



## Risk of multiple pancreatic cancers in *CDKN2A-p16-Leiden* mutation carriers

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### Abstract

*CDKN2A-p16-Leiden* mutation carriers have a substantial risk of developing pancreatic ductal adenocarcinoma (PDAC). One of the main clinical features of hereditary cancer is the development of multiple cancers. Since 2000, we have run a surveillance program for *CDKN2A-p16-Leiden* mutation carriers. The patients are offered a yearly MRI with optionally endoscopic ultrasound. In patients with a confirmed lesion, usually, a partial resection of the pancreas is recommended. A total of 18 PDAC (8.3%) were detected in 218 mutation carriers. In this report, we describe two *CDKN2A-p16-Leiden* patients with a synchronous and metachronous PDAC. Including two previously-reported cases, we identified four patients with multiple PDAC: two of 18 patients within the surveillance program (11%) and two patients with a proven *CDKN2A-p16-Leiden* mutation not participating in the surveillance program. In conclusion, this study demonstrated a high risk of developing multiple PDAC in *CDKN2A-p16-Leiden* mutation carriers. After detecting a primary tumor, it is very important to exclude the presence of a second synchronous tumor. Moreover, after a partial pancreatectomy for PDAC, close surveillance is necessary. In view of the current findings, offering a total pancreatectomy might be an appropriate option in patients with an early PDAC.

### Introduction

Hereditary factors account for 3–5% of all pancreatic ductal adenocarcinomas (PDAC) [1]. In approximately 4% of

familial PDAC, a cancer is caused by an underlying defect in genes including *BRCA2*, *CDKN2A*, *PALB2*, the mismatch repair (MMR) genes, and *STK11* [2]. The lifetime risk of developing PDAC for carriers of a gene defect in *CDKN2A-p16-Leiden* is 15–20% [3].

One of the main features of hereditary cancer is the high risk of developing multiple (synchronous or metachronous) cancer. However, multiplicity might be masked in hereditary PDAC because most patients die within 6–12 months [4].

Recently, we described two patients with a *CDKN2A-p16-Leiden* mutation with metachronous PDAC [5, 6]. In the current report, we describe two additional *CDKN2A-p16-Leiden* patients, one with a synchronous and one with a metachronous PDAC.

### Patients and methods

Since 2000, we have run a surveillance program in the Leiden University Medical Center (LUMC) for individuals with a founder mutation in the *CDKN2A* gene, called *p16-Leiden* (NM\_000077.4: c.225\_243del19, p.

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(Ala76Cysfs\*64)) [7]. The program consists of annual magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), and, optionally, endoscopic ultrasound (EUS). In patients with a suspicious lesion, additional EUS and computed tomography (CT) scanning is performed within two to three weeks. If the lesion is confirmed by two out of the three modalities, surgery is offered. To avoid the serious morbidity associated with total pancreatectomy, until recently a partial resection of the pancreas was recommended. Acquired data was submitted to a public *CDKN2A* gene variant database (<https://databases.lovd.nl/shared/genes/CDKN2A>; submission IDs # 00155215 and # 00155216).

## Results

A total of 218 *CDKN2A-p16-Leiden* mutation carriers are under surveillance as of 01-04-2017. Since 2000, the screening program has detected PDAC in 18 patients (8.3%) and nine of these patients have since died from metastatic disease. The mean follow-up time for all 18 patients is 24.1 months (median follow-up: 17.5 months).

The first patient with multiple PDAC was a 67-year-old female carrier of a *CDKN2A-p16-Leiden* mutation that first entered MRI/MRCP pancreas surveillance in 2006. The patient had a sister who died of PDAC at the age of 52. She reports drinking 1–2 glasses of wine a week and has never smoked. In 2016, 11 months after a previous normal MRI scan, the patient presented with painless jaundice. A new MRI scan showed a 14-mm lesion in the head of the pancreas, which was confirmed by EUS. The patient underwent a pancreaticoduodenectomy, and histopathological examination of the surgical specimen showed a moderately differentiated PDAC of 13 mm, and one tumor-positive lymph node out of the 18 removed. After surgery, the patient was treated with gemcitabine and capecitabine. Regrettably, 6 months later, a yearly review of all MRI scans of patients in the surveillance program revealed that this patient had a second tumor in the corpus, which was confirmed by CT scanning. Subsequently, the patient underwent an uneventful completion of pancreatectomy. Pathological examination of the surgical specimen confirmed the presence of a 19-mm PDAC with no tumor-positive lymph nodes out of three removed. Molecular analysis of both lesions through Next Generation Sequencing (NGS) showed a class 5 variant in *KRAS*, NM\_033360.2:c.34G>C, p.(Gly12Arg) and class 4 variant in *SMAD4*, NM\_005359.5:c.353C>T, p.(Ala118Val) for the first tumor in the head, and a class 5 variant in *KRAS*, NM\_033360.2:c.35G>T, p.(Gly12Val) together with a class 4 variant in *TP53*, NM\_000546.5:c.517G>T, p.

(Val173Leu) for the second tumor, besides the known p16-Leiden variant in *CDKN2A* [8].

Outside the surveillance program, a second patient with a proven *CDKN2A-p16-Leiden* mutation carrier at the LUMC was found to have a metachronous PDAC. This 57-year-old female underwent a Whipple operation due to an ampullary carcinoma 11 years back. She has never smoked or consumed alcohol. The family history revealed that her mother and maternal grandfather both had ampullary carcinomas previously. A maternal uncle and aunt, and the aunt's children have been diagnosed with melanoma. The patient was presented in March 2017 with liver and pulmonary metastases and a mass at the site of the anastomosis from the Whipple operation. The CA19.9 was >12,000. FNA biopsy showed a cancer of pancreaticobiliary origin. Molecular analysis using NGS of the ampullary carcinoma diagnosed 11 years ago revealed class 5 variant in *KRAS*, NM\_033360.2:c.35G>A, p.(Gly12Asp) and the known *p16-Leiden* variant in *CDKN2A*.

In tumor cells collected by fine-needle aspiration (FNA) from the recently diagnosed tumor, NGS also showed the same class 5 variant in *KRAS* and the *p16-Leiden* 19 bp deletion. In addition, a class 5 variant was found in *TP53*, NM\_000546.5:c.722C>T, p.(Ser241Phe), a class 3 *STK11* missense variant in NM\_000455.4/NG\_007460.2: c.598-1G>A, and a deletion of *SMAD4*, determined by copy number analysis. In view of the identification of the *p16-Leiden* variant, the observed partial differences in the gene variants between the two tumors and the long time-interval since the first cancer, the newly diagnosed tumor should be regarded as a second primary PDAC.

If we include the previously reported cases, we identified two *CDKN2A-p16-Leiden* patients with multiple PDAC out of the 18 screen-detected PDAC (11%), one with two synchronous PDAC and one with a metachronous PDAC. Two *CDKN2A-p16-Leiden* patients detected outside the program were both with metachronous PDAC.

## Discussion

The present study indicates that multiple PDACs can be found in a substantial proportion (up to 11%) of *CDKN2A-p16-Leiden* mutation carriers. As most patients with hereditary PDAC die within 1 year, the real risk is probably much higher.

The risk of synchronous or metachronous cancers is a well-known phenomenon in inherited forms of cancer [9, 10]. Owing to the current surveillance program for *CDKN2A-p16-Leiden* carriers, an increasing number of patients with PDAC are diagnosed at an early stage, resulting in a longer life expectancy [4]. As a consequence, we expect to diagnose more patients with multiple tumors.

Our findings have immediate clinical implications. Firstly, after detection of a primary PDAC, it is very important to exclude the presence of a second synchronous tumor. As the identification of a second synchronous tumor in patients with sporadic PDAC is very unusual, a second tumor can be easily overlooked, as illustrated by one of the patients presented here. Secondly, in patients with hereditary PDAC undergoing partial resection of a primary tumor, close surveillance (e.g., at six month intervals) of the remaining pancreas is of utmost importance, as three of our patients developed a second PDAC [5, 6].

The most challenging question is whether we should now offer total pancreatectomy to all *CDKN2A-p16-Leiden* mutation carriers with primary PDAC. In patients with PDAC with poor prognostic indicators, a partial pancreatectomy is probably still the best option because expected survival is usually less than 2 years and a total pancreatectomy would substantially reduce the remaining quality of life. However, patients with a small lesion (<15 mm) and no evidence of lymph node metastases have a much better prognosis, and total pancreatectomy could be considered. A well-known disadvantage of the total pancreatectomy is the development of diabetes and the associated significant impairment of general quality of life [11]. On the other hand, a disadvantage of a partial resection is that, even with intensive surveillance, the chance of detecting a second tumor at an early stage is limited. For *CDKN2A-p16* mutation carriers, a total pancreatectomy may therefore bring relief from the ongoing stress associated with the possibility of a second PDAC. Thus far, we have preferred to offer all patients with screen-detected PDAC a partial pancreatectomy and intensive follow-up after surgery. However, in view of the current findings, offering a total pancreatectomy might be an appropriate option in patients with early PDAC. We therefore suggest that all the pros and cons are discussed with a patient prior to surgery, resulting in a shared decision.

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