective surveillance of a large series of *CDKN2A/p16-Leiden* mutation carriers, *BRCA1/2* and *PALB2* mutation carriers, and individuals at risk (IARs) for FPC conducted at three expert centers

in Marburg, Germany; Leiden, the Netherlands; and Madrid, Spain. The aim of the study was to assess whether surveillance leads to detection of early-stage PDAC or to the detection of relevant PRLs and to evaluate whether the program leads to improvements in prognosis.

PATIENTS AND METHODS

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.^{22,23} 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 (the FaPaCa Registry) was established in 1999.²⁴ 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.²⁵

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

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

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.^{22,23} All participants were fully informed of the advantages and disadvantages of the program. The study was approved by the ethics committees of the respective centers.

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

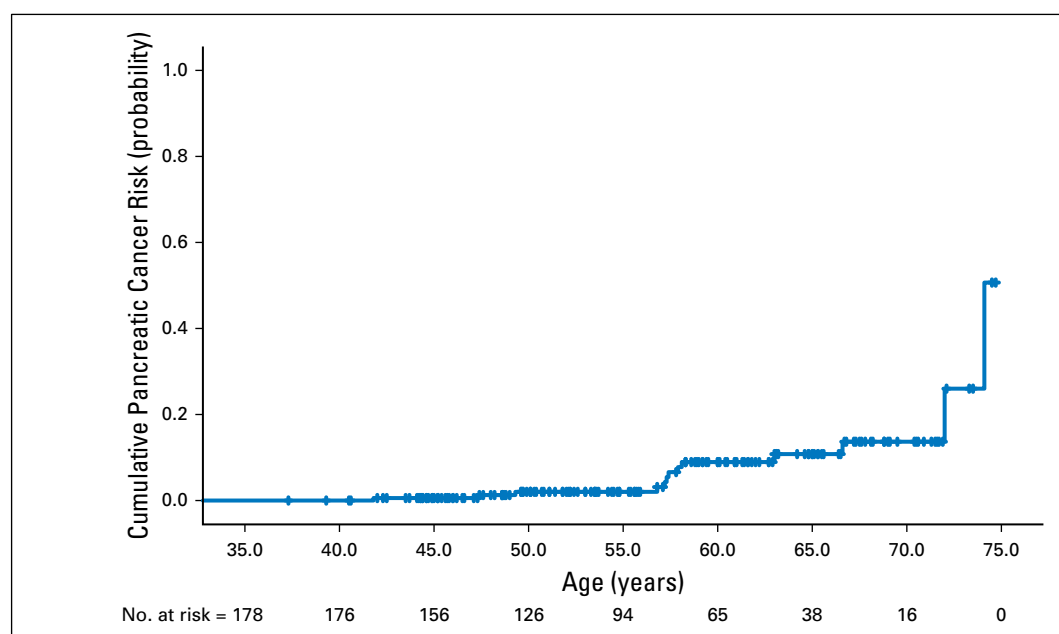


Fig 1. Cumulative incidence of pancreatic ductal adenocarcinoma for *CDKN2A/p16* mutation carriers.

Table 2. Detailed Information on CDKN2A Mutation Carriers Who Underwent Pancreatic Resection Under Surveillance

Patient No.	Age (years)/ Sex	MRI Findings	Interval From Previous MRI to Cancer Diagnosis (months)	Findings at Previous MRI	Management	Histology	TNM Staging	Outcome	Cause of Death
1	72/F	22-mm tumor in head-body	11.3	Two duct ectasias	Subtotal pancreatectomy (excluding duodenum)	Well-differentiated ductal adenocarcinoma, resection margin positive; one of two nodes positive	T4N1M0	Died 4.5 months after diagnosis	PDAC
2	57/F	CT scan: 48-mm tumor in tail	4	In retrospect, there was a 1-cm lesion visible	No surgery because of liver metastases	—	T3NxM1	Died 15 months after diagnosis	PDAC metastases
3	58/M	10-mm tumor in body	5.1	Slightly irregular pancreatic duct	No surgery because of pulmonary metastases of melanoma	—	T1N0M0	Died 10 months after diagnosis	Melanoma metastases
4	58/M	30-mm tumor in tail	12.2	Normal	Distal pancreatectomy	Moderately differentiated ductal adenocarcinoma, resection margin positive; four of four nodes positive	T4N1M0	Died 22 months after diagnosis	PDAC
5	63/F	20-mm tumor in head	12.0	Normal	Unresectable	Adenocarcinoma distant metastases with positive nodes in transverse mesocolon	T2N3M1	Died 8 months after diagnosis	PDAC metastases
6	56/F	9-mm tumor in tail	12.3	Normal	Distal pancreatectomy	Moderately differentiated ductal adenocarcinoma, resection margin free; zero of 10 nodes positive	T1N0M0	Alive 25 months after diagnosis	—
7	57/F	36-mm tumor in tail	28.3	Normal	Distal pancreatectomy including splenectomy	Ductal adenocarcinoma, resection margin free	T2N0M0	Died 21 months after diagnosis	PDAC metastases
8	58/M	CT scan: 35-mm tumor in head	9.6	Normal	Unresectable	—	T4NxM0	Alive 6 months after diagnosis	—
9	62/F	5-mm tumor in head-body	Not applicable	—	Whipple	Well-differentiated ductal adenocarcinoma, resection margin free; zero of seven nodes positive	T1N0M0	Alive 73 months after diagnosis	—
		7-mm tumor in corpus-tail			Distal pancreatectomy including splenectomy	Well-differentiated ductal adenocarcinoma, resection margin free; zero of 13 nodes positive	T1N0M0		
10	49/M	37-mm tumor in tail	Not applicable	—	Distal pancreatectomy including splenectomy	Moderately differentiated ductal adenocarcinoma, resection margin free; zero of 15 nodes positive	T3N0M0	Died 35 months after diagnosis	PDAC metastases
11	74/F	15-mm tumor in tail	12.2	Stenosis pancreatic duct	Distal pancreatectomy	Moderately differentiated ductal adenocarcinoma, resection margin free; zero of five nodes positive	T1N0M0	Alive 6 months after diagnosis	—
12	47/F	57-mm tumor in body	Not applicable	—	Resection of pancreatic body and distal pancreatectomy	Moderately differentiated ductal adenocarcinoma, resection margin free; four of 15 nodes positive	T3N1M0	Died 18 months after diagnosis	PDAC
13	39/M	23-mm tumor in head	Not applicable	—	Whipple	Moderately differentiated ductal adenocarcinoma, resection margin free; four of 24 nodes positive	T2N1M0	Alive 36 months after diagnosis	—

(continued on following page)

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

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

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 neoplasia.

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 metastases. 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 first MRI. Histologic examination revealed an IPMN gastric type with low-grade dysplasia. Seventeen months after surgery, the patient has slightly increased serum values of alkaline phosphatase and γ -glutamyltransferase but is asymptomatic and in a good health.

IARs for FPC

Patient characteristics. This patient group included 214 individuals, including 99 men and 115 women. One hundred

thirty-four individuals were from FPC2 families, and 80 were from FPC3 families.

Average age at start of the surveillance program was 48.2 years (range, 27 to 81 years), and the mean follow-up time was 2.8 years (range, 0.0 to 10.8 years). A total of 618 MRIs and 402 EUSs were performed as part of the follow-up program.

Surveillance outcomes: Pancreatic cancer. In the FPC group, the program detected a lesion suspected for PDAC in three female patients (1.4%). The first patient was a 53-year-old member of an FPC3 family. She missed two MRI screening visits and was diagnosed 26 months after the last normal screening visit with a 30-mm solid tumor in the head of the pancreas. The patient underwent a total pancreatectomy. Histologic examination showed 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 second patient was a 47-year-old member of an FPC3 family. At the first EUS, a 7-mm cystic lesion was visible in the body of the pancreas, which was subsequently confirmed by CT scanning. Two years later, the lesion was 10 mm. An EUS-guided FNA biopsy revealed malignant cells. The patient subsequently underwent a distal pancreatectomy and splenectomy. The surgical specimen showed a serous cystadenoma with atypical changes but no cancer. This patient is alive 1 year after surgery.

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

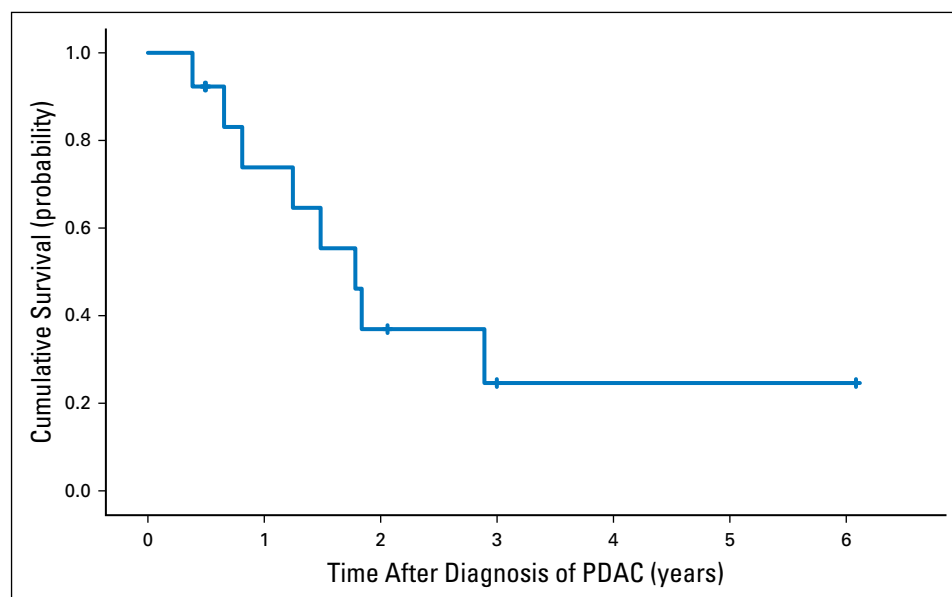


Fig 2. Overall survival of *CDKN2A/p16* mutation carriers with pancreatic ductal adenocarcinoma (PDAC) detected during surveillance.

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

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

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.

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

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

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

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.

DISCUSSION

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

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 Jungner⁸ 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.³ Likewise, the yield in terms of detection of relevant PRLs (grade 3 PanIN and high-grade IPMN) was low (1.9%). 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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2015. *CA Cancer J Clin* 65:5-29, 2015
2. Shi C, Hruban RH, Klein AP: Familial pancreatic cancer. *Arch Pathol Lab Med* 133:365-374, 2009
3. Bartsch DK, Gress TM, Langer P: Familial pancreatic cancer: Current knowledge. *Nat Rev Gastroenterol Hepatol* 9:445-453, 2012
4. de Snoo FA, Bishop DT, Bergman W, et al: Increased risk of cancer other than melanoma in *CDKN2A* founder mutation (p16-Leiden)-positive melanoma families. *Clin Cancer Res* 14:7151-7157, 2008
5. van Lier MG, Wagner A, Mathus-Vliegen EM, et al: High cancer risk in Peutz-Jeghers syndrome: A systematic review and surveillance recommendations. *Am J Gastroenterol* 105:1258-1264, 2010
6. Vasen HF, Gruis NA, Frants RR, et al: Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). *Int J Cancer* 87:809-811, 2000
7. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al: Cancer risks in *BRCA2* families: Estimates for sites other than breast and ovary. *J Med Genet* 42:711-719, 2005
8. Wilson JMG, Jungner G: Principles and Practice of Screening for Disease. Geneva, Switzerland, World Health Organization, 1968
9. Potjer TP, Schot I, Langer P, et al: Variation in precursor lesions of pancreatic cancer among high-risk groups. *Clin Cancer Res* 19:442-449, 2013
10. Al-Sukhni W, Borgida A, Rothenmund H, et al: Screening for pancreatic cancer in a high-risk cohort: An eight-year experience. *J Gastrointest Surg* 16:771-783, 2012
11. Canto MI, Goggins M, Yeo CJ, et al: Screening for pancreatic neoplasia in high-risk individuals: An EUS-based approach. *Clin Gastroenterol Hepatol* 2:606-621, 2004
12. Canto MI, Goggins M, Hruban RH, et al: Screening for early pancreatic neoplasia in high-risk individuals: A prospective controlled study. *Clin Gastroenterol Hepatol* 4:766-781, 2006
13. Harinck F, Konings IC, Kluij I, et al: A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. *Gut pii:gutjnl-2014-308008*, 2015
14. Langer P, Kann PH, Fendrich V, et al: Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut* 58:1410-1418, 2009
15. Harinck F, Nagtegaal T, Kluij I, et al: Feasibility of a pancreatic cancer surveillance program from a psychological point of view. *Genet Med* 13:1015-1024, 2011
16. Brentnall TA: Pancreatic cancer surveillance: Learning as we go. *Am J Gastroenterol* 106:955-956, 2011
17. Canto MI, Hruban RH, Fishman EK, et al: Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology* 142:796-804, 2012
18. Del Chiaro M, Verbeke CS, Kartalis N, et al: Short-term results of a magnetic resonance imaging-based Swedish screening program for individuals at risk for pancreatic cancer. *JAMA Surg* 150:512-518, 2015
19. Kimmey MB, Bronner MP, Byrd DR, et al: Screening and surveillance for hereditary pancreatic cancer. *Gastrointest Endosc* 56:S82-S86, 2002 (suppl 4)
20. Poley JW, Kluij I, Gouma DJ, et al: The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol* 104:2175-2181, 2009
21. Verna EC, Hwang C, Stevens PD, et al: Pancreatic cancer screening in a prospective cohort of high-risk patients: A comprehensive strategy of imaging and genetics. *Clin Cancer Res* 16:5028-5037, 2010
22. Schneider R, Slater EP, Sina M, et al: German national case collection for familial pancreatic cancer (FaPaCa): Ten years experience. *Fam Cancer* 10:323-330, 2011
23. Vasen HF, Wasser M, van Mil A, et al: Magnetic resonance imaging surveillance detects early-stage pancreatic cancer in carriers of a p16-Leiden mutation. *Gastroenterology* 140:850-856, 2011
24. Bartsch DK, Sina-Frey M, Ziegler A, et al: Update of familial pancreatic cancer in Germany. *Pancreatology* 1:510-516, 2001
25. Mocchi E, Guillen-Ponce C, Earl J, et al: PanGen-Fam: Spanish registry of hereditary pancreatic cancer. *Eur J Cancer* 51:1911-1917, 2015
26. Potjer TP, Bartsch DK, Slater EP, et al: Limited resection of pancreatic cancer in high-risk patients can result in a second primary. *Gut* 64:1342-1344, 2015

27. Aichler M, Seiler C, Tost M, et al: Origin of pancreatic ductal adenocarcinoma from atypical flat lesions: A comparative study in transgenic mice and human tissues. *J Pathol* 226:723-734, 2012
28. Integraal Kankercentrum Nederland: Dutch Cancer Registry. www.cijfersoverkanker.nl
29. Canto MI, Harinck F, Hruban RH, et al: International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 62:339-347, 2013
30. Kozuka S, Sassa R, Taki T, et al: Relation of pancreatic duct hyperplasia to carcinoma. *Cancer* 43: 1418-1428, 1979

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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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