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Research Article

Cancer Prevention Research

High Growth Rate of Pancreatic Ductal Adenocarcinoma in *CDKN2A-p16-Leiden* Mutation Carriers

Isaura S. Ibrahim[1], Martin N. Wasser[2], Yinghui Wu[3], Akin Inderson[1], Wouter H. de Vos tot Nederveen Cappel[4], Hans Morreau[5], Frederik J. Hes[6], Roeland A. Veenendaal[1], Hein Putter[7], Shirin Feshtali[2], Anneke M. van Mil[6], Nelleke A. Gruis[8], Rob A. Tollenaar[9], Wilma Bergman[8], Bert A. Bonsing[9], and Hans F.A. Vasen[1]

Abstract

CDKN2A-p16-Leiden mutation carriers have a 20% to 25% risk of developing pancreatic ductal adenocarcinoma (PDAC). Better understanding of the natural course of PDAC might allow the surveillance protocol to be improved. The aims of the study were to evaluate the role of cystic precursor lesions in the development of PDAC and to assess the growth rate. In 2000, a surveillance program was initiated, consisting of annual MRI in carriers of a *CDKN2A-p16-Leiden* mutation. The study cohort included 204 (42% male) patients. Cystic precursor lesions were found in 52 (25%) of 204 mutation carriers. Five (9.7%) of 52 mutation carriers with cystic lesions and 8 (7.0%) of 114 mutation carriers without cystic lesions developed PDAC ($P = 0.56$). Three of 6 patients with a cystic lesion of $\geq$10 mm developed PDAC. The median size of all incident PDAC detected between 9 and 12 months since the previous normal MRI was 15 mm, suggesting an annual growth rate of about 15 mm/year. In conclusion, our findings show that patients with and without a cystic lesions have a similar risk of PDAC. However, cystic precursor lesions between 10 and 20 mm increase the risk of PDAC substantially. In view of the large size of the screen-detected tumors, a shorter interval of screening might be recommended for all patients. *Cancer Prev Res; 11(9); 551–6. ©2018 AACR.*

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal form of cancer, with a 5-year survival rate of only 5% to 7% (1). Early detection may improve the prognosis of PDAC. Due to the overall low incidence of the disease and the lack of easily applicable screening tools, population-based screening for PDAC is currently not recommended. However, surveillance of individuals with an increased risk of PDAC might be more valuable and has increasingly been implemented worldwide over the last 15 years (2–9).

[1]Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, the Netherlands. [2]Department of Radiology, Leiden University Medical Centre, Leiden, the Netherlands. [3]Department of Radiology, West Suffolk Hospital, Bury St. Edmunds, United Kingdom. [4]Department of Gastroenterology and Hepatology, Isala Clinics, Zwolle, the Netherlands. [5]Department of Pathology, Leiden University Medical Centre, Leiden, the Netherlands. [6]Department of Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands. [7]Department of Medical Statistics, Leiden University Medical Centre, Leiden, the Netherlands. [8]Department of Dermatology, Leiden University Medical Centre, Leiden, the Netherlands. [9]Department of Surgery, Leiden University Medical Centre, Leiden, the Netherlands.

Corresponding Author: Isaura Shahnaaz Ibrahim, Leiden University Medical Centre, Albinusdreef 2, 2333ZA Leiden, the Netherlands. Phone: 31624555383; E-mail: i.s.ibrahim@lumc.nl

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It has been reported that 3% to 10% of patients with PDAC have a positive family history for this cancer (10). An estimated 3% to 5% of all PDAC are caused by an underlying gene defect (11). *CDKN2A* mutations together with *BRCA2-*, *ATM-* and *PALB2* mutations are the most frequent identified gene defects (12). In the Netherlands, a founder mutation in the *CDKN2A* gene, a 19-base pair deletion called *p16-Leiden*, is the most common cause of familial melanoma and PDAC. The lifetime risk of PDAC in *CDKN2A-p16-Leiden* mutation carriers is 20% to 25% (7, 13).

In a recent multicenter study, we demonstrated that annual surveillance of a large Dutch cohort of *CDKN2A-p16-Leiden* mutation carriers using MRI resulted in a higher resection rate of screen-detected PDAC compared with symptomatic PDAC (7). Although this study was the first to demonstrate success in detecting early cancers in a high-risk population (14), the surveillance program did not prevent all cancer deaths. Thorough understanding of the natural course of PDAC might be helpful to improve the screening protocol.

Pancreatic intraepithelial neoplasms (PanIN) and intraductal papillary mucinous neoplasms (IPMN) have been identified as common precursor lesions of PDAC (15–17).

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Recently, we reported a lower frequency of cystic precursor lesions in *CDKN2A-p16-Leiden* mutation carriers compared with patients from families with familial pancreatic cancer (FPC; ref. 18). This observation suggests that the process of carcinogenesis in *CDKN2A-p16-Leiden* mutation carriers might be different from that in FPC. To further understand this issue, we needed to determine whether cystic precursor lesions increase in size over time and develop into PDAC. If cystic lesions indeed play a role in carcinogenesis in this high-risk group, surveillance would be better targeted to patients with cystic precursor lesions. Finally, information on the growth rate of PDAC might be helpful in decision making regarding appropriate screening intervals.

The main aims of the present study are, therefore, (1) to evaluate the role of precursor lesions in the development of PDAC in *CDKN2A-p16-Leiden* mutation carriers and (2) to assess the size of screen-detected PDAC in relation to the screening interval.

Patients and Methods

Prospective surveillance cohort

In 2000, a surveillance program was initiated in *CDKN2A* mutation carriers ($n = 204$), including 201 with a *CDKN2A-p16-Leiden* founder mutation and 3 with a pathogenic *CDKN2A* variant. The median follow-up is 5.0 years (0.2–15.6 years). The program consists of annual MRI and, optionally, endoscopic ultrasound (EUS) at 6 months. In case of a highly suspicious lesion, additional EUS and CT-scanning is performed within 2 to 3 weeks. If there is little suspicion of malignancy, the MRI is repeated within 3 to 6 months. A detailed description of the surveillance protocol has been published previously (7, 8). The study was approved by the Institutional Review Board of the Leiden University Medical Centre (P00.107). Oral or written informed consent was received from all patients.

MRI techniques

MRI examinations were performed on a 1.5-T between 2000 and 2012 and since 2012 a 3T scanner (Philips). The examinations included T2-weighted images, (3D) MRCP series, and dynamic series before and after intravenous administration of contrast (Dotarem).

Data collection

Patients were selected for the study on the basis of a proven *CDKN2A* mutation. We re-evaluated the most recent MRI examination for all study participants. If a cystic lesion was detected, all previous MRI examinations were re-evaluated to assess whether the cystic lesion was already present at any earlier time point. The size of the cyst on all examinations was recorded. In a few cases with cystic lesions, the initial MRI examinations could not be re-evaluated due to insufficient resolution. If these cystic lesions were stable over many years but could not be detected on the first "old" suboptimal quality MRI examinations, we considered these lesions as "probably prevalent" cystic lesions. Data were collected on the type of lesions (cysts or IPMN), type of IPMN (side branch, main branch, or mixed IPMN), size, location, and multiplicity of the lesions. Side-branch IPMN was suspected if there was communication of the cystic lesion with the main duct. Main duct IPMN was defined as diffuse or segmental dilatation of the main pancreatic duct of >10 mm without any significant lesion except for IPMN (19). Progression of cysts or IPMN was defined as an increase in diameter of $\geq$3 mm or the development of PDAC. All studies were read on a digital PACS-workstation by a single abdominal radiologist (M.N. Wasser) with more than 20 years of MRI-reading experience.

Screen-detected PDAC

The collected data for all screen-detected PDAC included the size at diagnosis and the interval since the previous MRI. The size was based on measurements of the tumor in the surgical specimen or measurements of the diameter of the tumor on imaging. Previous MRI examinations were evaluated to assess whether cystic lesions were visible in retrospect, as well as the increase in diameter of these lesions over time. In addition, we evaluated the relation between the size of the PDAC at diagnosis and the surveillance interval.

Statistical analysis

The observation time was from the first until the last MRI performed before January 1, 2017. The Pearson χ^2 test and Student t test were used to compare variables between groups. The tests were considered statistically significant if $P < 0.05$. Data analysis was carried out in SPSS v. 22 for MAC.

Results

The study cohort included 204 patients (42% male) with a *CDKN2A*-mutation (mean age, 52 years; SD 8.0). A total of 11 patients (5.4%) were lost to follow-up. Of the 204 mutation carriers, 52 (25%) were found to have at least one prevalent cystic lesion including 2 patients with a prevalent PDAC. The total number of prevalent cysts was 98, 71 (72%) of which were suspected side-branch IPMN. Median cyst size was 3 mm (range, 2–19 mm), and 87 (89%) of the 98 cysts were smaller than 10 mm.

A total of 166 of the 204 patients in the study group had at least 2 MRIs. Fifty-two patients (31%) were found to have at least 1 prevalent or incident cystic lesion. The median follow-up of all patients with >2 MRIs from the first to the most recent MRI was 5.0 years (range, 0.2–15.6 years). Growth (3 mm or more) of a cystic lesion was observed in 7 (13.4%) of the 52 patients with prevalent or incident cysts. Six of the 52 patients had at least 1 cystic lesion of 10 mm or more, 3 of which developed PDAC.

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Table 1. Characteristics of patients with incident PDAC detected in the patients with cystic lesions

Patient number/sex (M/F)	Age at diagnosis (years)	Interval since previous MRI (months)	Size of cystic lesions at previous MRI	Site and size of PDAC	TNM staging
1. F	72	11	Head 13 mm Body 7, 8 mm Tail 2,2,3 mm	Head 22 mm	T4N1M0
2. F	67	21	Head 6 mm Uncinate 13 mm Body 19 mm Tail 14 mm	Head Diameter unknown	TxNxM0 Irresectable tumor
3. F	64	2	Head 17 mm[a]	Head/uncinate process 29 mm	T2N3M1
4. F	67	11	Tail 8 mm	Head 13 mm	T1N1M0
5. F	51	4.5	Head 3,3,3,3 mm Tail 3 mm	Body 18 mm	T1N0M0

[a]12 months after the normal previous MRI, a new cystic lesion of 17 mm was found; subsequent imaging 2 months later showed a tumor which was retrospectively also present at the previous MRI.

Five of all 52 (9.6%) patients with an incident or prevalent cystic lesion developed a PDAC after a mean follow-up of 6.5 years (SD 4.2). Three of these cancers developed at the site of the cyst (Table 1). Eight (7.0%) of the 114 patients with at least 2 MRIs and without a prevalent or incident cystic lesion developed PDAC ($P = 0.56$) after a median follow-up of 5.4 years (range, 0.5–15.6 years). The characteristics of the patients with and without cystic precursor lesions are shown in Table 2.

A total of 18 PDACs (7 males) were detected by the surveillance program in the 204 mutation carriers. One patient was excluded because the diameter of the tumor could not be determined. The mean age at diagnosis was 57.8 years (SD 8.9). Five (29%) of the cancers were detected at first screening and 12 (71%) during follow-up. The median follow-up of the 12 incident PDAC since the previous normal MRI was 12 months (range, 5–28 months). The size of the screen-detected PDAC in relation to the interval since the previous normal MRI is shown in Fig. 1. The median size of all screen-detected incident PDAC was 17 mm (range, 9–39 mm). The median size of the PDACs detected between 9 and 12 months since the last normal MRI was 15 mm (range, 9–39 mm).

Discussion

To investigate the role of cystic precursor lesions in the development of PDAC in high-risk individuals, we evaluated the outcome of MRI-based surveillance in a large cohort of *CDKN2A-p16-Leiden* mutation carriers. Cystic lesions were found in a quarter of all mutation carriers. Although most cystic lesions remained stable over time, 3 of 6 patients with at least 1 cystic lesion between 10 and 20 mm developed PDAC. Considering the entire group of mutation carriers, 5 patients with a cystic lesion (9.6%) developed PDAC and a similar proportion (7.0%) developed PDAC in the absence of cysts. The median size of all incident screen-detected PDAC was 17 mm (range, 9–39 mm).

It is generally accepted that PDAC originates from neoplastic epithelial proliferation, including PanIN lesions and IPMNs. The cystic lesions detected by imaging may represent such lesions (7, 18, 20). The prevalence of cystic lesions in our cohort appears to be comparable with frequencies reported in the general population (0.7% to 44.7%; refs. 21–26).

In the present study, 5 (9.6%) of the 52 *CDKN2A-P16-Leiden* mutation carriers with cystic lesions developed PDAC. This is higher than reported in population studies that examined the malignancy rate of cystic lesions (27, 28). However, we also found that the malignancy rate (7.0%) in mutation carriers without a cystic lesion was similar to the rate in the mutation carriers with cystic lesions. Moreover, two out of five mutation carriers with cystic lesions developed PDAC at a site other than the site of the cysts. On the other hand, 3 of 6 patients with a cystic lesion between 10 and 20 mm developed PDAC at the site of the cyst.

In order to investigate further possibilities for improvement of the surveillance program, we evaluated the size of screen-detected PDACs in relation to the screening interval. The median size of PDAC detected 9 to 12 months since the

Table 2. Characteristics of patients with and without cystic lesions

	With cystic lesions	Without cystic lesions	*P* value
Number of patients	52	114	
Sex distribution (M/F; male %)	18/34 (M 35%)	45/69 (M 39%)	0.55
Mean age first MRI (years)	52.6 (SD 7.2)	51.5 (SD 7.8)	0.36
Mean/median follow-up time since first MRI (years)	6.5 (SD 4.2)	5.4 (0.5–15.6)	0.08
Median follow-up time since diagnosis of cystic lesion (years)	4.3 (0.2–13)	n.a.	n.a.
Number of PDAC	5 (9.6%)	8 (7%)	0.56

Abbreviation: n.a., not applicable.

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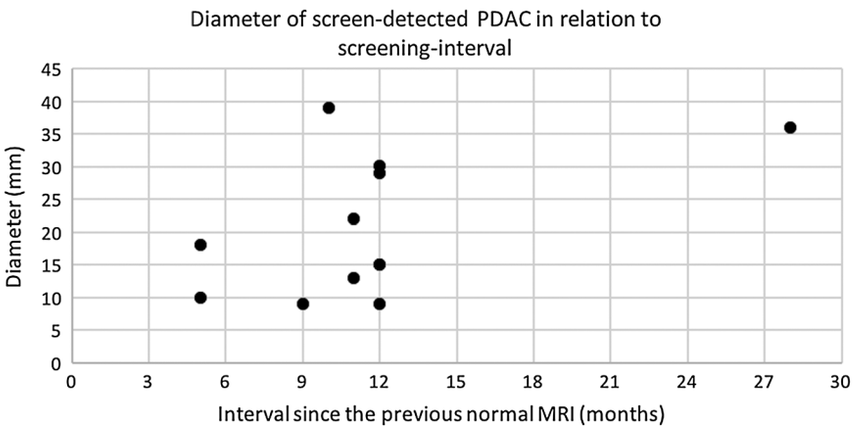

Figure 1.
Diameter of screen-detected PDAC in relation to screening interval.

previous normal MRI was 15 mm, indicating a growth rate of about 15 mm per year.

What are the explanations for our findings? In previous studies, we reported that cystic precursor lesions were less common in carriers of a *CDKN2A*-p16-Leiden mutation compared with individuals with FPC (7, 18). In contrast, the risk of PDAC was much higher in *CDKN2A*-p16-Leiden mutation carriers compared with FPC individuals. These findings suggest that cystic precursor lesions play a minor role in the development of PDAC in *CDKN2A*-p16-Leiden mutation carriers. The similar risk of PDAC observed in patients with and without cystic precursor lesions in the current study is in agreement with this hypothesis.

The development from PanIN grade 1 into PanIN grades 2 and 3, and ultimately PDAC is characterized by accumulation of mutations in genes associated with the development of PDAC including alterations of K-RAS, CDKN2A/P16, TP53, and DPC4 genes. Because the patients in our cohort have already such a (germline) mutation at birth, carcinogenesis and development of PDAC may be accelerated. Such accelerated development of PDAC arising from early (invisible) PanIN lesions may explain the similar risk of PDAC observed in the current study in patients with and without cystic precursor lesions. It may also explain the early age of diagnosis of screen-detected PDAC (56 years vs. 66 years reported for sporadic PDAC) and the high growth rate. More studies are needed to confirm this hypothesis.

The current study has several strengths. Firstly, two particularly robust aspects of the study were the prospective design and the long duration of follow-up. Secondly, the study group is the largest homogeneous group of carriers under surveillance, with almost all carrying a Dutch founder mutation. A limitation of the study is that the quality of the MRI technique changed over time with the replacement of a 1.5 T system by a 3.0 T system in 2012. A second limitation is that as the current study predominantly included individuals with a single Dutch founder mutation in *CDKN2A*, it may not be generalizable to other individuals with hereditary pancreatic cancer.

What are the consequences of our findings for clinical practice? In average risk subjects with cystic lesions suspected for BD-IPMNs, resection is considered if the patient has symptoms attributable to the cyst(s), if the cysts are >3 cm in size, or if the cysts contain mural nodules (17). At the meeting of the International Cancer of the Pancreas Screening Consortium (29), there was no consensus on the size criterion for resection of cystic lesions in high-risk individuals, but the majority agreed that surgery should be considered for suspected BD-IPMNs which were $\geq$2 cm. Although larger studies are needed to confirm our findings, a more aggressive approach in this specific group of mutation carriers appears to be justified by our results. In patients with a *CDKN2A-p16-Leiden* mutation with cystic lesions between 10 and 20 mm, the screening interval might be shortened to 6 to 9 months or additional EUS might be performed. If cystic lesions show worrisome features, surgery is recommended. In view of the substantial size of PDACs detected at 1-year intervals, shorter screening intervals might be recommended for all patients, if further studies show this approach to be cost-effective. Future studies should also address whether the known risk factors for PDAC such as smoking, body mass index, and a positive family history for PDAC are associated with an increased risk in high-risk groups. In a recent analysis of risk factors in our cohort of *CDKN2A-p16* mutation carriers, we found that smoking and a positive family history for PDAC were associated with an increased risk of PDAC, although the association was not statistically significant due to a lack of power.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: I.S. Ibrahim, M.N. Wasser, W.H. de Vos tot Nederveen Cappel, R.A. Veenendaal, H.F.A. Vasen

Development of methodology: I.S. Ibrahim, W.H. de Vos tot Nederveen Cappel

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.N. Wasser, Y. Wu, A. Inderson, H. Morreau, F.J. Hes, R.A. Veenendaal, A.M. van Mil, N.A. Gruis, R.A. Tollenaar, W. Bergman, B.A. Bonsing, H.F.A. Vasen
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I.S. Ibrahim, M.N. Wasser, Y. Wu, A. Inderson, H. Putter, B.A. Bonsing, H.F.A. Vasen
Writing, review, and/or revision of the manuscript: I.S. Ibrahim, M.N. Wasser, A. Inderson, W.H. de Vos tot Nederveen Cappel, F.J. Hes, R.A. Veenendaal, H. Putter, S. Feshtali, N.A. Gruis, R.A. Tollenaar, W. Bergman, B.A. Bonsing, H.F.A. Vasen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): I.S. Ibrahim, R.A. Veenendaal
Study supervision: I.S. Ibrahim, R.A. Veenendaal, H.F.A. Vasen

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