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Intraductal Papillary Mucinous Neoplasms in High-Risk Individuals: Incidence, Growth Rate, and Malignancy Risk

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BACKGROUND AND AIMS: **In high-risk individuals (HRIs), we aimed to assess the cumulative incidence of intraductal papillary mucinous neoplasms (IPMNs) and compare IPMN growth, neoplastic progression rate, and the value of growth as predictor for neoplastic progression to these in sporadic IPMNs.**

METHODS: **We performed annual surveillance of Dutch HRIs, involving carriers of germline pathogenic variants (PVs) and PV-negative familial pancreatic cancer kindreds. HRIs with IPMNs were compared with Italian individuals without familial risk under surveillance for sporadic IPMNs.**

RESULTS: **A total of 457 HRIs were followed for 48 (range 2–172) months; the estimated cumulative IPMN incidence was 46% (95% confidence interval, 28%–64%). In comparison with 442 control individuals, IPMNs in HRIs were more likely to grow ≥2.5 mm/y (31% vs 7%; $P < .001$) and develop worrisome features (32% vs 19%; $P = .010$). PV carriers with IPMNs more often displayed neoplastic progression (n = 3 [11%] vs n = 6 [1%]; $P = .011$), while familial pancreatic cancer kindreds did not (n = 0 [0%]; $P = 1.000$). The malignancy risk in a PV carrier with an IPMN was 23% for growth rates ≥2.5 mm/y (n = 13), 30% for ≥5 mm/y (n = 10), and 60% for ≥10 mm/y (n = 5).**

CONCLUSIONS: **The cumulative incidence of IPMNs in HRIs is higher than previously reported in the general population. Compared with sporadic IPMNs, they have an increased growth rate. PV carriers with IPMNs are suggested to be at a higher malignancy risk. Intensive follow-up should be considered for PV carriers with an IPMN growing ≥2.5 mm/y, and surgical resection for those growing ≥5 mm/y.**

Keywords: Pancreatic Cystic Lesions; Pancreatic Cancer; Intraductal Papillary Mucinous Neoplasm; Surveillance; Familial Pancreatic Cancer.

Abbreviations used in this paper: **CI, confidence interval; EUS, endoscopic ultrasonography; FPC, familial pancreatic cancer; HRI, high-risk individual; HRS, high-risk stigmata; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; MRI/MRCP, magnetic resonance imaging/magnetic resonance cholangiopancreatography; PC, pancreatic cancer; PV, pathogenic variant; WF, worrisome feature.**

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Imaging-based surveillance for pancreatic cancer (PC) is recommended in hereditary predisposed individuals.[1] Candidates may be carriers of a germline pathogenic variant (PV) of a PC susceptibility gene or familial PC (FPC) kindreds without a PV. To potentially improve survival of these high-risk individuals (HRIs), surveillance aims to detect the disease in an early stage. Preferably, PC is detected and treated while still confined to the pancreas or, even better, as a high-grade dysplastic precursor lesion.[1] The intraductal papillary mucinous neoplasm (IPMN) is one of such precursor lesions, detectable as a cystic lesion by imaging.[2,3]

In the general population, the prevalence of cystic lesions is 25% and increases with age and body mass index.[4] Of these, IPMNs concern a subgroup with an estimated malignant progression rate of <5% for branch duct IPMNs[5–9] and up to 50% for main-duct IPMNs.[10,11] In HRIs, a cyst prevalence of more than 38% has been observed, but with conflicting results as to whether the IPMN prevalence is higher in PV carriers or PV-negative FPC kindreds.[12–14] Also, the clinical significance of a higher prevalence of IPMNs, almost all of which concern branch-duct IPMNs, is unclear. An earlier pathology study of PCs in HRIs showed that most cancers developed from a solid precursor lesion, while IPMNs were seldom detected in these patients.[15] In addition, PCs in FPC kindreds were found to have genetic signatures consistent with a solid precursor, rather than a cystic one.[16] This branded IPMNs in HRIs as so-called bycatch, rather than the main target of surveillance. However, since then, long-term surveillance data showed that cysts growing 5 mm/y or developing solid components or mural nodules were predictive of malignancy in HRIs.[17,18] In addition, within the international Cancer of the Pancreas Screening Consortium, we analyzed surveillance-detected PCs and found that 43% arose from a previously detectable cystic lesion, and that resecting a cystic lesion was more likely to result in successful early detection than resecting a solid lesion.[19] These results have renewed the interest in IPMNs as a target of surveillance.

Thus, there is a need to establish if IPMNs indeed progress more often or faster in HRIs, and to what extent this determines their increased PC risk.[1] In addition, IPMNs at high risk of progression need to be identified timely to facilitate successful early detection of PC. The Cancer of the Pancreas Screening Consortium consensus recommendations contain criteria for the resection of pancreatic cystic lesions in HRIs, which are almost identical to the criteria for sporadic IPMNs in the general population.[1–3] Unfortunately, these criteria are not accurate enough for high-grade dysplasia or malignancy, underlining the need for improved selection criteria.[20] Of particular interest in this context is the cyst growth rate, as this may be an earlier and better differentiating sign than other classical worrisome features such as a dilated main pancreatic duct, mural nodule, or solid component.[19]

What You Need To Know

Background and context

High-risk individuals are at hereditary increased risk of pancreatic cancer and often harbor intraductal papillary mucinous neoplasms (IPMNs), of which the clinical relevance is unclear.

Findings

Compared with sporadic IPMNs, IPMNs in high-risk individuals grow faster, are more likely to develop worrisome features or high-risk stigmata, and might be at higher malignancy risk in pathogenic variant carriers.

Implications for patient care

Carriers of pathogenic variants of pancreatic cancer susceptibility genes with IPMNs growing ≥2.5 mm/y should undergo more intense follow-up, and surgical resection should be considered for those growing ≥5 mm/y. In pathogenic variant–negative familial pancreatic cancer kindreds, surveillance as recommended for sporadic IPMNs seems appropriate.

For the current study, within a population of HRIs, we aimed to (1) assess the cumulative incidence of IPMNs; (2) compare size measurement by endoscopic ultrasonography (EUS) with that by magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP); and (3) compare IPMN growth, neoplastic progression rate, and the value of growth as predictor for neoplastic progression to these in sporadic IPMNs.

Materials And Methods

Study Design

This study was performed with data from 2 ongoing multicenter prospective observational cohorts (Figure 1). The first consists of individuals at hereditary increased risk of PC undergoing surveillance in 3 university hospitals in the Netherlands (high-risk cohort). Ethical approval was given at the start (2007_024, Amsterdam University Medical Center) and continuation of the study (MEC-2012-448, Erasmus MC University Medical Center). Data obtained from this cohort between October 2006 and January 2021 were analyzed. The second (control) cohort consists of Italian individuals who underwent surveillance of an incidentally detected sporadic IPMN from 2009 to 2018 in 2 university hospitals. Ethical approval was obtained in both centers (133/2016 San Raffaele, 251/2012 Sant'Andrea). Participants of both studies gave written informed consent prior to enrollment. Patients and the public were not involved in the design or conduct or reporting of the study. This study and manuscript follow the STROBE (Strengthening

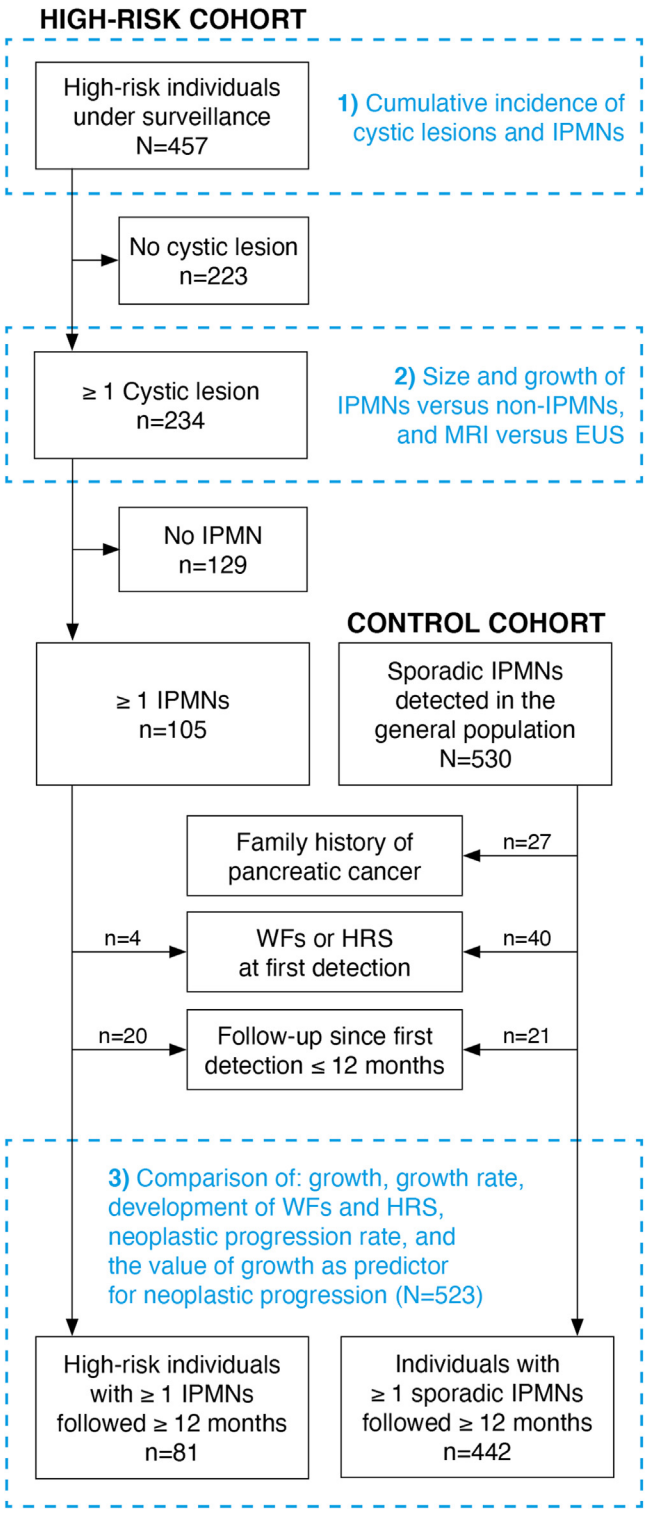

Figure 1. Study flowchart.

the Reporting of Observational Studies in Epidemiology) guidelines for observational cohort studies.

High-Risk Cohort

The high-risk cohort has been described in detail previously.[17] The study enrolls asymptomatic HRIs with a 10% or greater lifetime PC risk, as estimated by a clinical geneticist after a detailed evaluation of the family history, verification of cancer diagnoses, and genetic testing. The cohort includes carriers of a germline PV (classes 4 and 5) in one of the PC susceptibility genes and PV-negative FPC kindreds with a strong family history of PC. The complete risk assessment and inclusion, exclusion, and age criteria are listed in the Supplementary Materials. Participants were subjected to annual surveillance with EUS and MRI/MRCP at each visit. The surveillance interval was shortened to 3 or 6 months in case of an IPMN with worrisome features (WFs) that did not warrant immediate surgery (as defined by the international Fukuoka guidelines).[3] Surgical resection was performed in case of suspected malignancy, based on either the presence of high-risk stigmata (HRS) or multiple WFs, or cytology suspect or positive for malignancy. In case of unresectable disease, PC was confirmed through EUS-guided biopsy.

Control Cohort

The control cohort underwent IPMN surveillance as recommended by the clinical guidelines for sporadic IPMNs with EUS or MRI/MRCP. Equal to the surveillance strategy in HRIs, this consisted of annual surveillance, with a shortened interval in case of a WF and evaluation for surgical resection in case of multiple WFs or HRS.[2] Different from the high-risk cohort, surveillance did not automatically end at age 75 years, but rather continued for as long as the patient had no significant comorbidities and was a potential surgical candidate. As shown in Figure 1, from this database we excluded individuals who had a family member with PC.

Study Endpoints and Definitions

The study endpoints were (11) the cumulative pancreatic cyst and IPMN incidence; (2) median cyst size, growth, and growth rate; (3) development of WFs or HRS according to the Fukuoka criteria,[3] and neoplastic progression, defined as the development of histologically proven high-grade dysplasia or PC (either concomitant or IPMN associated). In both the high-risk and control cohorts, cysts were classified as IPMNs if they showed communication with the pancreatic duct on any modality at any visit. In the high-risk cohort, cyst sizes were measured for each individual cyst at each visit on both EUS and MRI. In the control cohort, the largest IPMN size was registered at detection and at the latest follow-up visit.

Statistical Analysis

Differences in patient and cyst characteristics were compared between groups using the *t* test, Mann Whitney *U* test, and chi-square test. We estimated the cumulative

Table 1. Patient and Cyst Characteristics of High-Risk Individuals With an IPMN and the Control Cohort (n = 523)

	High-Risk Cohort				
	All (N = 81)	FPC Kindreds (n = 54)	PV Carriers (n = 27)	Control Cohort (n = 442)	*P* Value: High-Risk vs Control
Patient characteristics					
Age at IPMN detection, y	59 ± 8 (37–74)	60 ± 8 (37–74)	57 ± 8 (41–72)	65 ± 11 (20–88)	<.001
Body mass index, kg/m^2	26 (6)	26 (6)	26 (7)	25 (5)	.013
Diabetes mellitus	7 (9)	4 (7)	3 (11)	60 (14)	.279
History of acute pancreatitis	4 (5)	4 (7)	0 (0)	3 (1)	.013
History of nonpancreatic malignancy	23 (28)	8 (15)	15 (56)	110 (25)	.491
Alcohol consumption, ever	55 (68)	39 (72)	16 (59)	121 (27)	<.001
Smoker, ever	35 (43)	23 (43)	12 (44)	151 (34)	.074
Cyst characteristics					
Location of dominant IPMN					.788
Head	43 (53)	30 (56)	13 (48)	169 (38)	—
Body	30 (37)	20 (37)	10 (37)	122 (28)	—
Tail	8 (10)	4 (7)	4 (15)	42 (10)	—
Missing	0 (0)	0 (0)	0 (0)	109 (25)	—
Multifocality	25 (31)	16 (30)	9 (33)	254 (58)	<.001
Largest size at first detection, mm	6 (7)	6 (7)	5 (3)	15 (10)	<.001
Cyst progression					
Follow-up since first detection, mo	47 (54)	45 (48)	61 (67)	41 (47)	.043
Largest size at last follow-up, mm	7 (8)	7 (5)	7 (11)	16 (12)	<.001
Absolute growth, mm	1 (3)	1 (2)	1 (9)	0 (5)	.008
Relative growth, %	14 (67)	8 (50)	33 (131)	0 (27)	.008
Absolute growth rate, mm/y	0.2 (1)	0.2 (0)	0.2 (1)	0.0 (1)	.008
Relative growth rate, %/y	2 (13)	2 (10)	5 (24)	0 (6)	.008
Growth rate					
≥2.5 mm/y at any moment	25 (31)	12 (22)	13 (48)	32 (7)	<.001
≥5 mm/y at any moment	14 (17)	4 (7)	10 (37)	6 (1)	<.001
≥10 mm/y at any moment	7 (9)	2 (4)	5 (19)	1 (0)	<.001
Development of WFs or HRS[a]					
Excluding growth rate	7 (9)	5 (9)	2 (7)	69 (16)	.123
Including growth rate	26 (32)	13 (24)	13 (48)	82 (19)	.010
Development of multiple WFs or HRS[a]					
Excluding growth rate	2 (3)	1 (2)	1 (4)	15 (3)	1.000
Including growth rate	6 (7)	4 (7)	2 (7)	31 (7)	.817
Development of PC	3 (4)	0 (0)	3 (11)	6 (1)	.150
Surgical resection	3 (4)	1 (2)	2 (7)	10 (2)	.435
Low-grade dysplasia	2 (2)	1 (2)	1 (4)	5 (1)	—
High-grade dysplasia	0 (0)	0 (0)	0 (0)	0 (0)	—
PC	1 (1)	0 (0)	1 (4)	5 (1)	—
All-cause mortality	5 (6)	0 (0)	5 (19)	14 (3)	.194
PC disease-specific mortality	3 (4)	0 (0)	3 (11)	3 (1)	.050
Treatment-specific mortality	0 (0)	0 (0)	0 (0)	0 (0)	—
Nonpancreatic mortality	2 (2)	0 (0)	2 (7)	11 (2)	1.000

Values are mean ± SD (range), median (interquartile range), or n (%).
FPC, familial pancreatic cancer; HRS, high-risk stigmata; IPMN, intraductal papillary mucinous neoplasm; PC, pancreatic cancer; PV, pathogenic variant (class 4 or 5); WF, worrisome feature.
[a]WFs and HRS as defined in the international Fukuoka criteria.[3]

incidence of any cystic lesion and of IPMNs within the high-risk cohort using the Kaplan-Meier method. Differences between subgroups were corrected for age using Cox proportional hazards regression analysis. Risk factors for the presence of an IPMN were also assessed with a multivariable Cox proportional hazards regression analysis.

To compare size measurements and growth of IPMNs, we fitted 2 linear mixed models on the outcome cyst size (Figure 1). To compare size measurements by EUS and MRI/MRCP, we used the data of all cystic lesions of the high-risk cohort. To compare IPMN growth, we used the combined data of IPMNs detected in the high-risk cohort and the IPMNs of the control cohort, excluding those who had been followed <12 months. Details of the methods of the linear mixed models are presented in the Supplementary Materials.

Last, we assessed the sensitivity, specificity, and positive and negative predictive values of cyst size, growth, and growth rate for the detection of neoplastic progression. Statistical analyses were performed using SPSS Statistics 23 (IBM Corporation, Armonk, NY) and R version 4.0.5 (2021-03-31; R Foundation for Statistical Computing, Vienna, Austria) using the packages Ime4 (version 1.1.27.1)[21] and blme (version 1.0.5).[22]

Results

Cumulative Incidence of Any Pancreatic Cystic Lesions and IPMNs in HRIs

The high-risk cohort consisted of 457 individuals: 203 (44%) germline PV carriers and 254 (56%) FPC kindreds (Table 1, Supplementary Table 1). They were followed for 2419 person-years with a median follow-up of 48 (interquartile range [IQR], 76; range 2–172) months. The cumulative incidence of any cystic lesion (IPMNs and non-IPMNs) during the total period was estimated at 71% (95% confidence interval [CI], 64% to 78%) in the entire cohort and 75% (95% CI, 65% to 85%) in the PV-negative FPC kindreds and 65% (95% CI, 55% to 75%) in PV carriers (Figure 2*A*). The cumulative incidence of IPMNs was 46% (95% CI, 28% to 64%) overall and 40% (95% CI, 31% to 50%) in FPC kindreds and 46% (95% CI, 20% to 73%) in PV carriers (Figure 2*B*). After correction for age, the cumulative incidences were not different between the 2 groups ($P = .196$ for any cyst and $P = .082$ for IPMNs). Age was the only independent risk factor for the presence of an IPMN (hazard ratio, 1.058; 95% CI, 1.033 to 1.084) (full results shown in Supplementary Table 2).

Size and Growth of IPMNs vs Non-IPMNs and Measurement by MRI vs EUS in HRIs

The linear mixed model showed that at first detection, IPMNs were estimated to be 0.309 log(mm) [95% CI, 0.209 to 0.413 log(mm)] larger than non-IPMNs (Supplementary Table 3 and Supplementary Figure 1*A*). The median absolute growth was 0 (IQR, 2) mm for IPMNs and 0 (IQR, 1) mm for non-IPMNs. After correction for possible confounders, IPMNs were observed to grow faster [0.032 log(mm); 95% CI, 0.012 to 0.048 log(mm)] than non-IPMNs (Supplementary Figure 1*A*). The observed cyst size was on average 0.8 ± 3.1 mm larger on MRI/MRCP measurements compared with EUS measurements (7.0 mm vs 6.2 mm) (Supplementary Figure 1*B*). This was independent of the other variables [0.128 log(mm); 95% CI, 0.053 to 0.202 log(mm)] (Supplementary Table 3 and Supplementary Figures 2 and 3). The full details of these analyses are described in the Supplementary Materials.

Progression of IPMNs in HRIs and Sporadic IPMNs

There were 105 HRIs with 1 or more IPMNs. Twenty individuals were excluded because they had been followed for <1 year, and 4 because they had a WF at detection (main pancreatic duct of 5 or 6 mm in all 4). The remaining 81 HRIs were compared with the 442 individuals from the control cohort. Compared with the control cohort, the HRIs were younger (mean 59 years of age vs 65 years of age; $P < .001$), less often had multifocal IPMNs (31% vs 58%; $P < .001$), and were followed longer (median 47 months vs 41 months, $P = .043$) (all characteristics shown in Table 1).

Seven individuals (2 high risk and 5 from the control cohort) were excluded from this second linear mixed model due to missing data of one of the included variables. Compared with the control cohort, IPMNs were smaller at baseline both in PV carriers [median 5 mm vs 15 mm; −0.865 log(mm); 95% CI, −1.162 to −0.435 log(mm)] and PV-negative FPC kindreds [median 6 mm vs 15 mm; −0.804 log(mm); 95% CI, −1.125 to −0.351 log(mm)] (Figure 3, Table 1, and Supplementary Table 5). IPMNs grew slightly but statistically significantly faster both in PV carriers [median 0.2 mm/y vs 0.0 mm/y; 0.041 log(mm); 95% CI, 0.010 to 0.081 log(mm)] and FPC kindreds [median 0.2 mm/y vs 0.0 mm/y; 0.047 log(mm); 95% CI, 0.004 to 0.090 log(mm)]. In addition, IPMNs in HRIs more often reached high growth rates (≥2.5 mm/y; 31% vs 7%; $P < .001$) (Table 1). This difference was especially noticeable between PV carriers (48% reaching ≥2.5 mm/y, 37% reaching ≥5 mm/y, and 19% reaching ≥10 mm/y) and the control cohort (7%, 1%, and 0%, respectively).

IPMNs in HRIs more often developed WFs or HRS (32% vs 19%; $P = .010$). The incidence of WFs or HRS excluding growth rate was 9% in HRIs vs 16% in the control cohort ($P = .123$) (Table 1). PC developed equally in the high-risk cohort (3 individuals, 4%) and in the control cohort (6 individuals, 1%; $P = .150$) (Table 1), with uncertain origin from the IPMN or surrounding parenchyma. However, because all PC cases in

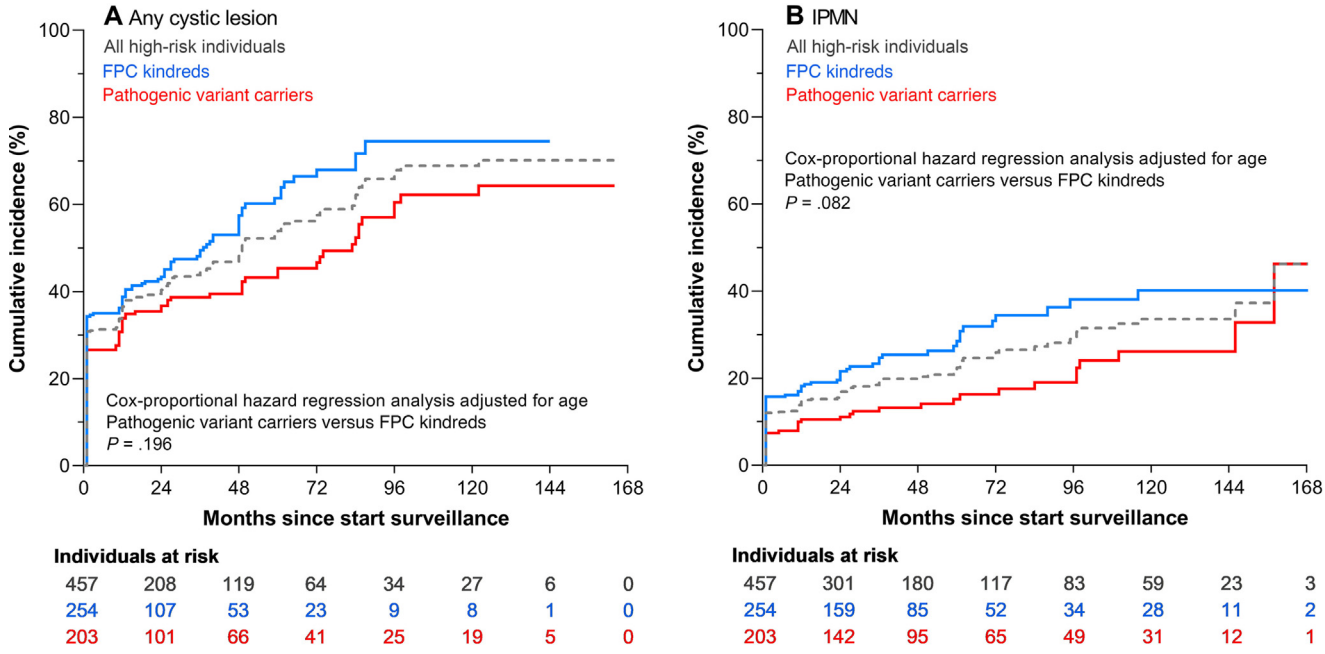

Figure 2. Cumulative incidence of (*A*) any pancreatic cystic lesion and (*B*) IPMNs only stratified for risk category.

HRIs concerned PV carriers, this group was at higher risk of neoplastic progression compared with the control cohort (11% vs 1%; $P = .011$), while PV-negative FPC kindreds were not (0% vs 1%; $P = 1.000$). Details on the clinical course of the 3 PV carriers who developed PC are presented in the Supplementary Materials. Detailed information on the type and number of WFs and HRS in individuals who developed PC and/or underwent surgery in both the high-risk cohort and control cohort are listed in Supplementary Table 4.

IPMN Size and Growth Rate as Predictors for Neoplastic Progression

Table 2 shows the predictive value for PC of IPMN size, growth, and growth rate within the PV carriers and control cohort. Growth rate was the most accurate predictor in PV carriers, with a sensitivity of 100% (95% CI, 29% to 100%) for absolute growth rates of 2.5, 5, and 10 mm/y and a relative growth rate of 100%/y, and specificities ranging from 58% (2.5 mm/y) to 92% (10 mm/y). The risk of a PV carrier with a fast-growing IPMN to harbor malignancy was 23% (95% CI, 16% to 33%) for 2.5 mm/y, 30% (95% CI, 19% to 44%) for 5 mm/y, and 60% (95% CI, 28% to 85%) for 10 mm/y. Conversely, the risk of a PV carrier with an IPMN growing <2.5 mm/y was 0%. In the control cohort, growth rate was less indicative of neoplastic progression, with much lower sensitivities (0%–33%) and positive predictive values (0%–5%) (Table 2). The predictive values for PC or main-duct IPMNs with lower-grade dysplasia are presented in Supplementary Table 6.

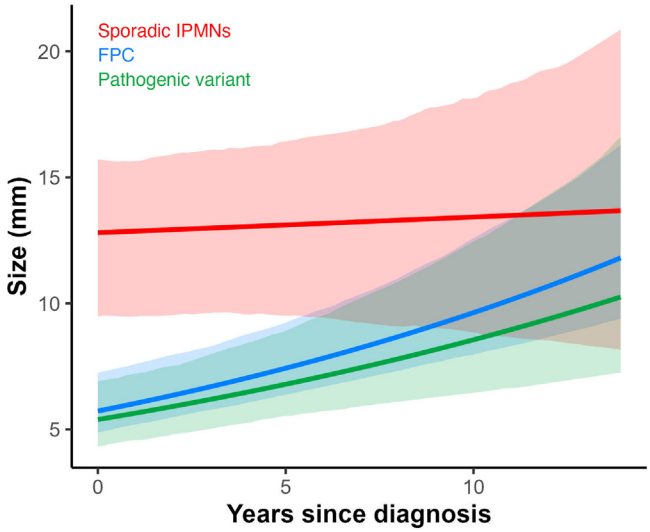

Figure 3. Estimated IPMN size and growth in HRIs and the control cohort.

Discussion

In this study, we performed an extensive analysis of IPMNs in HRIs. Similar to previous reports, we observed a higher cumulative incidence of IPMNs in PV carriers and PV-negative FPC kindreds than has been described for sporadic IPMNs in the general population in published literature.[4,12,13] In a direct comparison with control individuals with sporadic IPMNs, IPMNs in HRIs displayed a slightly faster growth and more often developed WFs, both of which are associated with a higher risk of progression to malignancy. In PV carriers, the malignant progression rate was much higher than in the control cohort (11% vs 1%), although the number of cases was low in both cohorts (n = 3 and n = 6). These results are supported by previously published long-term surveillance data of our and other programs, showing that the presence of an IPMN per se is not associated

Table 2. Predictive Value of IPMN Size and Growth for Neoplastic Progression

	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	NPV (95% CI) (%)
Size ≥3 cm				
General population	33 (4–78)	90 (87–93)	4 (1–13)	99 (98–99)
PV carriers	0 (0–71)	100 (86–100)	—	89 (89–89)
Size ≥4 cm				
General population	17 (0–64)	99 (97–100)	17 (3–60)	99 (98–99)
PV carriers	0 (0–71)	100 (86–100)	—	89 (89–89)
Absolute growth ≥10 mm				
General population	33 (4–78)	89 (86–92)	4 (1–12)	99 (98–99)
PV carriers	67 (9–99)	83 (63–95)	33 (13–62)	95 (80–99)
Absolute growth rate ≥2.5 mm/y				
General population	33 (4–78)	92 (89–94)	5 (2–15)	99 (98–99)
PV carriers	100 (29–100)	58 (37–78)	23 (16–33)	100 (—)
Absolute growth rate ≥5 mm/y				
General population	33 (4–78)	99 (97–100)	29 (9–63)	99 (98–99)
PV carriers	100 (29–100)	71 (49–87)	30 (19–44)	100 (—)
Absolute growth rate ≥10 mm/y				
General population	0 (0–46)	100 (99–100)	0 (—)	99 (99–99)
PV carriers	100 (29–100)	92 (73–99)	60 (28–85)	100 (—)
Relative growth ≥50%				
General population	17 (0–64)	83 (79–86)	1 (0–7)	99 (98–99)
PV carriers	67 (9–99)	42 (22–63)	13 (6–25)	91 (65–98)
Relative growth ≥100%				
General population	17 (0–64)	95 (92–96)	4 (1–21)	99 (98–99)
PV carriers	33 (1–91)	58 (37–78)	9 (2–35)	88 (75–94)
Relative growth rate ≥100%/y				
General population	0 (0–46)	100 (99–100)	0 (—)	99 (99–99)
PV carriers	100 (29–100)	75 (53–90)	33 (20–50)	100 (—)
Relative growth rate ≥200%/y				
General population	0 (0–46)	100 (99–100)	—	99 (99–99)
PV carriers	33 (1–91)	88 (68–97)	25 (5–69)	91 (82–96)

Predictive values could not be analyzed for PV-negative FPC kindreds because there were no cases with neoplastic progression. Neoplastic progression was defined as histologically proven high-grade dysplasia or pancreatic ductal adenocarcinoma.
CI, confidence interval; FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm; NPV, negative predictive value; PPV, positive predictive value; PV, pathogenic variant (class 4 or 5).

with neoplastic progression but that rapid growth and a large cyst size are.[17,18]

At the same time, the exact predictive value of rapid cyst growth for advanced neoplasia has not been studied extensively, nor has it been studied if it is a good sole predictor in the absence of other WFs or HRS. Cyst surveillance guidelines have recently incorporated high growth rate as a WF (international Fukuoka guidelines) or a relative resection criterium (European guidelines),[2,3] because growth of more than 2 mm/y was shown to be associated with other WFs and malignancy.[23] In incidentally detected sporadic IPMNs, Kwong et al[24] analyzed growth rate's predictive value for malignancy in 284 low-risk branch duct IPMNs and found a sensitivity of 78%, a specificity of 90%, a positive predictive value of 18%, and a negative predictive value of 99% for a cutoff of 2 mm/y, and 56%, 97%, 36%, and 99%, respectively, for a cutoff of 5 mm/y.[24] In their later follow-up study, the IPMNs with advanced neoplasia grew 2.6 mm/y vs 0.4 mm/y for benign IPMNs, but they could not establish statistical difference due to the low number of cases (n = 5).[25] In our control cohort, the predictive values were similar for both cutoffs. Compared with these outcomes in sporadic IPMNs, the sensitivity and positive predictive value of rapid growth in our high-risk cohort were higher, at the cost of a lower specificity. When looking at rapid growth as a sole predictor, we observed that 1 (33%) of the 3 HRIs with PC displayed only fast growth without additional WFs or HRS. Of the 6 individuals with PC in the control cohort, 1 had only size >40 mm as additional WF; the other 5 all had additional features such as a solid component or dilated pancreatic duct (Supplementary Table 4).

Previously, it was thought that pancreatic cancers in HRIs mostly stem from solid precursor lesions, based on the finding of predominantly pancreatic intraepithelial neoplasia in surgical specimens,[13,15] and genetic signatures that were consistent with a pancreatic

intraepithelial neoplasia origin.[16] Our study shows signs that in PV carriers, IPMNs are more likely to reach high growth rates and might be more likely to develop into malignancy, suggesting that the presence of IPMNs in these individuals does, in fact, add to their increased lifetime PC risk. In addition, a recent analysis of surveillance-detected PCs in HRIs showed that 43% of malignancies seemed to have stemmed from a previously visible cystic lesion.[19]

The current resection criteria for IPMNs in the international Fukuoka guidelines have a poor predictive value for malignancy in HRIs.[20] Better and more reliable criteria are needed to improve risk stratification and early detection and reduce unnecessary pancreatic surgery. Based on the current study, we recommend a diligent registration of growth rate for each IPMN in HRIs at each surveillance visit. In proven PV carriers, a growth rate of $\geq$2.5 mm/y should prompt for additional workup, including computed tomography and/or fine-needle aspiration of the IPMN (as is currently recommended). If this workup is negative, a surveillance interval of 3 months is likely more appropriate than the currently recommended 6 months.[1] IPMNs with a growth rate of $\geq$10 mm/y in PV carriers should be referred for surgical resection in light of a 60% risk of malignancy. This might also be considered for those growing $\geq$5 mm/y (30% malignancy risk). For IPMNs in PV-negative FPC kindreds, we did not find evidence to support a more aggressive workup or lower resection criteria. Thus, we recommend them to be followed according to the guidelines for sporadic IPMNs.

We observed that IPMNs were larger at first detection than non-IPMNs, which might be because an evident connection to the pancreatic duct is easier to establish in larger cysts. Our linear mixed model identified that cysts with a connection to the pancreatic duct (ie, IPMNs) grew faster than those without (non-IPMNs), which was irrespective of cyst size and the other included variables. This shows the establishment of pancreatic duct connection is of importance, possibly increasing the value of secretin-enhanced MRI/MRCP over EUS as a surveillance tool.

Strengths of this study are the large number of included HRIs, long follow-up period, and prospective strict surveillance protocol with measurement of each cyst by both MRI/MRCP and EUS. This enabled a high-quality growth analysis and comparison of size measurements by the 2 modalities. This is the first study to directly compare growth and progression between IPMNs in HRIs and sporadic IPMNs. The control cohort, which consisted of consecutive patients referred for pancreatic cyst surveillance, originated from a different (Italian) population, resulting in some differences compared with the high-risk cohort in the patient age, body mass index, and cyst multifocality and size. However, all of these differences were corrected for in the linear mixed model, which had more than sufficient data for robust statistical modeling. In addition, the control cohort underwent surveillance at the same intervals as the high-risk cohort and was highly comparable to previously published cohorts of incidentally detected low-risk branch duct IPMNs in terms of growth rate, development of WFs, and malignant progression rate.[6,7,9,24]

This study had several limitations. Firstly, the low number of PV carriers and cases with WFs or malignancy (3 PV carriers and none of the FPC kindreds) resulted in large CIs for the predictive values for malignancy and prevented us from correcting for possible confounders and from analyzing the predictive value in the PV-negative FPC kindreds. Ideally, the predictive values should be confirmed in other (larger) cohorts for both groups separately. Second, the diagnoses of IPMNs were not histologically confirmed, possibly resulting in a wrongful selection of cysts. However, this reflects current clinical practice, and we included only cysts displaying a clear connection to the pancreatic duct, in an attempt to improve the purity of the cohort and comparability between the high-risk and control cohorts. Third, there was not one standardized imaging protocol for both the high-risk and control cohorts, as they stemmed from different studies and centers. This may have led to an interobserver variability in the diagnosis of IPMNs. However, this has affected only a part of the results, as a large part of cyst surveillance was performed with EUS. Fourth, we acknowledge that using a control group from a different center led to additional limitations, including that we cannot guarantee a complete adherence to the published cyst surveillance guidelines. Additionally, we could not genetically profile the control cohort. Up to 3% of individuals with seemingly sporadic IPMNs may actually harbor PVs in pancreatic cancer susceptibility genes,[26] but genetic testing is currently not recommended in this group. Finally, we did not perform a genetic analysis of the pancreatic cancers and IPMNs to confirm their relationship. If the malignancies were in fact not genetically related to the neighboring IPMNs,[27] we may have overestimated the IPMNs' malignancy rate and their contribution to the PV carriers' PC risk.

In conclusion, compared with previous reports on sporadic IPMNs in the general population, IPMNs have a higher cumulative incidence in HRIs. In addition, their IPMNs grow faster and reach worrisome growth rates more often. IPMNs in the subgroup of PV carriers might be more likely to progress to malignancy, for which growth rate is a more important predictor than in the general population. Thus, growth rate should be rigorously assessed for each IPMN at every visit and corrected for the applied imaging modality. In PV carriers, an urgent workup with computed tomography and/or fine-needle aspiration should be performed for IPMNs growing $\geq$2.5 mm/y. In case of a negative workup, a surveillance interval of 3 months seems advisable. IPMNs growing $\geq$5 mm/y may be considered for surgical resection. In PV-negative FPC kindreds, there is no evidence supporting a more aggressive approach toward IPMNs than that used for sporadic IPMN.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.03.035.

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Djuna L. Cahen (Conceptualization: Supporting; Supervision: Equal; Writing – review & editing: Lead)

Marco J. Bruno (Conceptualization: Equal; Funding acquisition: Lead; Investigation: Lead; Methodology: Supporting; Project administration: Supporting; Resources: Lead; Supervision: Lead; Writing – review & editing: Equal)

Conflicts of Interest

These authors disclose the following: Paul Fockens has received research funding from Boston Scientific; and has served as a consultant for Olympus, Cook Medical, and Ethicon Endosurgery. Jan-Werner Poley has served as a consultant for Boston Scientific, Cook Medical, and Pentax Medical. Djuna L. Cahen has served as a consultant for Tramedico. Marco J. Bruno has received research funding from Boston Scientific, Cook Medical, and Pentax Medical; and served as a consultant for Boston Scientific, Cook Medical, Pentax Medical, and Mylan. The remaining authors disclose no conflicts.

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Supplementary Methods

Risk Assessment for the High-Risk Cohort

All participants were estimated to have an increased lifetime risk of pancreatic cancer (PC), after assessment by a clinical geneticist including a detailed evaluation of their family history, verification of cancer diagnoses by review of medical records, and genetic testing. Genetic testing was performed on a PC index case whenever possible, and otherwise in a healthy first-degree relative. If a class 4 or 5 pathogenic variant (PV) was found in a PC index case, only family members who tested positive were enrolled. If no PVs were found, but individuals had a family history of PC in at least 2 blood relatives (of which at least 1 was a first-degree relative), we included them as PV-negative familial PC kindreds (fourth category in subsequent inclusion criteria).

Inclusion Criteria for the High-Risk Cohort

Participants had to meet 1 of the following inclusion criteria: (1) carry a PV of the *CDKN2A* gene affecting the p16INK4A protein, regardless of PC family history; (2) have Peutz-Jeghers syndrome (proven *LKB1/STK11* pathogenic gene variant or clinical diagnosis), regardless of PC family history; (3) carry a *BRCA2*, *BRCA1*, *TP53*, *MLH1*, *MSH2*, or *MSH6* pathogenic gene variant, and have $\geq$2 blood relatives with PC, of which $\geq$1 was histologically proven; or (4) be a first-degree blood relative of a family member with PC, in a family with $\geq$1 histologically proven PC and either: PC in $\geq$2 blood relatives who were first-degree relatives to each other, PC in $\geq$3 blood relatives who were first or second-degree relatives to each other, or PC in $\geq$2 blood relatives, of whom $\geq$1 was under 50 years of age, who were first or second-degree relatives to each other.

Exclusion Criteria for the High-Risk Cohort

Participants were excluded if they either: (1) had a personal history of PC, (2) were under 18 years of age, (3) were unable to provide informed consent due to mental retardation or a language barrier, (4) had an upper gastrointestinal tract obstruction or stricture not allowing passage of the echoendoscope, or (5) had an American Society of Anesthesiologists score $\geq$3.

Age Criteria for the High-Risk Cohort

The minimum age of inclusion was 45 years until 2013 and 50 years thereafter, or 10 years younger than the age of the youngest relative diagnosed with PC, whichever was lowest. For individuals with Peutz-Jeghers syndrome (*LKB1/STK11*), the minimum age of inclusion was 30 years or 10 years younger than the youngest PC onset age in the family. Surveillance ended at the age of 75 years.

Statistical Methods of Linear Mixed Models

For objective 2, the model was fitted on the data of all cystic lesions of the high-risk cohort, with separate size measurements by endoscopic ultrasonography (EUS) and magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) for every cyst at each visit. For objective 3, from both the high-risk and control cohorts we excluded individuals with worrisome features (WFs) or high-risk stigmata at first detection of the cystic lesion (as defined by the international Fukuoka guidelines) or who had been followed for $<$12 months. The model was then fitted on the combined data of the remaining high-risk individuals in whom intraductal papillary mucinous neoplasms (IPMNs) were detected and the control cohort. For this model, we used the largest IPMN size per individual at first detection and at the latest follow-up visit. For both linear mixed models, the outcome (cyst size) was transformed using the natural logarithm to better comply with the assumption of conditional normality. For both models, the fixed effects structure contained effects for the time since first detection (linear effect), age (linear effect), risk group, number of blood relatives with PC, diabetes mellitus, body mass index, smoking and alcohol consumption (ever or never), and history of acute pancreatitis and nonpancreatic malignancy. In addition, the first model contained fixed effects for the used diagnostic modality (MRI/MRCP or EUS) and the cyst type (IPMN or non-IPMN), and the second model for IPMN multifocality. To investigate differences in growth between groups, interaction terms were added between the year since first detection and: the risk group, the number of relatives affected by PC, and the presence of an IPMN (only for the first model). The models contained random intercepts and slopes for the year since first detection of the cyst (using a natural cubic spline with 2 degrees of freedom) to take into account correlation between measurements of the same patient and to model differences in the subject-specific trajectories. Results from these models were visualized by plotting the expected cyst size over time for selected combinations of covariate values (and setting covariates not of interest to the median or reference category).

Supplementary Results

Size and Growth of IPMNs vs Non-IPMNs and Measurement by MRI vs EUS in High-Risk Individuals

In the high-risk cohort, 234 (51%) individuals had at least 1 pancreatic cystic lesion during surveillance

(median 2 cysts per individual). They harbored a total of 553 cysts: 186 (34%) IPMNs and 367 (66%) non-IPMNs. At detection, IPMNs measured a median of 5 (interquartile range [IQR], 6) mm and non-IPMNs a median of 4 (IQR, 2) mm. The linear mixed model (Supplementary Table 3) showed that at first detection, IPMNs were estimated to be 0.309 log(mm) [95% confidence interval (CI), 0.209–0.413 log(mm)] larger than non-IPMNs (Figure 1). A larger cyst size at first detection was associated with older age [0.006 log(mm); 95% CI, 0.001–0.010 log(mm)] and a higher number of relatives affected by PC [0.035 log(mm); 95% CI, 0.002–0.083 log(mm)]. No size difference between PV carriers and PV-negative familial PC kindreds was observed. The observed cyst size was on average 0.8 ± 3.1 mm larger on MRI/MRCP measurements compared with EUS measurements (7.0 mm vs 6.2 mm) (Figure 1). In the linear mixed model, this was independent of the other variables [0.128 log(mm); 95% CI, 0.053–0.202 log(mm)].

At the most recent follow-up visit, 46 (25%) IPMNs and 125 (34%) non-IPMNs were not detectable. The remaining 140 IPMNs had been followed a median 41 (IQR, 75; range 0–164) months and the 242 non-IPMNs 25 (IQR, 58; range 0–160) months ($P = .041$). After exclusion of 105 cysts (24 IPMNs and 81 non-IPMNs) with <1 year of follow-up, the median absolute growth was 0 (IQR, 2) mm for IPMNs and 0 (IQR, 1) mm for non-IPMNs. After correction for possible confounders in the linear mixed model, IPMNs were observed to grow faster [0.032 log(mm); 95% CI, 0.012–0.048 log(mm)] than non-IPMNs (Supplementary Figure 3A). There was no evidence for differences in growth between the different risk groups, nor an association with the number of affected relatives (Supplementary Materials).

Clinical Course of Pathogenic Variant Carriers Who Developed PC

Of the 3 PV carriers who developed PC, the first was an individual with Peutz-Jeghers syndrome, who had been followed 39 months since first detection of the branch duct IPMN (BD-IPMN). The IPMN developed a possible solid component, but fine-needle aspiration was negative, after which intensified surveillance was performed. After 2 years of shortened intervals, the IPMN developed a growth speed of 14 mm/y, but a second fine-needle aspiration was also negative, after which surveillance was resumed. One month later, the individual developed symptoms and computed tomography revealed a new hypodense lesion of 2 cm (T4N1M0). The second individual was a *BRCA2* PV carrier, followed for 83 months for a multifocal BD-IPMN. The IPMN developed a growth speed of 11 mm/y without other WFs. Regular surveillance intervals were maintained, and a year later the growth speed had reduced to 4 mm/y. However, five months after, the individual developed a symptomatic metastasized interval PC (T3N1M1). Radiologically, based on the locations, the PC seemed to be a concomitant lesion that had arisen independently of the BD-IPMN. The third individual was a *CDKN2A* PV carrier, followed for 37 months since first detection of a multifocal BD-IPMN. While asymptomatic, it developed a high growth speed of 12 mm/y, and surveillance was intensified, after which a second WF/high-risk stigmata developed (a solid component that seemed hypovascular after contrast enhancement). Surgery was performed, and pathology showed a T1cN1M0 tubular adenocarcinoma, most likely originating from an IPMN.

Supplementary Reference

1. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017;17:738–753.

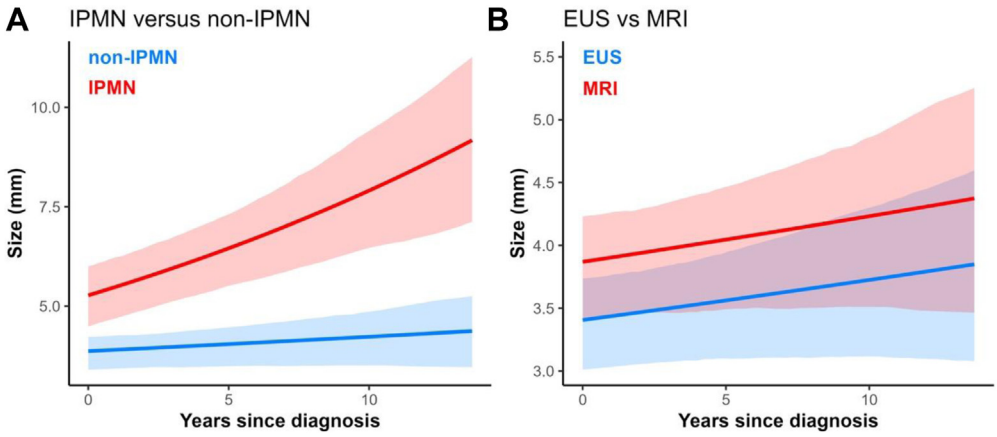

Figure 1. Estimated cyst size and growth (*A*) for intraductal papillary mucinous neoplasms (IPMNs) and non-IPMNs and (*B*) for magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) measurement within all high-risk individuals.

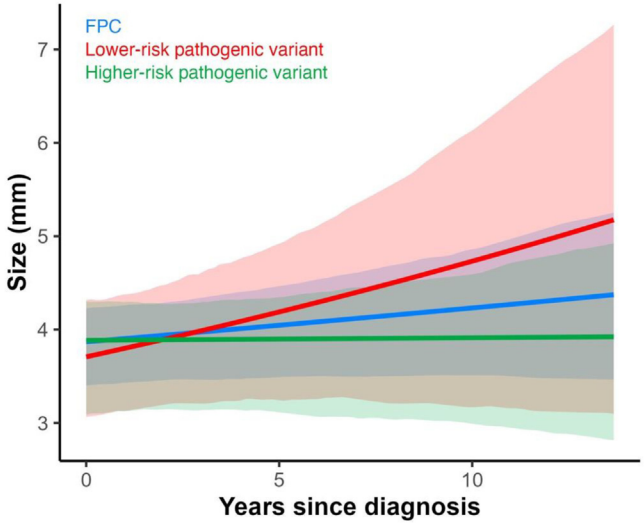

Figure 2. Estimated cyst size and growth in high-risk individuals stratified for the genetic risk groups. Lower-risk pathogenic variant: *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *TP53*. Higher-risk pathogenic variant: *STK11/LKB1*, *CDKN2A p16*. FPC, pathogenic variant–negative familial pancreatic cancer kindreds.

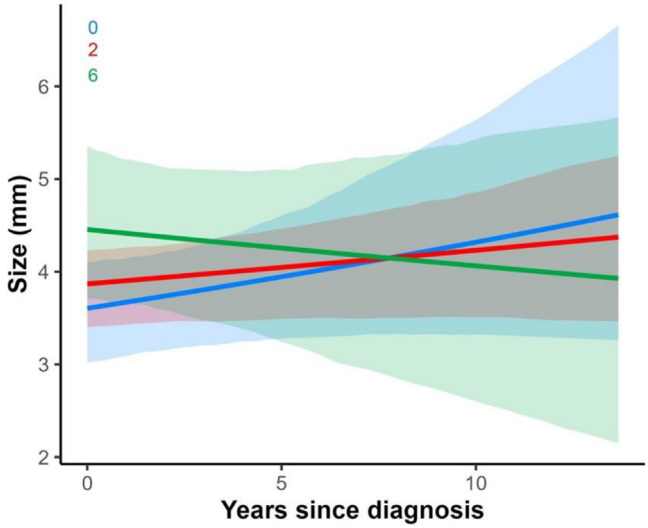

Figure 3. Estimated cyst size and growth in high-risk individuals stratified on the number of affected relatives.

Supplementary Table 1. Characteristics of the High-Risk Cohort Stratified for Genetic Risk Category (n = 457)

	PV-Negative FPC Kindreds (n = 254)	PV Carriers			*P* Value FPC vs PV Carrier
		All (n = 203)	Higher Risk (n = 134)	Lower Risk (n = 69)	
Pathogenic variant					—
STK11/LKB1	—	11 (5)	11	—	
CDKN2A p16	—	122 (60)	122	—	
CDKN2A p16 + *BRCA2*	—	1 (1)	1	—	
BRCA2 + ≥2 blood relatives with PC	—	51 (25)	—	51	
BRCA1 + ≥2 blood relatives with PC	—	7 (3)	—	7	
PALB2 + 3 blood relatives with PC	—	3 (2)	—	3	
TP53 + 2 blood relatives with PC	—	5 (3)	—	5	
MLH1/MSH2/MSH6	—	2 (1)	—	2	
ATM + 3 FDR with PC	—	1 (1)	—	1	
Age at baseline, y	56 (9.4)	52 (9.7)	52 (9.1)	53 (10.9)	<.001
Male	105 (41)	84 (41)	60 (45)	24 (35)	.993
BMI, kg/m^2	25 (5)	26 (4)	26 (5)	26 (4)	.544
Diabetes mellitus	15 (6)	3 (2)	1 (1)	2 (3)	.016
History of acute pancreatitis	7 (3)	0 (0)	0 (0)	0 (0)	.019
Number of blood relatives with PC	3 (1)	2 (2)	1 (3)	2 (1)	<.001
Follow-up, mo	44 (59)	51 (84)	52 (93)	50 (72)	.174

Values are n (%), n, or median (interquartile range).
BMI, body mass index; FDR, first-degree relative; FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm; PC, pancreatic cancer; PV, pathogenic variant (class 4 or 5).

Supplementary Table 2. Multivariable Cox Proportional Hazards Regression Analysis of Risk Factors for the Presence of an IPMN

Variable	IPMN (n = 106)	No IPMN (n = 351)	Hazard Ratio (95% CI)
Age, y	59 ± 9	54 ± 10	1.058 (1.033–1.084)
Pathogenic variant	36 (34)	167 (48)	0.641 (0.372–1.104)
Number of blood relatives with PC	2 (1)	2 (1)	0.974 (0.760–1.249)
Blood relative with PC <50 years of age	29 (27)	116 (33)	1.086 (0.665–1.773)
BMI, kg/m^2	25 (6)	25 (5)	1.026 (0.972–1.083)
Diabetes mellitus	7 (7)	11 (3)	1.087 (0.438–2.695)
History of acute pancreatitis	5 (5)	2 (1)	2.387 (0.859–6.632)
History of nonpancreatic malignancy	32 (30)	101 (29)	1.106 (0.642–1.904)
Smoking ever	46 (43)	171 (49)	0.865 (0.559–1.339)
Alcohol use ever	71 (67)	273 (780)	0.691 (0.430–1.110)

Values are mean ± SD, n (%), or median (interquartile range).
BMI, body mass index; CI, confidence interval; IPMN, intraductal papillary mucinous neoplasm; PC, pancreatic cancer.

Supplementary Table 3. Linear Mixed Model for Size of All Cystic Lesions in High-Risk Individuals (n = 553)

Variable	Coefficient [log(mm)]	95% CI
Years since cyst diagnosis	0.018	–0.008 to 0.049
Age	0.006[a]	0.001 to 0.010[a]
Lower-risk PV[b]	–0.042	–0.176 to 0.093
Higher-risk PV[c]	0.004	–0.160 to 0.124
Number of relatives with PC	0.035[a]	0.002 to 0.083[a]
BMI (at baseline)	0.002	–0.009 to 0.013
Diabetes mellitus	–0.067	–0.224 to 0.080
Smoker, ever	–0.042	–0.139 to 0.043
Alcohol consumption, ever	–0.040	–0.128 to 0.092
History of acute pancreatitis	0.052	–0.316 to 0.407
History of nonpancreatic malignancy	0.004	–0.076 to 0.185
MRI/MRCP used to measure cyst	0.128[a]	0.053 to 0.202[a]
Evident pancreatic duct connection (at any visit)	0.309[a]	0.209 to 0.413[a]
Interaction term: year/pancreatic duct connection	0.032[a]	0.012 to 0.048[a]
Interaction term: year/lower-risk PV[b]	0.015	–0.025 to 0.042
Interaction term: year/higher-risk PV[c]	–0.008	–0.029 to 0.013
Interaction term: year/number of relatives with PC	–0.005	–0.017 to 0.003

The 553 cysts were found in 229 high-risk individuals, and 5 high-risk individuals were excluded from the linear mixed model due to a missing value in one of the variables. All variables were assessed at every visit.
BMI, body mass index; CI, confidence interval; MRI/MRCP, magnetic resonance imaging/magnetic resonance cholangiopancreatography; PC, pancreatic cancer; PV, pathogenic variant (class 4 or 5).
[a]Independent association with cyst growth (interaction terms) or cyst size (other variables).
[b]*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *TP53*.
[c]*STK11/LKB1*, *CDKN2A p16*.

Supplementary Table 4. Characteristics of Individuals Who Developed a Malignancy and/or Underwent Surgery, Within the High-Risk and Control Cohorts

	Pathological Outcome	Surgery	Risk Category	Age at Diagnosis (y)	Follow-Up Since Cyst Diagnosis (mo)	Largest Size (mm)	Maximum Growth Rate (mm/y)	Enhancing Solid Component	Mural Nodule	Dilated Main Pancreatic Duct	Abrupt Change in Duct With Distal Atrophy	Outcome
High-risk cohort												
1	Advanced PC	No	*PJS*	65	39	15	14	Yes	Yes	No	No	Deceased
2	Advanced PC	No	*BRCA2*	74	83	20	11	No	No	No	No	Deceased
3	PC	Yes	*CDKN2A*	51	37	23	12	Yes	No	No	No	Deceased
4	LGD	Yes	*BRCA2*	47	48	15	14	No	No	No	No	Alive
5	LGD	Yes	PV-negative FPC	64	109	9	4	No	No	Yes	No	Alive
Control cohort												
6	PC	No[a]	—	89	20	36	6	Yes	No	Yes	Yes	Deceased
7	PC	Yes	—	73	17	9	0	Yes	No	Yes	No	Alive
8	PC	Yes	—	71	56	23	0	No	No	Yes	Yes	Deceased
9	PC	Yes	—	64	45	15	0	No	No	Yes	Yes	Deceased
10	PC	Yes	—	64	75	18	0	Yes	No	No	No	Alive
11	PC	Yes	—	56	52	42	5	No	No	No	No	Alive
12	LGD	Yes	—	42	154	35	1	Yes	No	No	No	Alive
13	LGD	Yes	—	48	20	30	5	No	No	No	No	Alive
14	LGD	Yes	—	67	62	33	3	No	No	No	No	Alive
15	LGD	Yes	—	74	20	20	2	No	No	No	No	Alive
16	LGD	Yes	—	74	19	26	0	No	No	No	No	Alive

None of the individuals had jaundice or pathological abdominal lymphadenopathy.

FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; PC, pancreatic cancer; PV, pathogenic variant.

[a]Surgery was not performed because of age and comorbidities.

Supplementary Table 5. Linear Mixed Model for Size of IPMNs in the High-Risk and Control Cohorts (n = 516[a])

	Coefficient [log(mm)]	95% CI
Years since cyst diagnosis	0.035	0.029 to 0.040
Age	0.007	0.004 to 0.010
PV carrier (vs general population)	–0.865	–1.162 to –0.435
PV-negative FPC kindred (vs general population)	–0.804	–1.125 to –0.351
Number of relatives with PC	–0.011	–0.174 to 0.086
Body mass index (at baseline)	0.010	0.002 to 0.019
Diabetes mellitus	–0.046	–0.152 to 0.111
Smoker, ever	0.074	0.004 to 0.150
Alcohol consumption, ever	0.039	–0.046 to 0.112
History of acute pancreatitis	0.024	–0.343 to 0.410
History of nonpancreatic malignancy	–0.094	–0.190 to –0.009
Cyst multifocality	0.026	–0.108 to 0.132
Interaction term: year/PV (vs general population)	0.041	0.010 to 0.081
Interaction term: year/PV-negative FPC kindred (vs general population)	0.047	0.004 to 0.090

Interaction terms indicate an association with cyst growth and the other variables with cyst size.
CI, confidence interval; FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm; PC, pancreatic cancer; PV, pathogenic variant (class 4 or 5).
[a]Seven individuals (2 high risk and 5 from the general population) were excluded due to a missing value in one of the variables. All variables were assessed at every visit.

Supplementary Table 6. Predictive Value of IPMN Growth for Neoplastic Progression or Main-Duct IPMN With Lower-Grade Dysplasia

	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	NPV (95% CI) (%)
Absolute growth speed ≥2.5 mm/y				
General population	33 (4–78)	92 (89–94)	5 (2–15)	99 (98–99)
PV carriers	100 (40–100)	61 (39–80)	31 (21–43)	100 (—)
Absolute growth speed ≥5 mm/y				
General population	33 (4–78)	99 (97–100)	29 (9–63)	99 (98–99)
PV carriers	100 (40–100)	74 (52–90)	40 (25–57)	100 (—)
Absolute growth speed ≥10 mm/y				
General population	0 (0–46)	100 (99–100)	0 (—)	99 (99–99)
PV carriers	100 (40–100)	96 (78–100)	80 (37–96)	100 (—)
Relative growth speed ≥100%/y				
General population	0 (0–46)	100 (99–100)	0 (—)	99 (99–99)
PV carriers	100 (40–100)	78 (56–93)	44 (27–63)	100 (—)

Predictive values could not be analyzed for PV-negative FPC kindreds because there were no cases with neoplastic progression or main-duct IPMN.
CI, confidence interval; IPMN, intraductal papillary mucinous neoplasm; NPV, negative predictive value; PPV, positive predictive value; PV, pathogenic variant (class 4 or 5).
[a]Neoplastic progression defined as histologically proven high-grade dysplasia or pancreatic cancer. However, there were no cases with only high-grade dysplasia.