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Gastroenterology 2022;162:772–785

# CLINICAL—PANCREAS

## Timeline of Development of Pancreatic Cancer and Implications for Successful Early Detection in High-Risk Individuals

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**BACKGROUND & AIMS:** To successfully implement imaging-based pancreatic cancer (PC) surveillance, understanding the timeline and morphologic features of neoplastic progression is key. We aimed to investigate the progression to neoplasia from serial prediagnostic pancreatic imaging tests in high-risk individuals and identify factors associated with successful early detection. **METHODS:** We retrospectively examined the development of pancreatic abnormalities in high-risk individuals who were diagnosed with PC or underwent pancreatic surgery, or both, in 16 international surveillance programs. **RESULTS:** Of 2552 high-risk individuals under surveillance, 28 (1%) developed neoplastic progression to PC or high-grade dysplasia during a median follow-up of 29 months after baseline (interquartile range [IQR], 40 months). Of these, 13 of 28 (46%) presented with a new lesion (median size, 15 mm; range 7–57 mm), a median of 11 months (IQR, 8; range 3–17 months) after a prior examination, by which time 10 of 13 (77%) had progressed beyond the pancreas. The remaining 15 of 28 (54%) had neoplastic progression in a previously detected lesion (12 originally cystic, 2 indeterminate, 1 solid), and 11 (73%) had PC progressed beyond the pancreas. The 12 patients with cysts had been monitored for 21 months (IQR, 15 months) and had a median growth of 5 mm/y (IQR, 8 mm/y). Successful early detection (as high-grade dysplasia or PC confined to the pancreas) was associated with resection of cystic lesions (vs solid or indeterminate lesions (odds ratio, 5.388; 95% confidence interval, 1.525–19.029) and small lesions (odds ratio, 0.890/mm; 95% confidence interval 0.812–0.976/mm). **CONCLUSIONS:** In nearly half of high-risk individuals developing high-grade dysplasia or PC, no prior lesions are detected by imaging, yet they present at an advanced stage. Progression can occur before the next scheduled annual examination. More sensitive diagnostic tools or a different management strategy for rapidly growing cysts are needed.

*Keywords:* Pancreatic Cancer; Surveillance; Screening; Familial Pancreatic Cancer.

Survival of pancreatic cancer (PC) is strongly related to disease stage,[1,2] creating a clear incentive for early detection through screening. Theoretically, there seems to be a window of opportunity for screening, because pancreatic malignancies have been associated with 3 well-defined precursor lesions, namely, pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms.[3] Current pancreas screening relies on imaging by endoscopic ultrasonography (EUS) or magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), or both.[4] There are no circulating biomarkers with sufficient diagnostic accuracy, and the low prevalence of PC in the general population has led experts to recommend against general population screening.[4,5]

Instead, research programs focus on surveillance of individuals at increased risk based on strong family history or a PC susceptibility gene mutation (high-risk individuals). Although there is no definitive evidence that such surveillance improves survival, there is evidence that PCs detected by surveillance are downstaged, and some patients achieve long-term survival.[4,6–8] Individuals with familial PC (FPC) have been found to harbor more and higher-grade precursor lesions in resected specimens than individuals with sporadic PC,[9] and surveillance has resulted in detection of early-stage PC and high-grade precursor lesions in some of these individuals.[6,10–12] Unfortunately, studies have found that most of the malignancies detected under surveillance have spread beyond the pancreas.[6,8,13,14]

For an imaging-based surveillance program to be successful, there must be a wide enough window of opportunity for detecting neoplastic precursor lesions at an early stage. Certain imaging features may be predictive for malignancy in pancreatic cysts, such as a dilated main pancreatic duct (MPD) or a mural nodule or solid component.[15,16] However, not all cystic lesions with such features harbor high-grade dysplasia or malignancy.[17–19] It is also unclear what proportion of patients who develop PC develop detectable imaging abnormalities associated with their PC precursors and how fast precursor lesions progress to invasive disease. Importantly, existing data on precancerous imaging abnormalities stem primarily from sporadic PC cases, although FPC is thought to undergo a similar molecular and histologic pathogenesis.[20,21]

To correctly identify high-grade dysplastic neoplastic lesions and early cancer to enable timely resection and potentially improve survival, a better understanding is needed of the timelines and patterns of development of precursor lesions and PC and how this correlates with imaging. The International Cancer of the Pancreas Screening (CAPS) consortium previously combined data from multiple surveillance programs to describe clinical outcomes of individuals who developed PC or underwent surgery, or both, while under surveillance.[13] For the current study, we updated this collective database and analyzed serial prediagnostic imaging studies. The primary objective was to describe the timeline of imaging abnormalities before diagnosing high-grade precursor lesions and PC in high-risk individuals. The secondary objective was to identify factors associated with neoplastic progression and successful early detection through imaging-based surveillance.

**WHAT YOU NEED TO KNOW**

BACKGROUND AND CONTEXT

To successfully improve survival of pancreatic cancer through imaging-based surveillance, its timeline of development must be understood and the window of opportunity for detecting neoplastic lesions in an early stage must be wide enough.

NEW FINDINGS

In high-risk individuals, almost half of the neoplastic lesions were detected a median of 11 months after an unremarkable examination. The other half progressed from previously visible lesions, mostly cystic, that displayed rapid growth over a median of 21 months. For both patterns, the majority of cancers had progressed beyond the pancreas at diagnosis.

LIMITATIONS

Limitations were the number of cases and the lack of genetic confirmation of the relationship between cancers and previously visible cystic lesions.

IMPACT

The window of opportunity was shown to be narrow, emphasizing the need for more sensitive diagnostic tools and a better management strategy for rapidly growing cystic lesions in high-risk individuals.

## Materials and Methods

### Study Design

The International CAPS consortium is a collaboration that aims to organize and facilitate research on PC surveillance in high-risk individuals on a global scale (www.caps-registry.com). All centers participating in the International CAPS consortium have ongoing PC surveillance research programs in which high-risk individuals undergo periodic imaging. Their surveillance protocols are largely based on the CAPS consortium consensus recommendations, which were formulated in 2013 and updated in 2020.[4,22] As recommended, all

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***Abbreviations used in this paper:*** **CAPS, Cancer of the Pancreas Screening; CI, confidence interval; CT, computed tomography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; OR, odds ratio; PanIN, pancreatic intraepithelial neoplasia; PC, pancreatic cancer.**

Most current article



0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2021.10.014

programs use MRI/MRCP, EUS, or both, at each visit, or they alternate between the two as surveillance tests, with additional diagnostic tests performed on indication, such as computed tomography (CT) and fine-needle aspiration (FNA). Other surveillance specifics, such as eligibility criteria and intervals, are also recommended in the CAPS consortium consensus recommendations and decided upon individually by each center.

For the current study, we collected data from 16 centers in 7 countries: Australia, Germany, Israel, Italy, the Netherlands, Spain, and the United States. The respective Ethics Committees approved the surveillance programs and international sharing of data. Participants provided informed consent, and programs were conducted in accordance with the Declaration of Helsinki.

## Study Population and Data Collection

Each surveillance program enrolls individuals with an inherited high risk of PC (estimated lifetime risk $\geq$5%), encompassing those with a proven germline mutation in 1 of the known PC susceptibility genes (often in the setting of a family history of PC), and individuals with a strong familial history of PC who tested negative for gene mutations or were untested. The genetic testing protocol was decided by each center individually and changed over time, varying from no genetic testing, to testing of specific susceptibility genes based on family history, to routine testing of all susceptibility genes in all participants. For the current study, we included all participants who were diagnosed with PC or underwent pancreatic surgery, or both.

Anonymized data were collected through an online electronic case record form, including data on demographics, medical history (including gene mutation status), family history of PC, imaging characteristics of pancreatic lesions, surveillance characteristics (eg, intervals, tests, and timing of detection), and pathologic outcomes. For incident lesions diagnosed or resected during follow-up, we collected additional detailed prediagnostic imaging data from the surveillance period before surgery or the diagnosis of unresectable malignancy. The MRI scans were read by radiologists according to the local surveillance protocol and were not re-read for the current study.

## End Points and Statistical Analysis

The end point for the primary objective was the development of neoplastic progression during follow-up. Neoplastic progression was defined as PC or a high-grade precursor lesion, namely PanIN-3 or IPMN with high-grade dysplasia. The end points for the secondary objective were neoplastic progression and successful early detection. Successful early detection was defined according the goals of surveillance, as recommended by the CAPS consensus statements, as malignancy confined to the pancreas and resected with negative margins, or high-grade precursor lesions.

The 2 objectives were studied in different selections of the cohort, for which high-risk individuals were grouped according to 3 determinants. First, whether the case was prevalent (detected at baseline) or incident (diagnosed during follow-up) (A and B in Figure 1).

Second, whether the case was a neoplastic progressor (defined above) or nonprogressor (diagnosed with benign pathologic outcome, pancreatic neuroendocrine tumors [NETs] $<$2 cm, or low-grade precursor lesions like PanIN-1, PanIN-2, and IPMN with low-or moderate-grade dysplasia) (F and G in Figure 1). In case of multiple lesions, participants were classified according to the lesion with the highest grade of dysplasia.

Third, neoplastic progressors were classified according to the goals of surveillance as surveillance success (defined

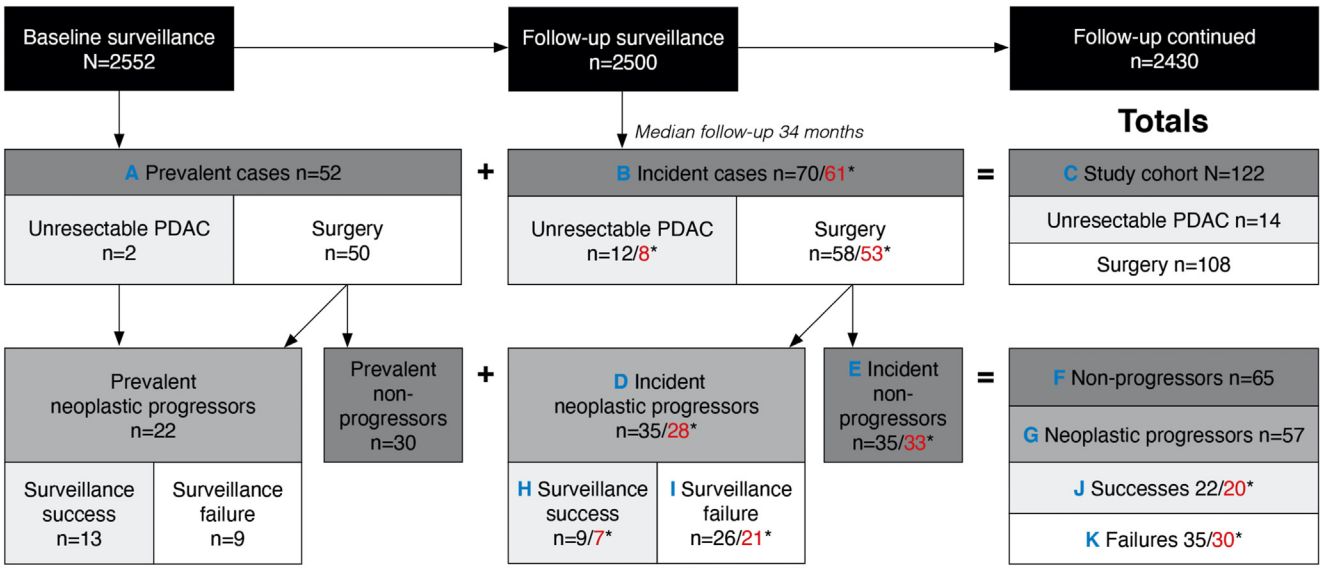


**Figure 1.** Patient selection and classification. *Numbers in *red* indicate the number of analyzed individuals after excluding those with limited surveillance information because of dropping out or temporarily undergoing surveillance elsewhere. Neoplastic progressors were defined as malignancy, PanIN-3, or IPMN with high-grade dysplasia; nonprogressors were defined as benign pathologic outcome, neuroendocrine tumors $<$2 cm, PanIN-1, PanIN-2, or IPMN with low- or moderate-grade dysplasia; surveillance success was defined as malignancy confined to the pancreas with negative resection margins, PanIN-3, or IPMN with high-grade dysplasia; surveillance failure was defined as malignancy spread beyond the pancreas as shown by imaging or the surgical specimen.

above) or failure (malignancy spread beyond the pancreas based on imaging or the surgical specimen (J and K in Figure 1).

The first objective was studied in incident cases with neoplastic progression (D in Figure 1). The second objective was studied in the incident cases (for neoplastic progression, D vs E; and for success of surveillance, H vs I in Figure 1) and in the entire cohort of prevalent and incident cases combined (for neoplastic progression, F vs G in Figure 1; and for success of surveillance, J vs K in Figure 1).

Differences between groups were assessed using the independent samples $t$ test and the Mann-Whitney $U$ test for continuous variables, depending on data distribution, and the $\chi^2$ test for categorical variables. Predictors for neoplastic progression were identified using univariable and multivariable logistic regression analysis, and predictors for surveillance success with univariable analysis only. A $P$ value of $<.05$ (2-sided) was considered statistically significant for all analyses. Statistical analysis was performed using SPSS Statistics 23 software (IBM, Armonk, NY).

# Results

## Study Population

From 1998 to 2019, the 16 centers together performed surveillance of 2552 individuals. Of these, 122 participants (5%) were included in the current study: 14 (11%) with unresectable PC and 108 (89%) who underwent pancreatic surgery for a suspect lesion (C in Figure 1). Men comprised 42% of the cohort, and the mean age at diagnosis was 60 (standard deviation, 11) years (range, 33–82 years) (Table 1).

CAPS consortium consensus criteria for a high-risk individual were met by 111 individuals (91%). These included 36 mutation carriers, 6 proven mutation-negative FPC kindreds, and 69 FPC kindreds who were untested or had unknown genetic test results. The remaining 11 individuals (9%) had a positive PC family history (but not meeting the FPC criteria; 7 individuals) or were a carrier of a



**Table 1.** Baseline Patient Characteristics Stratified by Time of Detection (N = 122)

| Characteristics | Prevalent at baseline (n = 52) | Incident cases (n = 70) | *P* value |
|---|---|---|---|
| Age at surgery/diagnosis unresectable PC, mean (SD), *y* | 60 (12) | 60 (11) | .943 |
| Male sex | 20 (39) | 31 (44) | .577 |
| Race/ethnicity | | | .348 |
| White | 49 (94) | 69 (99) | |
| Black | 2 (4) | 1 (1) | |
| Hispanic | 1 (2) | 0 (0) | |
| Body mass index, median (IQR), $kg/m^2$ | 28 (6) | 26 (5) | .126 |
| Diabetes mellitus | 10 (19) | 6 (8.6) | .113 |
| Smoking at baseline | 7 (14) | 9 (13) | 1.000 |
| Alcohol use at baseline | 9 (17) | 28 (40) | .005 |
| Risk category | | | .194 |
| Gene mutation carrier | 11 (21) | 25 (36) | — |
| Peutz-Jeghers syndrome | 3 (6) | 2 (3) | — |
| *CDKN2A* | 2 (4) | 9 (13) | — |
| BRCA2 with ≥1 FDR or ≥2 ADR | 2 (4) | 9 (13) | — |
| BRCA1 with ≥1 FDR | 1 (2) | 0 (0) | — |
| PALB2 with ≥1 FDR | 1 (2) | 2 (3) | — |
| ATM with ≥1 FDR | 1 (2) | 2 (3) | — |
| MLH1/MSH2/MSH6 with ≥ 1 FDR | 0 (0) | 1 (1) | — |
| PRSS1 | 1 (2) | 0 (0) | — |
| FPC kindred | 35 (67) | 40 (57) | — |
| Mutation-negative with ≥1 FDR and ≥2 ADR | 3 (6) | 3 (4) | — |
| Untested with ≥1 FDR and ≥2 ADR | 32 (62) | 37 (53) | — |
| Non–high-risk individual | 6 (12) | 5 (7) | — |
| Mutation carriers without sufficient family history | 2 (4) | 3 (4) | — |
| Untested or mutation-negative without sufficient family history | 4 (8) | 2 (3) | — |
| Family history of PC | 46 (89) | 66 (94) | .322 |
| ≥3 affected blood relatives | 25 (48) | 35 (50) | .834 |
| Age of onset in family <50 years | 13 (25) | 11 (16) | .146 |

NOTE. Categorical data are presented as n (%) and continuous data as indicated.
ADR, any-degree relative; FDR, first-degree relative.

susceptibility gene mutation without a PC family history (2 with a *BRCA2* gene mutation, 1 with *BRCA1*) or a carrier of a PC susceptibility gene mutation not included in the CAPS criteria (1 with a *TP53* gene mutation).

### Lesion Characteristics, Pathologic Outcome, and Time of Diagnosis

Of the 122 individuals, 115 (94%) had a distinct focal lesion (median size, 13 mm; IQR, 12.5; range, 3–57), 5 (4%) had a dilated MPD without a focal lesion, and 2 (2%) were resected because of features of chronic pancreatitis. Detailed lesion characteristics are stratified by pathologic outcome in Table 2.

A proven malignancy was found in 41 of the 122 individuals (34%), 18 (44%) of whom had a proven genetic mutation. Of these individuals with PC, 14 (34%) had unresectable disease, and 27 (66%) underwent resection. Of those who underwent resection, 6 (22%) had cancer confined to the pancreas with negative resection margins. Of the 81 individuals (66%) without PC, 16 (13%) had a high-grade precursor lesion, 3 (2%) a low-grade main-duct or mixed-type IPMN, and 43 (35%) had other low-grade precursor lesions. A pancreatic NET <2 cm in diameter was diagnosed in 14 individuals (11%), 8 of whom had concomitant low-grade precursor lesions. The other 5 individuals (4%) had benign pathology or no lesion was found in the resected specimen.

Of the 122 individuals, 52 (43%) were prevalent cases (diagnosed or resected at baseline) and 70 (57%) were incident cases who developed lesions that progressed to malignancy or required surgery during follow-up, diagnosed a median of 34 months (IQR, 46 months) after baseline (B in Figure 1). Detailed lesion characteristics and pathological outcome are stratified by the time of detection in Supplementary Table 1. Limited surveillance information was available for 9 individuals with incident PC who dropped out of surveillance or had temporarily undergone surveillance elsewhere. For the remaining 61 individuals with incident PC, the timeline of development is visualized in Figure 2.

### Timeline of Development of Neoplastic Progressors

The primary objective was studied in the 28 individuals who developed neoplastic progression to malignancy or high-grade dysplasia, diagnosed a median of 29 months (IQR, 40 months) after baseline (D in Figure 1). Of these, 13 (46%) presented with a new imaging-detected lesion (median size, 15 mm; IQR, 16; range, 7–57 mm) after a median of 11 months (IQR, 8; range, 3-17 months) since the previous visit. Ten malignancies (77%) had already progressed beyond the pancreas at the time of diagnosis (based on being unresectable or the surgical specimen). At the previous visit, the pancreas of 7 of the 13 individuals (25%) showed no abnormalities (Figure 2). In the other 6 (21%), cystic lesions were present in the same area of the pancreas, but based on location on imaging, the malignant lesion was judged to have arisen separately from the prevalent cyst (1 T1 PC and 5 PCs spread beyond the pancreas). In 3 of these 6, the MPD had been dilated without a visible obstructing lesion (2 in the head of 9 and 5 mm, one 6 mm in the body, and one 4 mm in the tail), 4 to 9 months before the PC diagnosis (Table 3).

The other 15 incident neoplastic progressors (54%) were considered to have developed from a preceding lesion. At the time of diagnosis, 11 of the 15 (73%) had already progressed beyond the pancreas. The preceding lesion was cystic in 12, indeterminate in 2, and solid in 1. The 1 solid lesion measured 15 mm at first detection, was unchanged in size at reevaluation after 1 month, and was then referred for surgery (T1 N0 M0 PC). One indeterminate lesion was 7 mm at detection and grew 16 mm in 15 months before being resected 8 months later (>T0 N0 M0 PC). The other indeterminate lesion was 5 mm at first detection, but the size at resection 19 months later was missing (also >T1 N0 M0 PC).

The 12 progressors with preceding cystic lesions had been monitored for a median of 21 months (IQR, 15; range, 7-41 months) and 3 visits (IQR, 4 visits). The cysts in this group had an initial median size of 11 mm (IQR, 9; range, 3–19 mm), grew a median of 10 mm (IQR, 13 mm), and measured a median of 23 mm (IQR, 10; range, 4–40 mm) at the time of resection or diagnosis of unresectable malignancy (3 high-grade precursor lesions, 9 >T1 N0 M0 PCs). Their median growth speed was 5 mm/y (IQR, 8 mm/y). Of these 12 originally cystic lesions, 6 (50%) developed a mural nodule or solid component at the time of resection, and 5 (42%) developed a dilated MPD (Figure 2).

### Incident Cases: Factors Associated With Neoplastic Progression and Successful Early Detection

When the 28 incident neoplastic progressors were compared to the 33 incident nonprogressors (D vs E in Figure 1), the only differentiating characteristic was the median size of the lesion at the last imaging test before diagnosis (21 mm [range, 4–57 mm] for progressors vs 8 mm [range, 4–34 mm] for the lesions in the nonprogressors; $P = .003$) (Table 3). Also, there was a trend for neoplastic progressors to show greater absolute growth (10 vs 2 mm) and faster growth (5 vs 1.5 mm/y), but this did not reach statistical significance ($P = .111$ and $P = .428$, respectively). There was no difference in the incidence of worrisome features, including a dilated MPD, mural nodule or solid component within a cyst, cyst with calcification, MPD with caliber change with distal atrophy, abdominal lymphadenopathy, elevated carbohydrate antigen 19-9, or positive FNA, at the diagnostic visit (54% vs 49%, $P = .799$), the last prediagnostic visit (29% vs 24%, $P = .775$), or at any time during surveillance (71% vs 52%, $P = .126$).

Of the incident neoplastic progressors, 7 (25%) were classified as a surveillance success (high-grade dysplasia or

**Table 2.** Patient and Lesion Characteristics Stratified by Pathologic Outcome (N = 122)

| Characteristics | Unresectable PC (n = 14) | Resectable PC spread beyond pancreas (n = 21) | Resectable PC confined to pancreas (n = 6) | High-grade precursor lesion[a] (n = 16) | Low-grade precursor lesion[b] (n = 46) | NET (n = 14) | No neoplasia (n = 5) |
|---|---|---|---|---|---|---|---|
| Patient characteristics | | | | | | | |
| Age at surgery/diagnosis unresectable PC, median (IQR), *y* | 66 (16) | 60 (18) | 53 (17) | 67 (11) | 57 (16) | 51 (10) | 43 (26) |
| Male sex | 5 (36) | 8 (38) | 1 (17) | 3 (19) | 23 (50) | 8 (57) | 3 (60) |
| Race/ethnicity | | | | | | | |
| White | 14 (100) | 20 (95) | 5 (83) | 16 (100) | 44 (96) | 14 (100) | 5 (100) |
| Black | 0 (0) | 1 (5) | 1 (17) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Hispanic | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Diabetes mellitus | 4 (29) | 4 (19) | 0 (0) | 2 (13) | 4 (9) | 2 (14) | 0 (0) |
| Smoking at baseline | 3 (21) | 1 (5) | 2 (33) | 2 (13) | 6 (13) | 1 (7) | 1 (20) |
| Alcohol use at baseline | 8 (57) | 6 (29) | 1 (17) | 1 (6) | 13 (28) | 6 (43) | 3 (60) |
| Risk category | | | | | | | |
| Gene mutation carrier | 6 (43) | 8 (38) | 4 (67) | 2 (13) | 11 (24) | 4 (29) | 1 (20) |
| FPC kindred | 7 (50) | 9 (43) | 1 (17) | 13 (81) | 33 (72) | 9 (64) | 3 (60) |
| Non–high-risk individual | 1 (7) | 4 (19) | 1 (17) | 1 (6) | 2 (4) | 1 (7) | 1 (20) |
| Family history of PC | 12 (86) | 18 (86) | 4 (67) | 15 (94) | 44 (96) | 14 (100) | 5 (100) |
| ≥3 affected blood relatives | 5 (36) | 9 (43) | 2 (33) | 8 (50) | 25 (54) | 8 (57) | 3 (60) |
| Age of onset in family <50 years | 2 (14) | 5 (24) | 2 (33) | 2 (13) | 7 (15) | 4 (29) | 2 (40) |
| Lesion characteristics | | | | | | | |
| Timing of surgery or diagnosis | | | | | | | |
| Prevalent at baseline | 2 (14) | 7 (33) | 2 (33) | 11 (69) | 24 (52) | 5 (36) | 1 (20) |
| Incident during follow-up | 12 (86) | 14 (67) | 4 (67) | 5 (31) | 22 (48) | 9 (64) | 4 (80) |
| Dilated MPD without focal lesion | 0 (0) | 1 (5) | 0 (0) | 1 (6) | 2 (4) | 1 (7) | 0 (0) |
| Chronic pancreatitis features | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (4) | 0 (0) | 0 (0) |
| Focal lesion | 14 (100) | 20 (95) | 6 (100) | 15 (94) | 42 (91) | 13 (93) | 5 (100) |
| Size, median (IQR), *mm* | 30 (27) | 19 (13) | 14 (6) | 11 (11) | 11 (8) | 8 (8) | 16 (23) |
| Location | | | | | | | |
| Head/uncinate | 8 (57) | 12 (60) | 3 (50) | 5 (33) | 11 (26) | 4 (31) | 0 (0) |
| Neck/body | 1 (7) | 2 (10) | 2 (33) | 5 (33) | 12 (29) | 1 (8) | 2 (40) |
| Tail | 0 (0) | 5 (25) | 1 (17) | 3 (20) | 13 (31) | 7 (54) | 3 (60) |
| Missing | 5 (36) | 1 (5) | 0 (0) | 2 (13) | 6 (14) | 1 (8) | 0 (0) |
| Aspect | | | | | | | |
| Solid | 7 (50) | 14 (70) | 5 (83) | 2 (13) | 14 (33) | 5 (38) | 1 (20) |
| Indeterminate | 1 (7) | 0 (0) | 0 (0) | 0 (0) | 2 (5) | 5 (38) | 1 (20) |
| Cystic | 1 (7) | 6 (30) | 1 (17) | 11 (73) | 20 (48) | 2 (15) | 3 (60) |
| Missing | 5 (36) | 0 (0) | 0 (0) | 2 (13) | 6 (14) | 1 (8) | 0 (0) |

NOTE. Categorical data are presented as n (%) and continuous data as indicated.
NET, neuroendocrine tumor.
[a]PanIN 3 or IPMN with high-grade dysplasia.
[b]PanIN 1 or 2 or IPMN with low- or moderate-grade dysplasia.

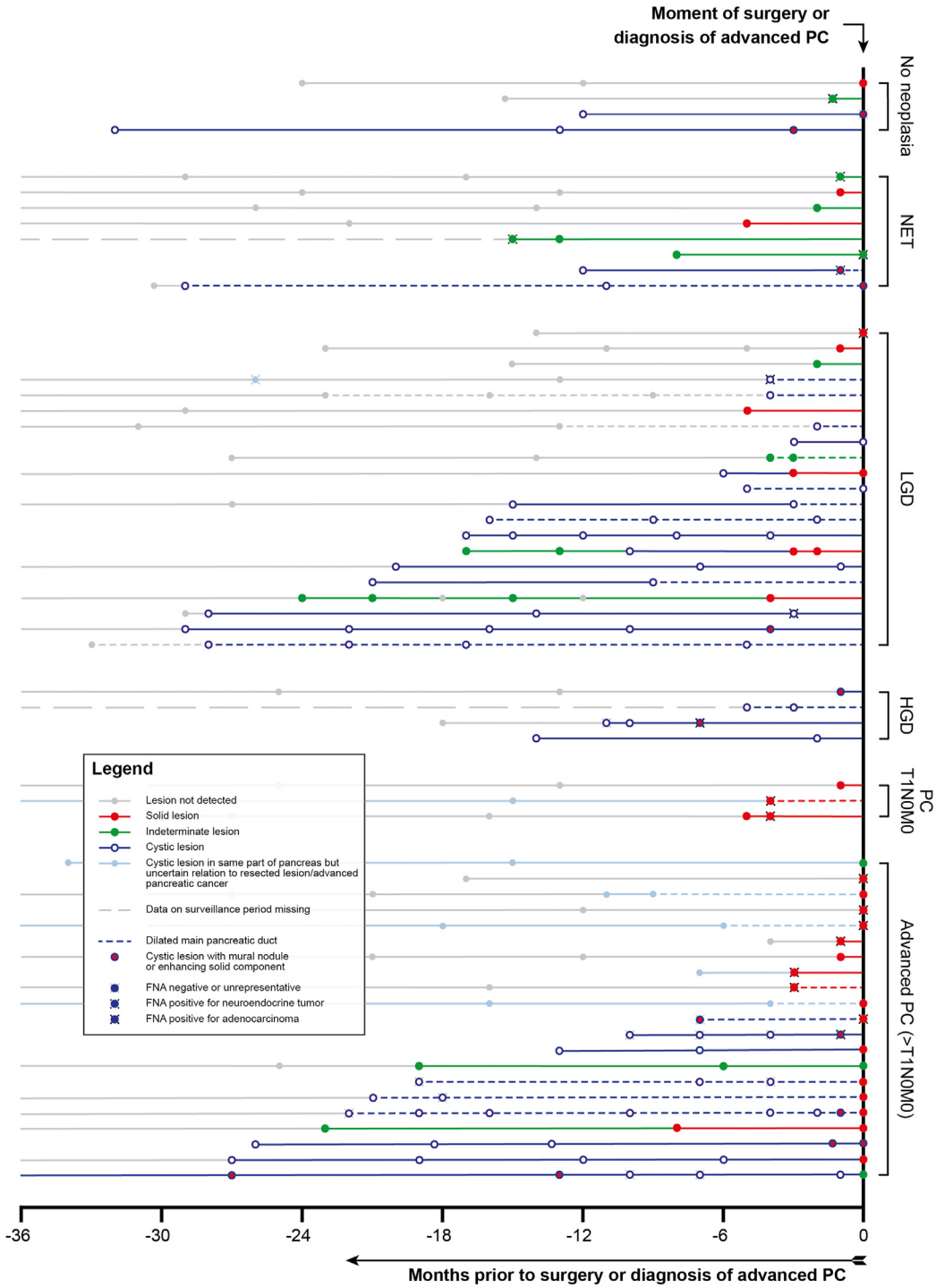


**Figure 2.** Timeline of development of incident resected lesions and unresectable PC, stratified by pathologic outcome, with each *line* representing 1 individual. HGD, high-grade dysplasia (PanIN 3 or IPMN with high-grade dysplasia); LGD, low-grade dysplasia (PanIN 1 or 2, or IPMN with low- or moderate-grade dysplasia). NET is a neuroendocrine tumor <2 cm.

PC confined to the pancreas) (H in Figure 1), and 21 (75%) as a failure (PC progressed beyond the pancreas) (I in Figure 1). No statistically significant differences in surveillance or lesion characteristics or the incidence of worrisome features were identified between the 2 groups. Failure was not due to a delay of surgery, because those in the failure group underwent their resections more quickly than those in the success group (median 1 vs 3 months after diagnosis by imaging with or without FNA, $P = .005$). Also, the time between detection of worrisome features and resection was not significantly different (data not shown).

**Table 3.** Surveillance and Lesion Characteristics of Incident Cases, Stratified By Neoplastic Progression and Surveillance Success (N = 61)[a]

| | Neoplastic progressors[b] (n = 28) | | | | |
|---|---|---|---|---|---|
| Characteristics | Surveillance success[d] (n = 7) | Surveillance failure[e] (n = 21) | All (n = 28) | Nonprogressors[c] (n = 33) | Neoplastic[b] progressors vs nonprogressors[c] *P* value |
| Surveillance characteristics | | | | | |
| Imaging test performed at prediagnostic visit | | | | | |
| EUS | 6 (86) | 17 (81) | 23 (82) | 26 (79) | 1.000 |
| MRI | 5 (71) | 15 (72) | 20 (71) | 24 (73) | .739 |
| CT | 1 (14) | 4 (19) | 5 (18) | 7 (21) | .751 |
| Lesion previously detected | 4 (57) | 11 (52) | 15 (54) | 20 (61) | .613 |
| Months since detection, median (range), *mo* | 10 (5–14) | 21 (7–41) | 19 (5–41) | 17 (3–32) | .616 |
| Surveillance visits since detection, median (range), *n* | 1 (1–2) | 3 (1–7) | 2 (1–7) | 2 (1–5) | .528 |
| Interval before prediagnostic visit, median (range), *mo* | 12 (0–13) | 6 (0–48) | 6 (0–48) | 7 (0–44) | .687 |
| 1–3 months | 2 (29) | 9 (43) | 11 (39) | 11 (33) | |
| 4–6 months | 0 (0) | 4 (19) | 4 (14) | 4 (12) | |
| 7–12 months | 3 (43) | 4 (19) | 7 (25) | 8 (24) | |
| >12 months | 1 (14) | 4 (19) | 5 (18) | 9 (27) | |
| Interval before diagnostic visit, median (range), *mo* | 11 (1–12) | 7 (1–18) | 7 (1–18) | 11 (1–24) | .514 |
| 1–3 months | 3 (43) | 4 (19) | 7 (25) | 5 (12) | |
| 4–6 months | 0 (0) | 6 (29) | 6 (21) | 6 (18) | |
| 7–12 months | 4 (57) | 6 (29) | 10 (36) | 16 (49) | |
| >12 months | 0 (0) | 5 (24) | 5 (18) | 6 (18) | |
| Overdue for diagnostic visit | 1 (14) | 8 (38) | 9 (32) | 9 (27) | .613 |
| Time overdue, median (range), *mo* | 6 (–) | 3 (1–12) | 3 (1–12) | 2 (1–10) | 1.000 |
| Time between diagnostic visit and surgery (unresectable PC excluded), median (range), *mo* | 3 (1–7) | 1 (0–8) | 1 (0–8) | 2 (0–13) | .084 |
| Lesion characteristics | | | | | |
| Dilated main pancreatic duct without focal lesion | 0 (0) | 0 (0) | 0 (0) | 2 (6) | .495 |
| Dominant focal lesion | 7 (100) | 21 (100) | 28 (100) | 31 (94) | .495 |
| Size at detection, median (range), *mm* | 15 (3–19) | 9 (3–18) | 9 (3–19) | 7 (3–30) | .422 |
| Absolute growth, median (range) , *mm* | 1 (0–8) | 12 (1–27) | 10 (0–27) | 2 (−3 to 7) | .111 |
| Relative growth, median (range), % | 33 (0–42) | 133 (8–1060) | 67 (0–1060) | 17 (−29 to 150) | .241 |
| Growth speed, median (range), *mm/y* | 1 (0–9) | 5 (1–25) | 5 (0–25) | 1.5 (−4 to 25) | .428 |
| Growth speed ≥5 mm/y | 1 (25) | 5 (46) | 6 (40) | 3 (16) | .087 |
| Size at last visit, median (range), *mm* | 11 (4–27) | 23 (8–57) | 21 (4–57) | 8 (4–34) | .003 |
| Worrisome features | | | | | |
| Pancreatic symptoms[f] | | | | | |
| At prediagnostic visit | 0 (0) | 0 (0) | 0 (0) | 3 (9) | .262 |
| At diagnostic visit | 0 (0) | 2 (10) | 2 (7) | 1 (3) | .553 |
| Dilated main pancreatic duct at any visit | 2 (29) | 8 (38) | 10 (36) | 11 (33) | .845 |
| Time since detection, median (range), *mo* | 4.5 (4–5) | 8 (2–22) | 7 (2–22) | 9 (1–29) | .670 |
| Present at prediagnostic visit | 1 (50) | 7 (88) | 8 (80) | 7 (64) | .635 |
| Preceded focal lesion | 0 (0) | 3 (38) | 3 (30) | 2 (18) | 1.000 |
| Time preceding focal lesion, median (range), *mo* | — | 6 (4–9) | 6 (4–9) | 15 (11–19) | .287 |
| Resected within 6 months | 2 (100) | 2 (25) | 4 (40) | 5 (46) | 1.000 |
| Mural nodule or enhanced solid component within cyst at any visit | 2 (29) | 4 (19) | 6 (21) | 5 (15) | .740 |

**Table 3.** Continued

| Characteristics | Neoplastic progressors[b] (n = 28) | | | Nonprogressors[c] | Neoplastic[b] progressors vs nonprogressors[c] |
|---|---|---|---|---|---|
| | Surveillance success[d] | Surveillance failure[e] | All | | |
| | (n = 7) | (n = 21) | (n = 28) | (n = 33) | *P* value |
| Time since detection, median (range), *mo* | 4 (1–6) | 4 (1–41) | 4 (1–41) | 1 (0–4) | 1.000 |
| Present at prediagnostic visit | 0 (0) | 1 (25) | 1 (14) | 0 (0) | — |
| Resected within 1 month | 1 (50) | 1 (25) | 2 (33) | 2 (40) | 1.000 |
| FNA suggestive or positive for adenocarcinoma | 3 (43) | 8 (38) | 11 (39) | 5 (15) | N/A |
| Time since positive FNA, median (range), *mo* | 4 (4–7) | 1 (0–3) | 1 (0–7) | 1.5 (0–4) | N/A |
| Resected within 1 month | 0 (0) | 6 (75) | 2 (40) | 2 (40) | N/A |
| FNA negative for adenocarcinoma | 1 (14) | 6 (29) | 7 (25) | 3 (9) | N/A |

NOTE. Categorical data are presented as n (%) and continuous data as indicated.
N/A, not applicable because positive FNA defines neoplastic progression.
[a]Nine incident cases were excluded because of lacking information on the period prior to resection.
[b]Malignancy, PanIN-3, or IPMN with high-grade dysplasia.
[c]Benign pathologic outcome, neuroendocrine tumors <2 cm, PanIN-1, PanIN-2, or IPMN with low- or moderate-grade dysplasia.
[d]PC confined to the pancreas and resected with negative margins, or high-grade precursor lesions.
[e]PC spread beyond the pancreas, regardless of being resectable.
[f]Including symptoms typically related to PC, such as abdominal pain, back pain, jaundice, weight loss, or anorexia.



### *Prevalent and Incident Cases Combined: Factors Associated With Neoplastic Progression and Successful Early Detection*

When the 57 individuals with advanced neoplasia (high-grade dysplasia or malignancy) were compared with the 65 nonprogressors (G vs F in Figure 1), multivariable analysis showed that independent predictors of neoplasia were advanced age (odds ratio [OR], 1.099/y; 95% confidence interval [CI], 1.036–1.166/y), female sex (OR, 4.289; 95% CI, 1.318–13.958), lesion size of ≥15 mm at the last imaging test (OR, 4.964; 95% CI, 1.635–15.075), and location in the head or uncinate process (OR, 4.953; 95% CI, 1.547–15.856). Being a mutation carrier and having ≥2 affected relatives with PC were predictors of advanced neoplasia (high-grade dysplasia or malignancy) in the univariable but not the multivariable analysis (Supplementary Table 2). The age at which neoplastic progression occurred was not associated with the youngest affected relative's age at PC diagnosis ($P = .534$).

In addition, all 22 screening/surveillance successes (prevalent and incident cases combined) were compared with the 35 failures (J vs K in Figure 1). Surveillance success was inversely associated with any alcohol consumption (OR, 0.080; 95% CI, 0.009–0.681), the lesion being resected at follow-up vs at the baseline visit (OR, 0.240; 95% CI, 0.077–0.748), a larger lesion (OR, 0.890/mm; 95% CI, 0.812–0.976/mm), a location in the head or uncinate process (OR, 0.291; 95% CI, 0.085–0.991), and a solid lesion (OR, 0.222; 95% CI, 0.064–0.766). In contrast, surveillance success was associated with a cystic lesion as the indication for surgery (OR, 5.388; 95% CI, 1.525–19.029) (Table 4).

When the 19 cystic lesions that were neoplastic progressors were compared with the 25 cystic lesions that were not, there were no significant differences (Supplementary Table 3).

## Discussion

This study shows that in high-risk individuals, neoplastic pancreatic lesions became apparent on imaging according to 2 distinct patterns. Almost half (46%) were detected as a newly developed lesion (mostly solid, with a median size of 15 mm), after a median of 11 months since a normal examination. The other half (54%) progressed from a previously visible lesion (generally with a cystic aspect) over a median of 19 months after the first detection. Unfortunately, the PC in >70% of both groups was diagnosed at a stage beyond T1 N0 M0 and thus judged to be failures of surveillance. Therefore, for both patterns, the window of opportunity for timely detection and treatment was shown to be narrow. Further reducing the chance of successful early detection is that the neoplastic progression that arose from an identifiable preceding lesion had evidence of rapid growth of their precursor lesion (median, 5 mm/y) and that the development of classical worrisome features for malignancy in cystic lesions did not differentiate neoplastic progressors from nonprogressors.

This is a unique multicenter international cohort of individuals with a proven or suspected genetic predisposition who underwent periodic imaging before and during the development of neoplastic lesions. It is the largest collection of surveillance-detected PC cases to date and provides important insights into PC development's morphology. Until

**Table 4.** Predictors of Surveillance Success Among Prevalent and Incident Cases Combined (N = 57)

| Predictors | Surveillance success[a] (n = 22) | Surveillance failure[b] (n = 35) | OR (95% CI) |
|---|---|---|---|
| Patient characteristics | | | |
| Age at surgery/diagnosis, median (IQR), *y* | 66 (19) | 64 (17) | 0.994 (0.941–1.049) |
| Male sex | 4 (18) | 13 (37) | 0.398 (0.110–1.442) |
| Body mass index, median (IQR), $kg/m^2$ | 28 (5) | 26 (6) | 1.019 (0.894–1.163) |
| Diabetes mellitus | 2 (9) | 8 (23) | 3.040 (0.578–15.994) |
| Smoking at baseline | 4 (18) | 4 (11) | 1.611 (0.358–7.621) |
| Alcohol use at baseline | 1 (5) | 14 (40) | 0.080 (0.009–0.681) |
| Gene mutation carrier | 7 (32) | 17 (49) | 0.494 (0.162–1.508) |
| Family history of PC | 19 (86) | 30 (86) | 1.056 (0.226–4.936) |
| ≥3 affected blood relatives | 10 (46) | 14 (40) | 1.250 (0.425–3.673) |
| Age of onset in family <50 years | 4 (18) | 7 (20) | 0.838 (0.208–3.374) |
| Lesion characteristics | | | |
| Detected at follow-up | 9 (41) | 26 (74) | 0.240 (0.077–0.748) |
| Dilated main pancreatic duct without focal lesion | 1 (5) | 1 (3) | 1.619 (0.096–27.290) |
| Focal lesion | 21 (95) | 34 (97) | 0.618 (0.037–10.411) |
| Size, median (IQR), *mm* | 12 (9) | 23 (22) | 0.890 (0.812–0.976) |
| Size ≥15 mm | 6 (29) | 20 (59) | 0.240 (0.065–0.883) |
| Located in the head/uncinate (vs neck/body/tail) | 8 (38) | 20 (59) | 0.291 (0.085–0.991) |
| Aspect | | | |
| Solid | 7 (33) | 21 (62) | 0.222 (0.064–0.766) |
| Indeterminate | 0 (0) | 1 (3) | — |
| Cystic | 12 (57) | 7 (21) | 5.388 (1.525–19.029) |
| Missing | 2 (10) | 5 (15) | — |

NOTE. Categorical data are presented as n (%) and continuous data as indicated.
[a]PC confined to the pancreas and resected with negative margins, or high-grade precursor lesions.
[b]PC spread beyond the pancreas, regardless of being resectable.



now, the timeline of PC development has been mostly investigated using genomic, autopsy, and simulation model studies. These studies, performed in sporadic PC cases, have estimated very long progression times from low-grade precursor lesions to invasive carcinoma, supporting a long indolent course and a potentially wide window of opportunity for early detection.[23–25]

A recent study by Noë et al[26] performed whole-exome sequencing of 17 individuals with IPMN-associated malignancy and estimated that high-grade IPMNs took a median of 3.7 years to develop into a PC founder cell. Because these studies are based on pathologic and genetic aspects, they do not establish at what stage of progression these lesions become identifiable on imaging.

Another study investigated the age at detection of symptomatic sporadic PC in a large epidemiologic database and found that patients with stage I PC (confined to the pancreas) were 1.48 years (95% CI, 0.17–2.79 years) younger than patients with stage IIA PC (progressed beyond the pancreas), narrowing the window of opportunity.[27] The only other study that also used serial prediagnostic imaging to assess what abnormalities become apparent before the diagnosis of PC was performed in a cohort of 128 patients with sporadic PC.[28] The first sign on their CT scans was an abrupt duct cutoff or duct dilation, which was observed at a median 11 months before the PC diagnosis in 31% (MPD dilatation) or 22% (MPD narrowing/cutoff) of patients. This is of interest, because these results are similar to ours. Of the 21 incident surveillance failures, 3 (14%) had a dilated MPD that preceded the malignant lesion by 4 to 9 months, suggesting that in individuals with a proven high risk of PC, a dilated MPD may be the first sign of malignancy and warrant an urgent workup with CT and possibly surgery or intensified surveillance, also in the absence of a visible associated focal lesion,

As explained, the results of the current study support the notion that the window of opportunity to detect a relevant lesion is narrow. These results have significant implication for PC surveillance programs. Whether shortening the surveillance interval to 6 months would increase the chance of successful early detection is unknown but would greatly intensify the burden of surveillance for patients and would increase costs. Theoretically, malignancies that develop from a detectable preceding lesion may present the best chance at improving successful early detection. Recent studies have highlighted that sporadic IPMNs are at continuous risk of malignant progression and can progress after having been stable on imaging for years.[29,30]

Factors associated with successful early detection included undergoing resection for small lesions after the baseline visit, cystic lesions, and lesions located in the body or tail. They also included the absence of any alcohol consumption, although this remains an exploratory predictor, because we could not investigate the degree of alcohol consumption in this cohort, and previous studies showed

that only high alcohol intake increases PC risk, whereas low to moderate alcohol intake does not.[31]

Among incident cases, a more favorable outcome was suggested—but could not be statistically proven—in cases that were not overdue for surveillance, had shorter follow-up before resection, and had lesions with a slower growth rate measured by imaging and less absolute growth. This seems to underline the rapid progression of some neoplastic lesions, at least as observed with conventional imaging (EUS and MRI/MRCP). Trying to identify the (pre)malignant small cystic lesions that are progressing, such as those with rapid growth, is not straightforward.

Cystic lesions are highly prevalent in high-risk individuals,[10,11,32] and only a minority of these cysts develops into an invasive malignancy. The predictive value of imaging to detect neoplastic changes in a pancreatic cyst is limited; hence, there is a high chance for a negative resection if the threshold for surgery is set too low. A recent study analyzed the performance of the criteria for surgical management of cystic lesions in high-risk individuals, as recommended by the updated international CAPS consensus guidelines, and found that the proposed criteria had a positive predictive value of only 50%.[33] In the current cohort, 43 individuals underwent resection for a suspicious cystic lesion, but less than half (18 of 43 [42%]) had high-grade dysplasia or malignancy in the resected specimen. Although most of these 18 neoplastic progressors showed $\geq$1 signs that have previously been associated with malignancy, such as a dilated MPD, mural nodule, or solid component, these features could not differentiate them from nonneoplastic cases.

Different criteria for resection of surveillance-detected cystic lesions should be developed and validated prospectively in high-risk individuals. Recent updates of cyst surveillance guidelines in the general population have emphasized cyst growth (speed) as a potentially important predictor for malignancy.[15,16] In our cohort, we observed a higher absolute growth, relative growth, and percentage of rapid growers ($\geq$5 mm/y) in the cystic neoplastic progressors, but our study lacked the power to establish statistical significance. The growth of a cystic lesion as a possible first hallmark of neoplastic progression on imaging is of interest and warrants further study, as more precise growth monitoring may improve successful early detection.

Regarding the definition of study end points in the current study, success of surveillance was defined as resected high-grade dysplasia or malignancy, with negative resection margins. Any PC spread beyond the pancreas was regarded a surveillance failure. This definition originates from the recommendations of the CAPS consortium, but is relatively strict.[4] Even when spread beyond the pancreas, the prognosis of these individuals may still be better compared with those with sporadic PC outside of surveillance. The few published long-term surveillance studies report higher resectability rates and lower cancer stages at diagnosis compared with those with sporadic PC, which is associated with longer survival.[6,8,34] However, lead-time bias may have influenced these surveillance results, and a true survival benefit remains to be proven.

Resection of lesions with worrisome features that are suspect for malignancy is also recommended by clinical guidelines for non–high-risk individuals outside surveillance. Even if these lesions have progressed beyond the pancreas, the treatment and outcomes are still according to the current best clinical practice.

In addition, we chose to classify main-duct and mixed-type IPMNs without high-grade dysplasia (3 cases) and pancreatic NETs (14 cases, all $<$2 cm) as nonprogressors. Although it can be argued that these cases should be considered a success when resected in high-risk individuals, the detection and treatment of these lesions is currently not defined as a goal of surveillance in the CAPS consortium recommendations.[4] When classified as a success, the proportion of included cases that is regarded as a success increases from 18% to 32%.

The current study has some limitations that must be acknowledged. Albeit representing the largest cohort of surveillance-detected PC cases to date, the number of incident neoplastic cases was still limited, and we were only able to analyze the primary end point in 28 of the 35 neoplastic progressors in the cohort. This precluded more advanced statistical analysis, including modeling of lesion growth.

Secondly, with the retrospective design of this study, selection and reporting bias may have affected our study results. Also because of the retrospective design and the large number of participating centers, there is variation over time and between centers regarding the surveillance tests and review and interpretation of radiologic images and pathologic specimens. At the time the imaging was performed, there was not yet a centralized uniform template for the scoring of abnormalities. No centralized rereading of images was performed.

With the ongoing prospective CAPS registry (www.caps-registry.com) in which data are collected of all high-risk individuals under surveillance, we will eventually be able to overcome most of these limitations. In addition, we did not have enough data to fully explore environmental (and possibly modifiable) risk factors for progression, such as precise alcohol consumption, smoking behavior, and obesity.

Lastly, genetic analyses have shown that PCs and neighboring IPMNs can arise from different precursors that are genetically different.[35,36] We were not able to perform such genetic analyses on resected neoplastic lesions, for which reason we cannot be certain about the natural evolvement and origin of the PC, more in particular, whether the tumor arose from the known precursor lesion or a different lesion.

## Conclusion

In the framework of an imaging-based PC surveillance research program in high-risk individuals, almost half of the individuals developed a neoplastic lesion without prior signs on imaging, and by the time of detection or surgical treatment, or both, most had already progressed beyond an early stage (T1 N0 M0). Progression to advanced PC

therefore can occur before the next annual surveillance examination, posing the question whether in certain (selected) high-risk individuals, shorter surveillance intervals are required. The other half developed from a preceding lesion that was most often cystic, but also in this group, timely identification of malignant transformation was challenging. Importantly, although progressing neoplastic cysts displayed fast growth, the presence of worrisome features could not reliably differentiate cysts with neoplastic progression from those without. The implementation of novel tools, such as improved imaging techniques and the artificial analysis of images and, most likely more promising, new, and accurate biomarkers are urgently needed to improve the outcome of PC surveillance research programs in high-risk individuals and to detect high-grade dysplasia and early cancer.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.10.014

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**Received May 28, 2021. Accepted October 15, 2021.**

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**Acknowledgments**
The authors acknowledge all collaborators in the CAPS consortium, 9 Knots Business Solutions for the development and maintenance of the online database system, and the research coordinators who have assisted in data collection in their respective centers: Tara Dhingra, Patil Prithvi, Anne Aronson, Chinedu Ukaegbu, Erika Koeppe, Georgia Castrigano, and Nancy Furey.

**CRediT Authorship Contributions**
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**Conflicts of interest**
These authors disclose the following: Paul Fockens received research funding from Boston Scientific and is a consultant to Olympus, Cook Medical, and Ethicon Endo-Surgery. Jan-Werner Poley is a consultant to Boston Scientific, Cook Medical, and PENTAX Medical. Nirav C. Thosani is a consultant to PENTAS of America and Boston Scientific, a speaker for AbbVie, and receives royalties from UpToDate. Aimee L. Lucas has received research funding from Immunovia. Sapna Syngal has served as a consultant to Myriad Genetics. Randall E. Brand has received research funding from Immunovia and Freenome. Alfredo Carrato is a consultant to Bristol Myers Squibb and has received honoraria from Bayer, Shire, and Celgene. Frank P. Vleggaar is a consultant to Boston Scientific. Djuna L. Cahen is a consultant to

Tramedico. Jeanin E. van Hooft received research funding from Abbott and Cook Medical and is a consultant to Boston Scientific, Cook Medical, Olympus, and Medtronic. Marcia Irene Canto received research funding from PENTAX Medical C2 CryoBalloon and EndoGastric Solutions. Marco J. Bruno received research funding from Boston Scientific, Cook Medical, and PENTAX Medical and is a consultant to Boston Scientific, Cook Medical, PENTAX Medical, and Mylan. The other authors disclose no conflicts.

**Funding**
No commercial financial support was received for the execution of this study. The study was partly funded by a charity donation from the Living with Hope Foundation.

**Data availability**
Data will be made available upon request.

**Supplementary Table 1.** Lesion Characteristics and Pathologic Outcome Stratified by Time of Detection (N = 122)

| Variables | Prevalent at baseline (n = 52) | Incident cases (n = 70) | *P* value |
|---|---|---|---|
| Lesion characteristics at resection or diagnosis of unresectable PC | | | |
| Dilated main pancreatic duct without focal lesion | 3 (6) | 2 (3) | .650 |
| Chronic pancreatitis features | 2 (4) | 0 (0) | .180 |
| Focal lesion | 47 (90) | 68 (97) | .135 |
| Size, median (IQR), *mm* | 13 (8) | 12 (16) | .924 |
| Location | | | .468 |
| Caput/uncinate | 15 (32) | 28 (41) | — |
| Genu/corpus | 7 (15) | 18 (27) | — |
| Cauda | 14 (30) | 18 (27) | — |
| Missing | 11 (23) | 4 (6) | — |
| Aspect | | | .049 |
| Solid | 18 (35) | 30 (43) | .357 |
| Indeterminate | 0 (0) | 9 (13) | .007 |
| Cystic | 19 (37) | 25 (36) | .925 |
| Missing | 10 (19) | 4 (6) | — |
| Pathologic outcome | | | |
| Advanced PC (>T1 N0 M0) | 9 (17) | 26 (37) | .025 |
| Early PC (T1 N0 M0) | 2 (4) | 4 (6) | 1.000 |
| PanIN-3 or IPMN with high-grade dysplasia | 11 (21) | 5 (7) | .031 |
| Main-duct or mixed-type IPMN with low- or moderate-grade dysplasia | 2 (4) | 1 (1) | .575 |
| PanIN-1, PanIN-2, or branch-duct IPMN with low- or moderate-grade dysplasia | 22 (42) | 21 (30) | .159 |
| Neuroendocrine tumor and low-grade precursor lesion | 4 (8) | 4 (6) | .722 |
| Neuroendocrine tumor | 1 (2) | 5 (7) | .238 |
| No neoplasia | 1 (2) | 4 (6) | .392 |

NOTE. Categorical data are presented as n (%) and continuous data as indicated.

**Supplementary Table 2.** Independent Predictors of Neoplastic Progression (N = 122)

| Predictors | Neoplastic progressors[a] (n = 57) | Nonneoplastic progressors[b] (n = 65) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Patient characteristics | | | | |
| Age at surgery/diagnosis, median (IQR), *y* | 66 (17) | 56 (15) | 1.079 (1.038–1.122) | 1.099 (1.036–1.166) |
| Female sex | 39 (68) | 31 (48) | 2.516 (1.189–5.323) | 4.289 (1.318–13.958) |
| Body mass index, median (IQR), $kg/m^2$ | 26 (5) | 27 (6) | 0.988 (0.918–1.065) | — |
| Diabetes mellitus | 10 (18) | 6 (9) | 0.463 (0.156–1.372) | — |
| Smoking at baseline | 8 (14) | 8 (12) | 1.213 (0.423–3.477) | — |
| Alcohol use at baseline | 15 (26) | 22 (34) | 0.862 (0.389–1.911) | — |
| Gene mutation carrier | 24 (42) | 16 (25) | 2.227 (1.030–4.817) | 2.707 (0.750–9.772) |
| Family history of PC | 49 (86) | 63 (97) | 0.194 (0.040–0.957) | — |
| ≥2 affected blood relatives | 42 (74) | 59 (91) | 0.285 (0.102–0.794) | 0.367 (0.072–1.859) |
| Age of onset in family <50 years | 11 (19) | 13 (20) | 0.983 (0.394–2.456) | — |
| Lesion characteristics | | | | |
| Detected during follow-up | 35 (61) | 35 (54) | 1.364 (0.662–2.809) | — |
| Dilated MPD without focal lesion | 2 (4) | 3 (5) | 0.752 (0.121–4.665) | — |
| Chronic pancreatitis features | 0 (0) | 2 (3) | — | — |
| Focal lesion | 55 (96) | 60 (92) | 2.292 (0.427–12.298) | — |
| Size, median (IQR), *mm* | 17 (17) | 11 (8) | 1.075 (1.025–1.128) | — |
| Size ≥1.5 cm | 26 (47) | 15 (25) | 3.467 (1.480–8.118) | 4.964 (1.635–15.075) |
| Located in head/uncinate (vs neck/body/tail) | 28 (51) | 15 (25) | 3.733 (1.620–8.601) | 4.953 (1.547–15.856) |
| Solid aspect (vs indeterminate or cystic) | 28 (51) | 21 (35) | 2.133 (0.963–4.725) | — |

NOTE. Categorical data are presented as n (%) and continuous data as indicated.
MPD, main pancreatic duct.
[a]PC, PanIN-3, or IPMN with high-grade dysplasia.
[b]Benign pathologic outcome, neuroendocrine tumors < 2 cm, PanIN-1, PanIN-2, or IPMN with low- or moderate-grade dysplasia.

**Supplementary Table 3.** Characteristics of Cystic Lesions, Stratified by Neoplastic Progression and Time of Detection (N = 44)

| Characteristics | Cystic neoplastic progressors[a] (n = 19) | | | Cystic nonneoplastic progressors[b] (n = 25) | | | All cystic neoplastic[a] vs all cystic nonneoplastic[b] progressors | Incident cystic neoplastic[a] vs incident cystic nonneoplastic[b] progressors |
|---|---|---|---|---|---|---|---|---|
| | Prevalent cases | Incident cases[c] | All | Prevalent Cases | Incident Cases[c] | All | | |
| | (n = 9) | (n = 10) | (n = 19) | (n = 10) | (n = 15) | (n = 25) | *P* value | *P* value |
| Patient characteristics | | | | | | | | |
| Age at surgery/diagnosis, median (IQR), *y* | 65 (13) | 65 (22) | 66 (16) | 60 (16) | 56 (19) | 58 (18) | .233 | — |
| Male sex | 3 (33) | 3 (30) | 6 (32) | 5 (50) | 4 (27) | 9 (36) | 1.000 | — |
| Body mass index, median (IQR), $kg/m^2$ | 26 (6) | 24 (5) | 25 (5) | 28 (5) | 25 (6) | 27 (5) | .595 | — |
| Diabetes mellitus | 1 (11) | 2 (20) | 3 (16) | 0 (0) | 0 (0) | 0 (0) | .073 | — |
| Smoking at baseline | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (13) | 2 (8) | .498 | — |
| Alcohol use at baseline | 0 (0) | 3 (30) | 3 (16) | 3 (30) | 2 (13) | 5 (20) | 1.000 | — |
| Gene mutation carrier | 3 (33) | 4 (40) | 7 (37) | 3 (30) | 3 (20) | 6 (24) | .507 | — |
| Family history of PC | 7 (78) | 9 (90) | 16 (84) | 9 (90) | 15 (100) | 24 (96) | .300 | — |
| ≥3 affected blood relatives | 4 (44) | 3 (30) | 7 (37) | 4 (40) | 9 (60) | 13 (52) | .372 | — |
| Age of onset in family <50 years | 2 (22) | 1 (10) | 3 (16) | 1 (10) | 0 (0) | 1 (4) | .312 | — |
| Surveillance characteristics | | | | | | | | |
| Previously detected | — | 7 (88) | — | — | 12 (86) | — | — | 1.000 |
| Time since detection, median (IQR), *mo* | — | 12 (20) | — | — | 16 (14) | — | — | |
| Surveillance visits since detection, median (range), *n* | — | 3 (1–6) | — | — | 2 (1–4) | — | — | |
| Last surveillance interval, median (IQR), *mo* | — | 5 (10) | — | — | 11 (7) | — | — | .659 |
| Overdue for last visit | — | 1 (13) | — | — | 2 (14) | — | — | 1.000 |
| Time between last visit and surgery (unresectable PC excluded), median (range), *mo* | — | 2 (0–7) | — | — | 3 (0–9) | — | — | .380 |
| Lesion characteristics | | | | | | | | |
| Location | | | | | | | | — |
| Head/uncinate | 5 (56) | 3 (30) | 8 (42) | 1 (10) | 4 (27) | 5 (20) | .105 | — |
| Neck/body | 1 (11) | 4 (40) | 5 (26) | 4 (40) | 5 (33) | 9 (36) | .744 | — |
| Tail | 2 (22) | 3 (30) | 5 (26) | 5 (50) | 6 (40) | 11 (44) | .348 | — |
| Size at detection, median (range), *mm* | | 12 (3–19) | — | — | 7 (3–30) | — | — | .265 |
| Absolute growth, median (range), *mm* | — | 5 (1–11) | — | — | 2 (−2 to 7) | — | — | .620 |
| Relative growth, median (range), % | — | 33 (8–92) | — | — | 17 (−29 to 150) | — | — | .131 |
| Growth speed, median (range), *mm/y* | — | 1 (1–9) | — | — | 2 (−1 to 25) | — | — | 1.000 |
| Growth speed ≥5 mm/y | — | 2 (29) | — | — | 2 (17) | — | — | .538 |
| Size at last visit, median (range), *mm* | 12 (6) | 21 (18) | 13 (12) | 15 (9) | 10 (7) | 12 (9) | .934 | — |
| Size ≥2.0 cm | 1 (11) | 4 (40) | 5 (26) | 2 (20) | 3 (30) | 5 (20) | .457 | — |

**Supplementary Table 3.** Continued

| Characteristics | Cystic neoplastic progressors[a] (n = 19) | | | Cystic nonneoplastic progressors[b] (n = 25) | | | All cystic neoplastic[a] vs all cystic nonneoplastic[b] progressors | Incident cystic neoplastic[a] vs incident cystic nonneoplastic[b] progressors |
|---|---|---|---|---|---|---|---|---|
| | Prevalent cases | Incident cases[c] | All | Prevalent Cases | Incident Cases[c] | All | | |
| | (n = 9) | (n = 10) | (n = 19) | (n = 10) | (n = 15) | (n = 25) | *P* value | *P* value |
| Worrisome features at any visit | | | | | | | | |
| Dilated main pancreatic duct | — | 2 (25) | — | — | 8 (57) | — | — | .204 |
| Time since detection, median (range), *mo* | — | 6 (5–7) | — | — | 11 (1–28) | — | — | .620 |
| Preceded cystic lesion | — | 0 (0) | — | — | 2 (25) | — | — | 1.000 |
| FNA suggestive or positive for adenocarcinoma | — | 3 (38) | — | — | 1 (7) | — | — | .117 |
| Time since positive FNA, median (range), *mo* | — | 1 (0–7) | — | — | 3 (–) | — | — | 1.000 |
| FNA negative for adenocarcinoma | — | 4 (50) | — | — | 2 (14) | — | — | .137 |

NOTE. Categorical data are presented as n (%) and continuous data as indicated.
[a]PC, PanIN-3, or IPMN with high-grade dysplasia.
[b]Benign pathologic outcome, neuroendocrine tumors <2 cm, PanIN-1, PanIN-2, or IPMN with low- or moderate-grade dysplasia.
[c]For variables concerning the 3 surveillance years before diagnosis or resection, 2 neoplastic cases and 1 nonneoplastic case were excluded due to missing information.