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Cost-effectiveness of pancreas surveillance: The *CDKN2A*-p16-*Leiden* cohort

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Abstract

Background: *CDKN2A*-p16-*Leiden* mutation carriers have a high lifetime risk of developing pancreatic ductal adenocarcinoma (PDAC), with very poor survival. Surveillance may improve prognosis.

Objective: To assess the cost-effectiveness of surveillance, as compared to no surveillance.

Methods: In 2000, a surveillance program was initiated at Leiden University Medical Center with annual MRI and optional endoscopic ultrasound. Data were collected on the resection rate of screen-detected tumors and on survival. The Kaplan–Meier method and a parametric cure model were used to analyze and compare survival. Based on the surveillance and survival data from the screening program, a state-transition model was constructed to estimate lifelong outcomes.

Results: A total of 347 mutation carriers participated in the surveillance program. PDAC was detected in 31 patients (8.9%) and the tumor could be resected in 22 patients (71.0%). Long-term cure among patients with resected PDAC was estimated at 47.1% ($p < 0.001$). The surveillance program was estimated to reduce mortality from PDAC by 12.1% and increase average life expectancy by 2.10 years. Lifelong costs increased by €13,900 per patient, with a cost-utility ratio of €14,000 per quality-adjusted life year gained. For annual surveillance to have an acceptable cost-effectiveness in other settings, lifetime PDAC risk needs to be 10% or higher.

Conclusion: The tumor could be resected in most patients with a screen-detected PDAC. These patients had considerably better survival and as a result annual surveillance was found to be cost-effective.

KEYWORDS
CDKN2A-p16-*Leiden* mutation carriers, cost-effectiveness, high-risk, PDAC, surveillance, survival

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death. Most PDACs in patients who present with symptoms are diagnosed at an advanced stage and, as a consequence, only 13%–21% of tumors can be resected.[1] The 5-year survival rate of all PDAC patients is approximately 8%.[2] At the present time, early detection and surgery is the only way to potentially cure this disease.

Hereditary factors play a role in the development of PDAC in 5%–10% of all cases, with either a positive family history for PDAC or a recognized underlying gene defect associated with PDAC.[3] During the last two decades, surveillance programs for individuals with an increased risk of PDAC have been implemented in many centers worldwide, resulting in higher curative resection rates and better survival.[4–8]

Relatively few studies have investigated the cost-effectiveness of surveillance programs for individuals at increased risk of pancreatic cancer. The available studies concluded that pancreatic cancer screening is generally cost-effective in various high-risk groups.[9–12] These studies did not include carriers of a *CDKN2A*-p16 mutation which represent a group with a very high risk of developing PDAC. In the present study, we evaluate the cost-effectiveness of a surveillance program in the large Dutch cohort of *CDKN2A*-p16-*Leiden*-mutation carriers.

Key summary

Established knowledge on this subject

- Pancreatic ductal adenocarcinoma (PDAC) is often diagnosed at an advanced stage, resulting in very poor survival.
- Surveillance among high-risk individuals may improve prognosis.

New findings of this study

- In our annual surveillance program, the tumor could be resected in most patients with a screen-detected PDAC, resulting in considerably better survival.
- Surveillance was found to be cost-effective.

PATIENTS AND METHODS

Surveillance program and data collection

The surveillance program was initiated in 2000 at the Department of Gastroenterology and Hepatology, Leiden University Medical Center.[4] Only patients with a proven *CDKN2A*-p16-*Leiden* founder mutation or other pathogenic variant were selected for the program. The surveillance protocol consists of an MRI once a year, with an optional endoscopic ultrasound (EUS). In case of suspicion of a malignant lesion, the MRI is repeated within 3 months. In case of a small parenchymal abnormality, probably too small for EUS-guided fine-needle aspiration (<5 mm), the MRI is repeated within 3 months. In case of a larger solid lesion of approximately 10 mm, an additional EUS (including biopsy) and CT are performed within 2–3 weeks. All cases with a significant abnormality on the MRI were discussed in a multidisciplinary team with surgeons, radiologists, oncologists, pathologists and gastroenterologists. Decisions on the need for surgical resections were made by this team. Most patients with PDAC are also offered chemotherapy.

The study was approved by the institutional review board of the Leiden University Medical Center (P00.107). All authors had access to the study data and reviewed and approved the final manuscript. All calculations were performed in Stata/IC 14.2 for Windows (StataCorp LLC, Texas, USA).

Survival analysis

Survival data have been reported recently.[4] For the current analysis, we performed parametric survival analyses on these data to allow for extrapolation beyond the duration of follow-up. Survival after surgery among resected and non-resected patients was estimated using a cure model, that is, a mixture of either cure from PDAC or Weibull-distributed survival.[13] The cure probability was only maintained if the probability had a statistically significant non-zero value at $p \leq 0.05$. The same parametric model was used to estimate the time until detectable PDAC.[14] Kaplan–Meier analysis was performed to validate the estimated parametric survival curves, with log-rank test to compare resected and non-resected patients.

Cost-effectiveness model

A state-transition model was constructed for the surveillance program and subsequent management of PDAC (Figure 1 and Table 1). Individuals are at risk for developing detectable PDAC (incidence rate λ) and dying (mortality rates μ_0, μ_1, μ_2). Patients with detectable PDAC are identified and treated surgically after a lead time (rate τ). When identified, patients may or may not be resectable (with probabilities π_1 and $1 - \pi_1$). When resected, patients may or may not be cured (with probabilities π_2 and $1 - \pi_2$).

The model was used to simulate individual patient histories, both with and without a surveillance program.[16] Each simulated history started at age 45, for either a female or a male individual. First, survival time without PDAC was simulated based on national Dutch survival data, assuming a Weibull distribution fitted to the mean and SD as obtained from the life tables of Statistics Netherlands.[17,18] Secondly, for the annual surveillance policy, the time until detection of PDAC and resectability of the tumor were estimated from the surveillance data of the surveillance program.[4,14] No further

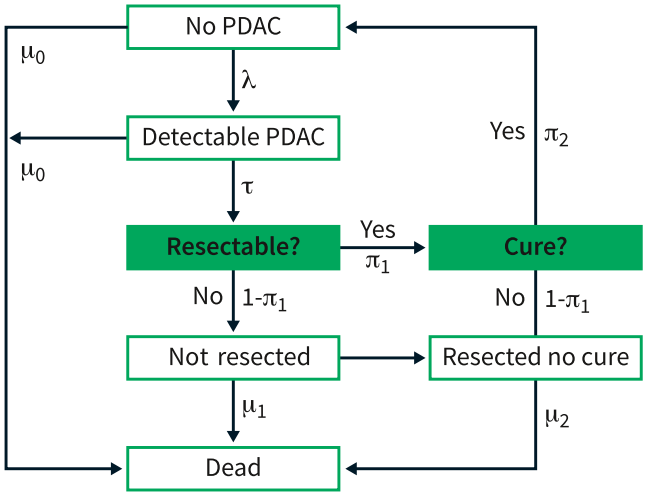

FIGURE 1 State-transition model for pancreatic cancer surveillance. PDAC, pancreatic ductal adenocarcinoma

TABLE 1 Parameters in the state-transition model

Parameter		Estimates and assumptions
λ	Incidence rate for detectable PDAC	
	Age distribution	Mean = 76.5 years (SD = 10.8) truncated to only values below 75
τ	Lead time before PDAC is detectable	
	With surveillance	Mean = 0.5 years
	Without surveillance	Mean = 1.0 years
π_1	Probability that detected PDAC is resectable	
	With surveillance	π_1 = 71.0% (95% CI 54.0%–87.9%)
	Without surveillance	π_1 = 15%[15]
π_2	Probability that resected patient is cured	
	With surveillance	π_2 = 47.1% (95% CI 25.1%–69.1%)
	Without surveillance	π_2 = 0%[8]
μ_0	Mortality rate without detected PDAC	
	Female life expectancy	Mean = 84.5 years (SD = 10.8)
	Male life expectancy	Mean = 81.5 years (SD = 10.7)
μ_1	Mortality rate after non-resected PDAC	
	Life expectancy	Mean = 1.10 years (SD = 0.65)
μ_2	Mortality rate after resected non-cured PDAC	
	Life expectancy	Mean = 1.90 years (SD = 0.76)

Abbreviation: PDAC, pancreatic ductal adenocarcinoma.

surveillance for PDAC was assumed beyond 75 years of age and after a first PDAC. The survival time after PDAC was simulated from either the estimated cure model for resected patients or the estimated Weibull distribution for non-resected patients. Overall lifetime was then estimated as the minimum of the survival time without PDAC and the survival after PDAC. Thirdly, the policy without surveillance program was modeled to have a longer lead time before PDAC is detected. Due to lack of data, we assumed exponentially-distributed lead times between the origin and detection of PDAC. Moreover, without a surveillance program, detected PDAC was assumed to be resectable with probability π_1 = 15%,[15] and curable with probability π_2 = 0.[8]

QALYs and costs

For each simulated patient history, we estimated lifetime costs and quality-adjusted life years (QALYs). QALYs were estimated using utility values obtained from the literature. For utility without PDAC, with undetected PDAC and after cured PDAC we used a utility value of 0.85, based on the Dutch EQ-5D valuations above age 40.[19] For utility after non-resected PDAC and after non-cured resected PDAC we used a utility value of 0.75, based on a reported range from 0.72 to 0.78 for EQ-5D values in representative publications.[20–25]

Costs were assessed from a healthcare perspective (Supplementary Table S1), including only healthcare associated with PDAC surveillance (visits, MRI, EUS, and CT), PDAC treatment (surgery and chemotherapy), and follow-up after diagnosis (visits). Prices of healthcare were obtained from Dutch national averages as reported by hospitals (n = 45 out of 84, www.ziektekosten.nl), or otherwise from benchmark costs for Dutch university medical centers (n = 4 out of 8, www.performation.nl). Costs are reported at 2022 price level. Costs and QALYs over time were discounted at 4% and 1.5%, respectively, in accordance with Dutch guidelines for economic evaluations in healthcare.[26]

Cost-effectiveness analysis

Model outcomes were estimated by averaging 10,000,000 simulated patient histories, which was sufficient to reduce the half-width of the 95% confidence interval (CI) to at most one unit of the last reported decimal.

Sensitivity analyses were performed for lifetime PDAC risk (±50%, by changing the incidence rate), cure probability (over the 95% CI), discount rate for costs (0%–5%), surveillance costs (±50%), treatment costs (±50%), lead time without surveillance (range 0.5–2 years), utility after PDAC (±0.10), and starting age (range 45–70).

We also modeled two surveillance programs with a shorter (i.e., biannual) screening interval. In program 1, we assumed that with biannual screening the annual surveillance costs would double and resectability would improve to 90%. In program 2, we additionally assumed that cure after surgery would improve to 70%. Cost-effectiveness for these programs was calculated as compared to annual screening.

In the Netherlands, a willingness-to-pay threshold of €80,000 per QALY is recommended by the Dutch Council for Public Health and Health Care for conditions with a high disease burden, like diagnosed PDAC. For low disease burden and prevention, a lower

threshold of €20,000 per QALY is used. In the current paper we will consider cost-effectiveness acceptable for cost–utility ratios up to an intermediate threshold of €50,000 per QALY.[27]

RESULTS

A total of 347 mutation carriers were included in the study, of whom 201 were female (57.9%). The median age at start of surveillance was 49 years (IQR 44–55 years), with a median follow-up time of 6 years (IQR 2–10 years, range 0–17 years). A total of 31 (8.9%) primary PDAC were detected by the screening program, of which 20 in female patients (65%). The median age at diagnosis was 60 years (range 39–74 years). The tumor could be resected in 22 patients (71.0%). Extensive details have been reported before.[4]

Survival analysis

The Kaplan–Meier survival curve (Figure 2) was significantly better among patients with resected PDAC than with non-resected PDAC ($p < 0.001$, median 36 vs. 16 months).

The parametric survival curves provided a close visual fit to the Kaplan–Meier curves. For resected patients, the long-term cure probability was estimated at 47.1% ($p < 0.001$, 95% CI 25.2%–69.1%). Among the resected but non-cured patients, average survival time was 23 months. Among patients with non-resected tumor the average survival time was 13 months.

Cost-effectiveness analysis

Patient outcomes with and without the surveillance program are shown in Table 2. With surveillance the lifelong probability of a PDAC diagnosis is slightly higher, because without surveillance some patients die before diagnosis. More importantly, with surveillance the majority of patients (71.0%) with PDAC are diagnosed at a resectable stage and about one in three of diagnosed patients (33.5%) is estimated to have long-term cure after surgery. As a result, mortality from PDAC is estimated to decrease by 12.1%, life expectance increases by 2.10 years, and QALYs by 0.97 years.

Nevertheless, screening does come with additional costs. The lifelong healthcare costs for individuals undergoing surveillance were estimated at €15,400, compared to only €1500 without surveillance. Of the cost difference, 82% is due to surveillance costs. Although treatment costs are also substantial, they apply to only part of the population and receive less discounted weight because they occur on average more than 20 years in the future. Cost-effectiveness ratios are estimated at €115,000 per prevented PDAC death or €14,000 per QALY gained.

Sensitivity analyses

In all sensitivity analyses cost-effectiveness remained below €30,000 per QALY (Figure 3), which is well below the acceptability threshold of €50,000 per QALY. The most influential variables were the lifetime

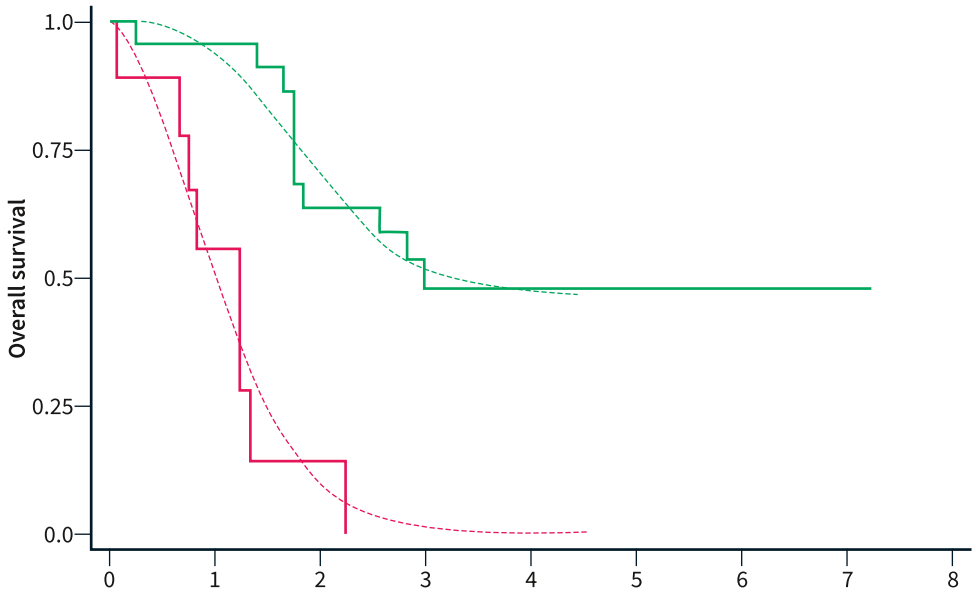

FIGURE 2 Estimated parametric survival distributions (dashed lines) among resected ($n = 22$) and non-resected ($n = 9$) PDAC patients, in comparison to Kaplan–Meier curves. PDAC, pancreatic ductal adenocarcinoma

TABLE 2 Average lifelong outcome with and without MRI surveillance from age 45–75 years, for a 45-year-old person in the *CDKN2A*-p16-*Leiden* population

Outcome parameter	Surveillance	No surveillance	Difference
Lifetime probability of diagnosed PDAC	37.6%	37.3%	0.3%
Of which non-resected	29.0%	85.0%	−56.0%
Resected, non-cured	37.5%	15.0%	22.5%
Resected, cured	33.5%	0.0%	33.5%
Mortality from PDAC	24.3%	36.4%	−12.1%
Age at PDAC diagnosis	66.40 years	66.90 years	−0.49 years
Life years	33.74 years	31.64 years	2.10 years
QALYs	21.76 years	20.79 years	0.97 years
Costs of screening (in €)	11,400	0	11,400
Costs of surgery (in €)	3100	700	2400
Costs of chemotherapy (in €)	700	700	0
Costs of follow-up after PDAC (in €)	200	100	100
Costs in total (in €)	15,400	1500	13,900
Cost-effectiveness ratio	€115,000 per prevented PDAC death		
Cost-utility ratio	€14,000 per QALY gained		

Abbreviations: PDAC, pancreatic ductal adenocarcinoma; QALY, quality-adjusted life year.

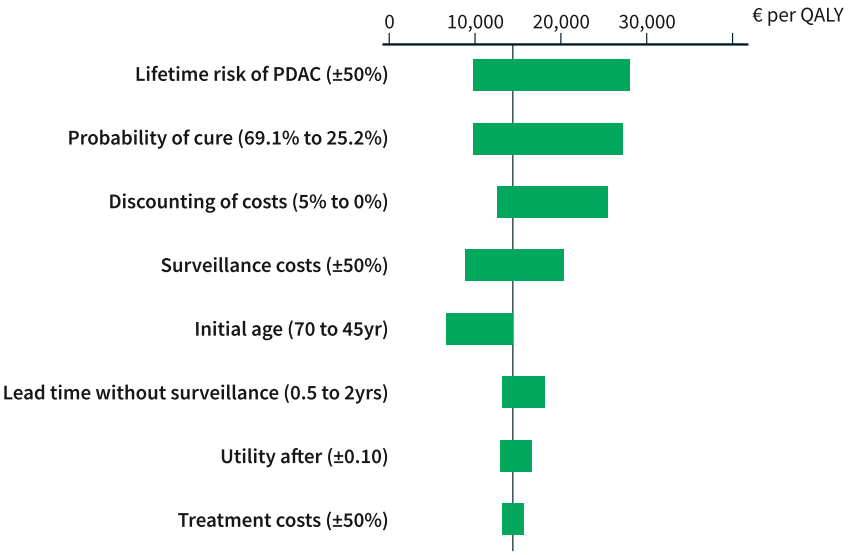

FIGURE 3 Tornado diagram, showing the impact of model parameters on the estimated cost-effectiveness of annual surveillance. PDAC, pancreatic ductal adenocarcinoma; QALY, quality-adjusted life year

risk of PDAC and the probability that surgery results in long-term cure. Figure 4 shows how lower PDAC risk results in worse cost-effectiveness. For annual surveillance to have an acceptable cost-effectiveness below €50,000 per QALY, lifetime PDAC risk needs to be 10% or higher.

The figure also shows the estimated cost-effectiveness of more expensive bi-annual surveillance. The first program is bi-annual surveillance with improved 90% resectability (instead of the 71.0% for annual screening), but without improved cure among resected patients. This program 1 will only be cost-effective for a lifetime PDAC risk of at least 32%. The second program, in addition, improves cure to 70% (instead of 47.1%). The cost-effectiveness of this program 2 will be very similar to annual surveillance, with about double the costs but also about double the QALY gain.

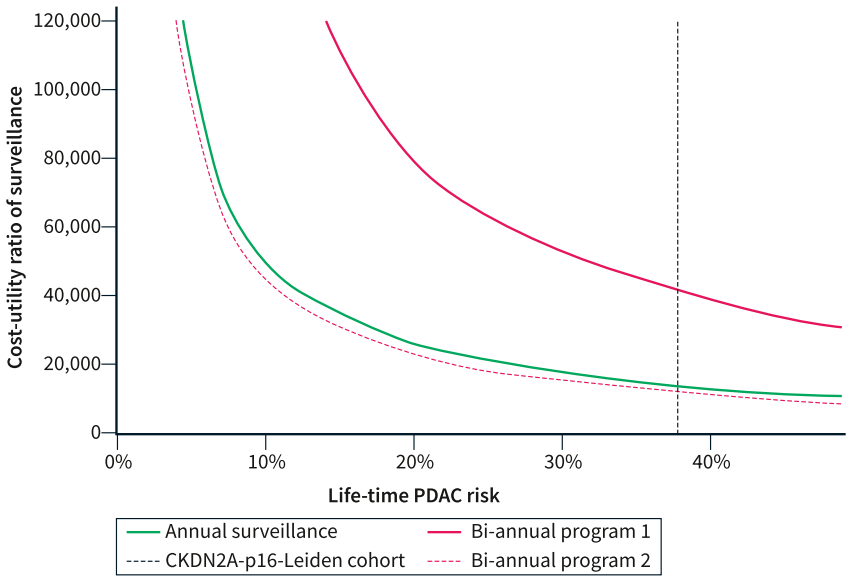

FIGURE 4 Estimated cost-utility ratio of annual and bi-annual pancreas surveillance, depending on the lifetime PDAC risk in the population. PDAC, pancreatic ductal adenocarcinoma

DISCUSSION

In the current study we evaluated the cost-effectiveness of a surveillance program aimed at *CDKN2A*-p16-*Leiden*-mutation carriers. Of the 347 mutation carriers, 31 individuals (8.9%) developed PDAC and the tumor was resectable in 22 cases (71.0%). The long-term survival rate for patients with resected PDAC was estimated at 47.1%, compared to 0% for patients with a non-resected tumor. Cost-effectiveness of annual surveillance was estimated at a very acceptable €14,000 per QALY.

Over the last two decades, interest for surveillance amongst individuals at high-risk of pancreatic cancer has increased substantially. Following the identification of a large cohort of carriers of a *CDKN2A* founder mutation close to Leiden University Medical Center, we initiated MRI-based pancreas surveillance in 2000. In previous studies[14,15] we reported a high PDAC detection rate, confirming the high-risk of developing PDAC previously calculated for these carriers,[28,29] and our most recent study reported improved survival, although the number of screen-detected PDACs was relatively small.[14] In the current study, which now includes a substantial number of screen-detected PDACs,[4] we can confirm the high resection rate and better survival.

As surveillance for PDAC involves use of relatively expensive screening tools, it is important to understand its cost-effectiveness. The four studies that addressed cost-effectiveness to date all showed that PDAC surveillance was cost-effective, with varying assumptions on the populations analyzed (familial pancreatic cancer [FPC], carriers of various mutations associated with PDAC development), the screening strategies (once in a lifetime, annual, or bi-annual screening) and screening methods (EUS or MRI/MRCP). One study evaluated one-time screening using EUS in hypothetical FPC population.[9] They concluded that for screening to be cost-effective the probability of dysplasia needs to be sufficiently high and the screening method sufficiently sensitive. Another study developed a bi-yearly MRI screening protocol[10] using data from a literature search for various high-risk individuals (e.g., Peutz-Jehghers syndrome, hereditary pancreatitis (HP), FPC, *CDKN2A*-p16-*Leiden*, and new-onset diabetes > age 50 with weight loss or smoking).[10] MRI screening was affordable for high-risk individuals, although the authors also stated that the substantial costs of screening for asymptomatic individuals influence compliance because some or all of the costs of screening are not covered by healthcare systems in the United States (in contrast to the Dutch healthcare system). A third study from Denmark reported the outcome of surveillance in a cohort of individuals with FPC and HP and calculated the related costs of surveillance.[11] They concluded that surveillance was most cost-effective in patients with FPC. The most recent study used a Markov model and comparing no surveillance to MRI surveillance and EUS surveillance.[12] This study found that MRI surveillance was most cost-effective for individuals with a moderately increased risk of PDAC and EUS surveillance was the most cost-effective strategy for individuals with a more than 20-fold increased risk.

In the current study, the cost-effectiveness of annual surveillance was estimated at €14,000 per QALY, an estimate that is likely to be acceptable in most countries. We observed that several variables in particular influenced our study results. One important factor was the elevated genetic risk of our patient cohort, as *CDKN2A*-p16-*Leiden*-mutation carriers show a model-estimated lifetime PDAC risk of 37.6%. We estimated that surveillance could be cost-effective for populations with a lifetime risk of at least 10%. This figure matches earlier studies using hypothetical simulation models which suggested that pancreas screening is ineffective in the general population but effective in individuals with a substantial risk.[26,30,31] Screening of low-risk individuals was associated with a reduced life expectancy, an

outcome attributed to the increased discovery of insignificant lesions and subsequent unnecessary surgical intervention. As an international consortium of experts currently and recent guidelines (American Society for Gastrointestinal Endoscopy) recommend pancreatic surveillance for high-risk individuals with an estimated lifetime risk of PDAC of >5%,[32,33] more studies are needed to assess the cost-effectiveness of surveillance of individuals with a relatively low risk (i.e., <10%).

The other key factor in cost-effectiveness was the ability of the surveillance program to detect PDAC at an earlier stage, which resulted in a considerable increase in patients with resected PDAC (from 15% to 71.0%). Furthermore, a substantial proportion (47.1%, $p < 0.001$) of these patients show long-term cure. Without this observed cure, it would be difficult to exclude the possibility that improved survival due to surveillance was simply due to lead time bias (whereby improved survival after diagnosis is due to earlier diagnosis rather than longer survival). Under the current surveillance program an estimated 33.5% of diagnosed patients are considered cured, which is enough for the program to be cost-effective. Nevertheless, a few patients developed an advanced cancer within the recommended annual surveillance interval of the current program.[4] Shorter intervals might therefore be considered in individuals with additional risk factors for development of PDAC (e.g., smoking, strong family history for PDAC). The sensitivity analysis indicated that bi-annual surveillance could be cost-effective, if it further improved the probability of cure after surgery.

Our study had both strengths and limitations. All previous cost-effectiveness studies, except the study from Denmark, were based on hypothetical models. An advantage of the current study is that we used real data from our 347 participants with a *CDKN2A*-p16-*Leiden*-mutation collected over two decades. A limitation of our study is that the group of carriers of a *CDKN2A*-p16 mutation is uncommon and conclusions may not be representative for individuals at risk for PDAC in other contexts (e.g., chronic pancreatitis). Similarly, we used costs specific to the Dutch healthcare system, which may not be representative of other countries. A second limitation is that for ethical reasons there was no control group of individuals not under surveillance. Data on natural history were therefore derived from historical controls with symptomatic PDAC known at the Dutch familial atypical multiple mole melanoma registry.[15] And thirdly, several simplifying assumptions needed to be made for which limited or no evidence was available, including assumptions on utilities, lead times and other risks in this population. In particular, we assumed that neither surveillance nor a new PDAC occurs beyond the age of 75, as we have not observed a case in our cohort. However, we note that the incidence rate increases with age and therefore suggests that longer follow-up is needed to assess the cost-effectiveness of surveillance at older ages.

In conclusion, this study demonstrated that screening for PDAC is cost-effective for *CDKN2A*-p16-*Leiden*-mutation carriers. In most patients a screen-detected PDAC could be resected and these patients subsequently benefited from considerably better survival.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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