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Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance

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Abstract

Background & Aims—Screening of individuals who have a high risk of pancreatic ductal adenocarcinoma (PDAC), due to genetic factors, frequently leads to identification of pancreatic lesions. We investigated the incidence of PDAC and risk factors for neoplastic progression in individuals at high risk for PDAC enrolled in a long-term screening study.

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Methods—We analyzed data from 354 individuals at high risk for PDAC (based on genetic factors of family history), enrolled in Cancer of the Pancreas Screening cohort studies at tertiary care academic centers from 1998 through 2014 (median follow-up time, 5.6 years). All subjects were evaluated at study entry (baseline) by endoscopic ultrasound and underwent surveillance with endoscopic ultrasound, magnetic resonance imaging, and/or computed tomography. The primary endpoint was the cumulative incidence of PDAC, pancreatic intraepithelial neoplasia grade 3, or intraductal papillary mucinous neoplasm with high-grade dysplasia (HGD) after baseline. We performed multivariate Cox regression and Kaplan-Meier analyses.

Results—During the follow-up period, pancreatic lesions with worrisome features (solid mass, multiple cysts, cyst size >3 cm, thickened/enhancing walls, mural nodule, dilated main pancreatic duct >5 mm, or abrupt change in duct caliber) or rapid cyst growth (>4 mm/year) were detected in 68 patients (19%). Overall, 24/354 patients (7%) had neoplastic progression (14 PDACs and 10 HGDs) over a 16-year period; the rate of progression was 1.6%/year and 93% had detectable lesions with worrisome features before diagnosis of the PDAC or HGD. Nine of the 10 PDACs detected during routine surveillance were resectable; a significantly higher proportion of patients with resectable PDACs survived 3 years (85%) compared with the 4 subjects with symptomatic, unresectable PDACs (25%), which developed outside surveillance (log rank $P<.0001$). Neoplastic progression occurred at a median age of 67 years; the median time from baseline screening until PDAC diagnosis was 4.8 years (inter-quartile range, 1.6–6.9 years).

Conclusions—In a long-term (16-year) follow-up study of individuals at high-risk for PDAC, we found most PDACs detected during surveillance (9/10) to be resectable, and 85% of these patients to survive for 3 years. We identified radiologic features associated with neoplastic progression.

Keywords

PanIN-3; IPMN; familial pancreatic cancer; early detection

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the third, and is projected to soon become the second leading cause of cancer deaths in the USA[1]. The estimated incidence rate of developing PDAC is 1.5%, with 53,670 new cases and 43,090 death expected in 2017[2, 3]. The 5-year survival rates of patients with PDAC remains low (8.2%)[2]. Screening for pancreatic cancer is not recommended for the general population (U.S. Preventive Services Task Force, http://www.uspreventiveservicestaskforce.org/) but is being evaluated for patients with a significantly elevated risk. Risk can be estimated by considering the number of affected blood relatives who have had pancreatic cancer (familial pancreatic cancer or FPC kindred defined as having at least 2 first degree relatives with pancreatic cancer)[4, 5] and knowing whether an individual carries a deleterious germline mutation in a pancreatic cancer susceptibility gene[6]. The latter include germline mutations in *BRCA1, BRCA2, ATM, PALB2, CDKN2A (familial atypical multiple mole melanoma syndrome)*, mismatch repair genes *MLH1*, *MSH2*, *MSH6*, *PMS2* (Lynch syndrome), STK11 (Peutz-Jeghers syndrome), and *PRSS1* (hereditary pancreatitis)[7–13]. Several large academic centers have conducted screening programs for these asymptomatic high-risk individuals (HRIs)[14–24]. An

international consortium of experts recommended pancreatic screening and surveillance be evaluated for HRI with an estimated lifetime risk of PDAC of > 5%[4].

Pancreatic cancer surveillance programs utilizing a combination of endoscopic ultrasound, magnetic resonance imaging, and computed tomography scans have detected a high prevalence of asymptomatic pancreatic lesions, mostly cysts, that represent the major associated precursor lesions (pancreatic intraepithelial neoplasia, PanINs; intraductal papillary mucinous neoplasms, IPMNs), in HRI. Most of the pancreatic cysts identified in HRI are small (<1 cm) and often multiple; their prevalence is much more common than in the general population and increases with patient age[18]. Depending on the age and other characteristics of the study population and the imaging modalities, the prevalence of precursor lesions identified by screening has ranged from 6%-52%[16, 18, 21, 22, 24–26]. Pancreatic neuroendocrine tumors (PanNETs) have also been detected[16, 18, 21, 22, 24–26]. Most studies evaluating the diagnostic yield of pancreatic screening have only reported lesions detected at baseline screening[12, 14,15, 16, 17, 18, 20, 21, 24, 26]. Identification of screening abnormalities and other risk factors that predict neoplastic progression to PDAC or high grade precursor neoplasms might improve surveillance programs and guide management of detected lesions.

The aims of this study were to determine the cumulative incidence of PDAC and high grade precursor neoplasms (IPMN-HGD and PanIN-3) and identify risk factors that predict neoplastic progression in HRI undergoing long term surveillance after baseline screening. We also report the outcomes of HRI with detected neoplasms.

METHODS

Study Design and Patients

From 1998 to 2014, 581 asymptomatic HRI were prospectively enrolled into one of the Johns Hopkins Cancer of the Pancreas Screening studies (CAPS 1[17], CAPS 2[16], CAPS 3[18], or CAPS 4) at participating tertiary referral American academic medical centers with comprehensive multidisciplinary pancreas screening programs. The institutional review boards of The Johns Hopkins Medical Institutions and all participating sites approved the CAPS studies. All subjects provided informed consent for baseline screening and follow-up.

Inclusion criteria for HRI in the CAPS studies:

1. Patients who met clinical criteria for Peutz-Jeghers syndrome, or who had a mutation in the *STK11* gene, and who were at least 30 years old;
2. Individuals from a familial pancreatic cancer (FPC) kindred who had at least one affected first-degree relationship to the HRI, and were at least 50 years old (CAPS studies 1-3, from 1998-2010) or at least 55 years (CAPS 4 study, from 2010) or 10 years younger than the youngest pancreatic cancer in the family.
3. Individuals with confirmed germline mutations in the *BRCA1, BRCA2, PALB2, PRSS1, CDKN2A*, or *MLH1*, *MSH2*, *MSH6*, *PMS2* (Lynch syndrome), with at least 1 affected first or second degree relative, and at least 50 years old, or 10 years younger than the youngest pancreatic cancer in the family.

Since this study evaluated predictors of progression during surveillance, we did not include HRI enrolled in the CAPS studies who had: 1) less than 6 months of follow-up after baseline screening, 2) surveillance at an outside institution without available medical records or clinical follow-up (lost to follow-up at John Hopkins Hospital), 3) prior surgery that prevented complete EUS examination of the pancreas. From 584 HRI enrolled in the CAPS 1-4 studies from 1998-2014, 104 patients were excluded from the current study because they continued surveillance at an outside institution, and 123 patients were excluded for less than six months of follow-up after baseline screening.

Surveillance Methods, Clinical Management, and Final Diagnosis—HRI were referred to the CAPS studies through the Johns Hopkins National Familial Pancreas Tumor Registry (NFPTR) (www.nfptr.org), physicians, genetic counselors, or by self-referral. After providing informed consent and completing a detailed questionnaire, all HRI were screened at baseline with EUS. Individuals who participated in the CAPS3 study also underwent baseline CT, individuals who enrolled in the CAPS 1 study (1998-2002, n = 38) underwent baseline EUS only[17] and those in the CAPS 2 study (2002-2004, n = 78) underwent both EUS and CT[16].

Since 2005, surveillance after baseline screening was performed on the CAPS 3 subjects (n = 216)[18] continuing follow-up at Johns Hopkins and all CAPS 4 subjects enrolled at Hopkins (n = 249) using a combination of endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRI/MRCP), and/or computed tomography (CT) at intervals dependent upon the presence or absence of neoplastic-type pancreatic lesions. HRI with a normal pancreas or EUS features of chronic pancreatitis were followed annually. Those with pancreatic cysts or indeterminate radiologic lesions underwent more frequent imaging with EUS and/or MRI or CT, according to published international guidelines[4, 27, 28]; every 6-12 months for those without a mural nodule or dilated pancreatic duct and every 3-6 months for larger cysts or cysts with worrisome features. Stable or improved appearance of pancreatic lesions resulted in decreased surveillance imaging frequency to every 12 months.

EUS-guided fine needle aspiration was not routinely performed on small cystic lesions < 1 cm.

Recommendations for pancreatic surveillance and surgical treatment were discussed at CAPS multidisciplinary clinical conferences and decision-making was individualized. After Sendai[27] and Fukuoka[28] international consensus guidelines for management of sporadic IPMNs became available, these were used as a guides for data collection and patient management, recognizing that these guidelines were not developed primarily for high risk individuals. Worrisome features were defined in this study according to the Sendai and Fukuoka International Consensus Guidelines for management of a mucinous cysts[27, 28], included cyst size ≥ 3 cm, thickened/enhancing cyst walls, main pancreatic duct (MPD) dilation >5 mm, mural nodule in the cyst or main pancreatic duct, abrupt change in MPD caliber, or rapid cyst growth rate > 2 mm in 6 months or > 4 mm in 1 year. The latter was defined based upon studies reporting rapid cyst growth rate in sporadic IPMNs of > 2-5 mm per year associated with increased risk of malignancy[29, 30] Suspicious cytology for

pancreatic malignancy, when available, was also considered a worrisome feature[27, 28, 31]. For this study, any solid mass > 5 mm was considered a worrisome feature, if confirmed by repeat EUS, at least two imaging modalities, and/or increasing size.

Surgical intervention was offered to those suspected of having pancreatic cancer or high-grade dysplasia, based on imaging or cytology. In some cases, surgical resection was undertaken because of concern that it might be difficult to detect an early-stage pancreatic cancer in HRI with numerous pancreatic cysts. HRIs with pancreatic lesions with any worrisome feature were discussed in a multidisciplinary clinical conference consisting of a team of surgeons, gastroenterologists, radiologists, and pathologists. Decision-making was individualized, using clinical criteria and published guidelines for pancreatic cyst management. Most pancreatic resections were performed at The Johns Hopkins Hospital by highly experienced surgeons specializing in pancreaticobiliary diseases (CJY, RDS, CW, MW).

The final diagnoses were made by surgical pathology or cytology (percutaneous or EUS-guided fine needle aspirates). All pathological diagnoses were made by an expert pathologist (RHH) using standard and consensus international classification systems. Pathological reports and slides were reviewed for HRI who had surgery outside of Johns Hopkins. If the pathological specimen had multiple pancreatic lesions, the lesion with the highest pathologic grade was considered for endpoint analysis. Clinical findings and imaging characteristics were tracked over time to the last follow-up by prospective recording of imaging test results at Johns Hopkins Hospital and retrospective review of outside medical records and images, when applicable, up to December 2016.

Statistical Analysis—"Neoplastic progression" was defined the development of pathologically-proven PDAC and/or high grade PDAC precursor neoplasms (PanIN-3, IPMN-HGD). "Radiologic progression" was defined as the development of a lesion with one or more worrisome features after baseline imaging. Pancreatic neuroendocrine neoplasms (PanNET) were defined as well-differentiated neoplasms greater than 0.5 cm in size with predominantly neuroendocrine differentiation and low proliferation indices (2010, 2017 World Health Organization)[32, 33] PanNETs were not included in the primary and secondary outcome variables but listed separately as one of the final pathological diagnoses.

Primary study outcome variables were: 1) the demographic clinical, and imaging factors associated with neoplastic progression (analyzed using Chi-square/Fisher's exact test for categorical variables and t-test/Mann-Whitney test for continuous variables), 2) the rate of neoplastic progression stratified by age and adjusted for varying rates of radiologic progression(analyzed by Kaplan Meier and Cox regression analyses), and, 3) the hazard rates of neoplastic progression among all radiologic progressors and those with different types of lesions(solid mass, cyst or pancreatic duct lesions), adjusted for clinical factors and baseline pancreatic abnormalities (analyzed by Cox proportional hazards regression modeling).

Secondary study outcome variables were: 1) the cumulative incidence of pathologically proven PDAC and high grade PDAC precursors (PanIN-3, IPMN-HGD), 2) the resectability

and tumor stage of clinically relevant pancreatic neoplasms detected by screening/surveillance, and 3) the median survival time, 3-year survival rate, and overall mortality of neoplastic progressors. All statistical analysis were performed using Stata® version 14.1 (Stata Corp, College Station, Texas).

RESULTS

Baseline Characteristics of Screened HRI

The baseline characteristics of the 354 HRI are summarized in Table 1. The majority of HRI (97%) were familial PC relatives, 16% of those screened had a known deleterious germline variant. About half the study population was male, predominantly Caucasian race, with the mean age at baseline of 56.4 years (range 22-81).

One hundred eighty-five HRI (52% of 354) had no lesions detected at baseline. Fourteen HRI (4%) had solid hypoechoic masses > 1 cm or nodules < 1 cm at baseline, and 4 (1.1%) had both cysts and solid lesions. The remaining 151 (43% of 354) HRI had no solid lesions and one or more cystic lesions detected at baseline, and 14% (49/354) had 3 or more cysts. The mean size of the largest cyst at baseline was 8 mm (range 1.6 mm – 28 mm). At baseline, 76 (21.4%) HRI had a mildly dilated main pancreatic duct according to the Rosemont criteria[34] (≥ 3.5 mm in the head, ≥ 2.5 mm in the body, and/or ≥ 1.5 mm in the tail) but < 5 mm (Table 1).

Cumulative Incidence of Neoplastic Progression and Types of Detected Neoplasms

The median follow-up time for the entire cohort was 5.6 years (interquartile range 3.9-8.9 years). Fifty-four (79%) of the 68 HRI with pancreatic lesions with worrisome features detected by surveillance had diagnostic pathology either by surgical resection (n = 44) and/or percutaneous or EUS-guided fine needle aspiration (n = 6). Thirty of these 54 asymptomatic HRI (8.5% of the entire cohort) were diagnosed with a clinically significant primary pancreatic neoplasm: 14 had PDAC (4% or the entire cohort), 10 had IPMN-HGD and/or PanIN-3 (3% of the cohort) and 6 had PanNET > 5 mm (1.7% of the entire cohort). The overall detection rate for PDAC or a high grade dysplasia in 354 HRI over the 16-year study period was 7%, including prevalent and incident neoplasms. Detailed information about the 24 patients with PDAC or high grade dysplasia is summarized in Table 2. The cumulative incidence for PDAC or a high grade precursor neoplasm during the study period (excluding 2 asymptomatic cancers detected at baseline) was 22/339 or 6.5%.

One patient with multiple pancreatic lesions and abdominal lymphadenopathy was diagnosed with a metastatic pancreatic B cell lymphoma by EUS-guided fine needle aspiration. The remaining 23 of the 54 HRI (43%) with a pathologic diagnoses had lower grade dysplasia or non-dysplastic lesions in their resection specimens (IPMN-LGD/MGD, PanIN-1/2, benign PanNET microadenomas <0.5 cm, serous cyst adenoma). Most of these patients underwent resection in the early years of the CAPS program.

Outcomes of Non-Operated HRI with Worrisome Features

Of the 68 HRI who had lesions with worrisome radiological features at any time during the study period, 24 (35%) did not undergo surgery; and were followed for an average of 5.8 years (range 1-12 years). Five of these 24 HRI had cyst growth during follow-up but otherwise no evidence of neoplastic progression. Fourteen HRI with a dilated MPD had stable or improved duct diameter. Five non-operated HRI developed a solid mass diagnosed by EUS-FNA: 3 HRI had advanced PDAC (stopped or late for surveillance, Table 2), one HRI had the lymphoma mentioned above, and one HRI had a PanNET confirmed by EUS-FNA but the patient declined surgery.

Factors Associated with Neoplastic Progression

The mean age of HRI who developed PDAC or high grade dysplasia in this cohort was significantly greater than non-progressors ($p < 0.0001$, Table 1). Age > 60 years at baseline was associated with radiologic progression (HR 3.1, adjusted model, Supplementary Table 2). However, age was not a significant predictor of neoplastic progression in the multivariate analyses (hazard ratio or HR 1.64, 95% CI 0.65-4.14, Table 3). A greater proportion of HRI who developed PDAC or a high grade precursor neoplasm had a dilated main pancreatic duct at baseline compared to non-progressors (64% and 50% versus 19%, respectively, $p <0.0001$, Table 1) but the hazard ratio for a dilated main pancreatic duct was not significant in the multivariate analysis (HR 1.68, 95% CI 0.70-4.06, Table 3).

Neoplastic progressors were more likely to have multiple cysts (3 or more) at baseline, compared to non-progressors (PDAC 36% and high grade precursor neoplasm 80%, versus others 11%, $p <0.0001$), even after adjusting for other factors (HR 4.85, 95% CI 2.02-11.64, Table 3). Specific EUS and radiologic features (worrisome features) were associated with neoplastic progression (univariate and multivariate analysis, Supplementary Tables 1 and 2). In particular, the presence of a solid mass, mural nodule, thickened cyst wall, rapid cyst growth rate, and a MPD dilated to > 5 mm at any time during surveillance, were associated with the development of PDAC or high grade precursor neoplasm.

After adjusting for time varying rates of radiologic progression, Cox-proportional multivariate regression analysis showed that any radiologic progression was the strongest predictor for developing PDAC or a high grade precursor neoplasm (23-fold, $p < 0.0001$, Table 3; Figure 2). Specifically, the adjusted risk for neoplastic progression was 41-fold higher (95% CI 12.52-135.53, Table 3) for HRI with radiologic progression in a pancreatic cyst or in the main pancreatic duct, and 423-fold higher for HRI with a solid mass (95% CI 102.42-1743.74).

Rates of Progression and Time to Radiologic and Neoplastic Progression

The estimated rate of radiological progression after baseline screening, after excluding the 17 HRI that had a solid mass or cyst with worrisome features at baseline, was 4.3% per year (Supplementary Figure 1A). Progression rates were higher among those HRI > 60 years old at baseline screening (Supplementary Figure 1B). The median time for any radiologic worrisome feature to occur in HRI after baseline was 13.1 months (IQ range 0.2 – 52

months). The median time for radiologic progression in HRI who developed PDAC was 4.3 years (IQ range 1.0-6.5 years).

Neoplastic progression occurred at a rate of 1.6% per year (Figure 1) and at a much higher and faster rate in HRI with a lesion with a worrisome feature (Figure 2A). Twelve of the 14 HRI with PDACs and 8 of the 10 with high grade precursor neoplasms (IPMN-HGD and PanIN-3) resected were incident lesions detected during follow-up (Table 2). The median time to neoplastic progression from baseline screening for the 14 HRI who developed invasive PDAC after baseline screening was 4.8 years (IQ range 1.6-6.9 years), but was significantly shorter in those beginning screening at 60 years or older (median 1.7 years, IQ range 0.5-4.4 years) compared to younger HRI (median 5.2 years, IQ range 0.4-8 years) (Figure 2B). The mean age for HRI who developed PDAC was 67.6 years, (IQ range 59-74). Twelve of the 14 PDAC patients and 7 of the 10 HRI with HGD were > 60 years old at the time of diagnosis.

Outcomes of Surveillance and Treatment

Detailed information on the HRI with pancreatic neoplasia is summarized in Table 2. The mean diameter of the screening-detected PDACs was 24.8 mm (range 7-45 mm). The two stage 1 pancreatic cancers were detected by EUS and not visualized by preoperative MRI or CT. Two of the resected PDACs were TNM stage IA (size 5 and 7 mm) (Figure 3), two were stage IIA (size 15 and 27 mm), and 7 were state IIB (size range 13-36 mm). Nine of the 10 invasive PDACs detected in patients followed according to the CAPS surveillance schedule were asymptomatic and resectable, whereas only 1 of the 4 patients presenting with symptoms had resectable disease. The latter had either stopped or were late for surveillance (Patients 21-24 Table 2) by a median of 37 months (IQ range 10.8-66 months). The other advanced metastatic PDAC developed in the remnant pancreas of Patient 6 five years after a Whipple operation for a main duct IPMN, despite annual CT surveillance.

As of last follow-up, the overall mortality for HRI with PDAC was 64% (9/14). PDAC-specific mortality was 8/14 (57%), with one patient surviving 13 years before passing from complications related to a metachronous early gastric cancer surgery (Patient 2, Table 2). None of the 10 HRI with IPMN-HGD/PanIN3, and 6 with PanNet have died as of last follow-up.

The median survival time for the 20 HRI with PDAC or high grade precursor neoplasm (targets of screening) diagnosed during surveillance was significantly greater than that for 4 HRI who were late or stopped surveillance-5.3 years (IQ range 1.2 – 11.1 years) versus 1.4 years (IQ range 0.39-3.5 years, $p < 0.0001$. The overall 3-year survival rate was 57% for the 14 PDAC patients but the survival was significantly greater for the 10 asymptomatic HRI diagnosed during surveillance, compared to that for 4 HRI presenting with symptomatic advanced disease developing outside surveillance (85% versus 25%, respectively, log rank, $p<0.0001$, Figure 3).

DISCUSSION

Pancreatic lesions are frequently detected in HRI by EUS and/or MRI in pancreatic cancer screening programs[18, 14, 16, 20, 21, 23–25]. The majority of detected lesions are small cysts[15, 18, 20, 25]. In this study, we found that neoplastic progression is more common in HRI older than age 60, and those with multiple cysts, and/or a mildly dilated MPD at baseline. Although having multiple cysts (≥ 3) at baseline was a robust predictor of radiologic and neoplastic progression, it has not been identified as a significant predictor of progression in cohorts of sporadic IPMN[35, 36].

Close to 19% of HRI developed evidence of a worrisome radiologic feature while undergoing surveillance, corresponding to an average rate of radiological progression of 4.3% per year. One important question for pancreatic cancer screening programs is the age to begin screening. There was no consensus among experts on this question in the 2012 CAPS Consensus Summit[4]. In the CAPS 1-3 studies (1998-2010), age 50 was selected as the age to initiate pancreatic screening for FPC relatives. After 2010, this age was raised to 55 years, but in all studies, screening would start at age 10 years less than that of the youngest PDAC relative. Two of the 14 PDAC patients and 3 of the 24 with PDAC or high grade precursor neoplasms in our cohort were younger than age 55 at the time of diagnosis, but both of these patients had young-onset pancreatic cancers in their family that made them eligible for screening using the age 55 or 10 year rule. Determining the optimal age to begin PDAC screening requires additional studies.

After initial screening, the cumulative incidence of invasive PDAC in our cohort was 3.4% (12/354 HRI). Our overall PDAC detection rate is higher than reported in other screening programs of FPC relatives, most of which are closer to 1% or less[14, 15, 20, 25, 26]. This probably reflects the longer period of surveillance, and the older average age of our cohort. In our study consisting mostly of familial PDAC relatives, the number of individuals needed to undergo regular screening and surveillance (using EUS and MRI) to detect a PDAC or high-grade precursor neoplasm was 23. Recently, three European centers performing prospective screening with MRI and EUS in 411 HRI reported a detection of incident PDAC in 13 (7.3%) of 178 *CDKN2A* mutation carriers and 3(1.4%) of 214 familial PC relatives[25]. In patients with sporadic IPMNs, the cumulative incidence for PDAC over 5 years is generally lower but varies considerably depending upon the cohort studied[35, 37, 38]. The National Cancer Institute estimates the lifetime risk for PDAC is 1.6%, based on 2012-2014 data[2](http://seer.cancer.gov/statfacts/html/pancreas.html).

The majority (71%) of PDACs detected during surveillance in our high risk cohort were asymptomatic resectable TNM stage I and II cancers, which compares favorably with the tumor stage and resectability rate (15-20%) of symptomatic PDAC[2]. A similar down staging was found in the European study that followed mostly CKDN2A/p16-Leiden mutation carriers; 75% of screening-detected PDACs were resectable[25]. Furthermore, the overall 3-year survival rate of our HRI with PDAC was substantially higher than that of PDAC patients in the United States (57% vs. 8.9%, Surveillance, Epidemiology, and End Results Program or SEER data, http://seer.cancer.gov/statfacts/html/pancreas.html)). The difference is even greater when considering only screening-detected PDAC in our cohort (3-year

survival 90%). Similarly, the 5-year survival rate for *13 CDKN2A/p16 Leiden* mutation carriers with screening-detected PDAC (24%) was higher than that for symptomatic mutation carriers (15%)[25] or sporadic PDAC (4-7%)[2]. Even with the limited number of progressors in large high risk cohorts, these accumulated data of increased resectability and improved survival rates suggest a potential benefit of surveillance for HRI.

Our screening program using EUS and MRI also identified IPMN-HGD and PanIN-3 in resection specimens of 3.1% of the cohort (10/354). Other high risk surveillance programs have detected and treated a low number of patients with high grade precursor neoplasms, ranging from none to 1.9%; this lower rate may result from the demographic profile of the patients undergoing screening[20,25,26]. Precursor neoplasms with high grade dysplasia have been recommended by the International Cancer of the Pancreas Screening Consortium as ideal targets for detection and treatment[4].

The selection of asymptomatic HRI for pancreatic resection to treat PDAC or to remove concerning pancreatic lesions is challenging. Currently, selection of cases for surgery relies on the detection of specific concerning radiologic and EUS features that are predictive of high-grade pancreatic neoplasia or PDAC. The criteria for surgical resection have evolved over the 16 year study period with improved understanding of the natural history of pancreatic cysts and other lesions identified in both HRI and those with incidentally detected pancreatic abnormalities. The selection of patients for surgery is still far from perfect and reflects the limitations of pancreatic imaging to detect high grade precursor neoplasms, particularly PanIN-3. Better biomarkers than can detect high grade pancreatic neoplasia in secretin-stimulated pancreatic juice, pancreatic cyst fluid, and blood are needed to improve the selection of patients for surgery[39–41, 42, 43, 44].

The current study has several limitations. First, the methods for surveillance and management of pancreatic precursor lesions evolved thanks to improvements in imaging and better understanding of the natural history of these lesions. Second, we were unable to track the outcomes of HRI who chose to continue surveillance at other centers. In addition, the gene mutation status for the pancreatic cancer risk in most HRI in our cohort was not known. Furthermore, the estimation of the prevalence of high grade precursor neoplasms in our cohort is limited by the inability of standard pancreatic imaging tests to detect PanIN-3. Our results are derived from a predominantly FPC cohort followed at a single institution, which may limit generalizability. Finally, we do not have a concurrent control group.

In conclusion, the results of our long-term pancreatic cancer screening program show that continued follow-up of HRI can successfully detect resectable PDAC and high-grade precursor neoplasms. Among individuals undergoing pancreatic surveillance, specific detectable lesions with worrisome features predicted neoplastic progression. The short-term outcomes of patients with screening-detected PDAC s are improved. Large prospective multicenter studies are needed to further evaluate the potential benefits of PDAC screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

PDAC	pancreatic ductal adenocarcinoma
IPMN	intraductal papillary mucinous neoplasm
PanIN	pancreatic intraepithelial neoplasia
PanNET	pancreatic neuroendocrine tumor
PJS	Peutz-Jeghers syndrome
CT	computed tomography
EUS	endoscopic ultrasonography
FNA	fine-needle aspiration
MRCP	magnetic resonance cholangiopancreatography
CAPS	Cancer of the Pancreas Screening
FPC	familial pancreatic cancer
HGD	high grade dysplasia
MGD	moderate grade dysplasia
LGD	low grade dysplasia

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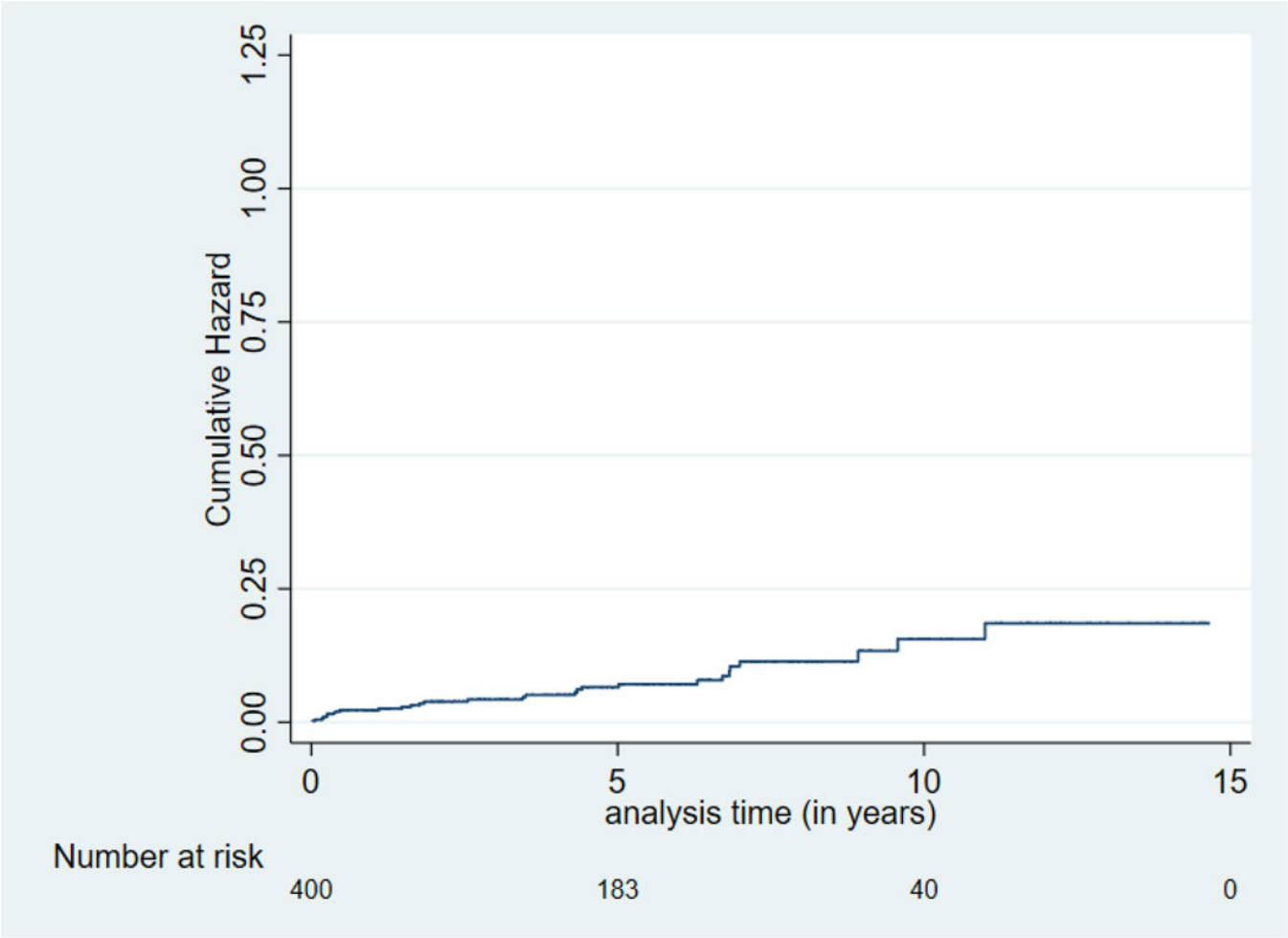
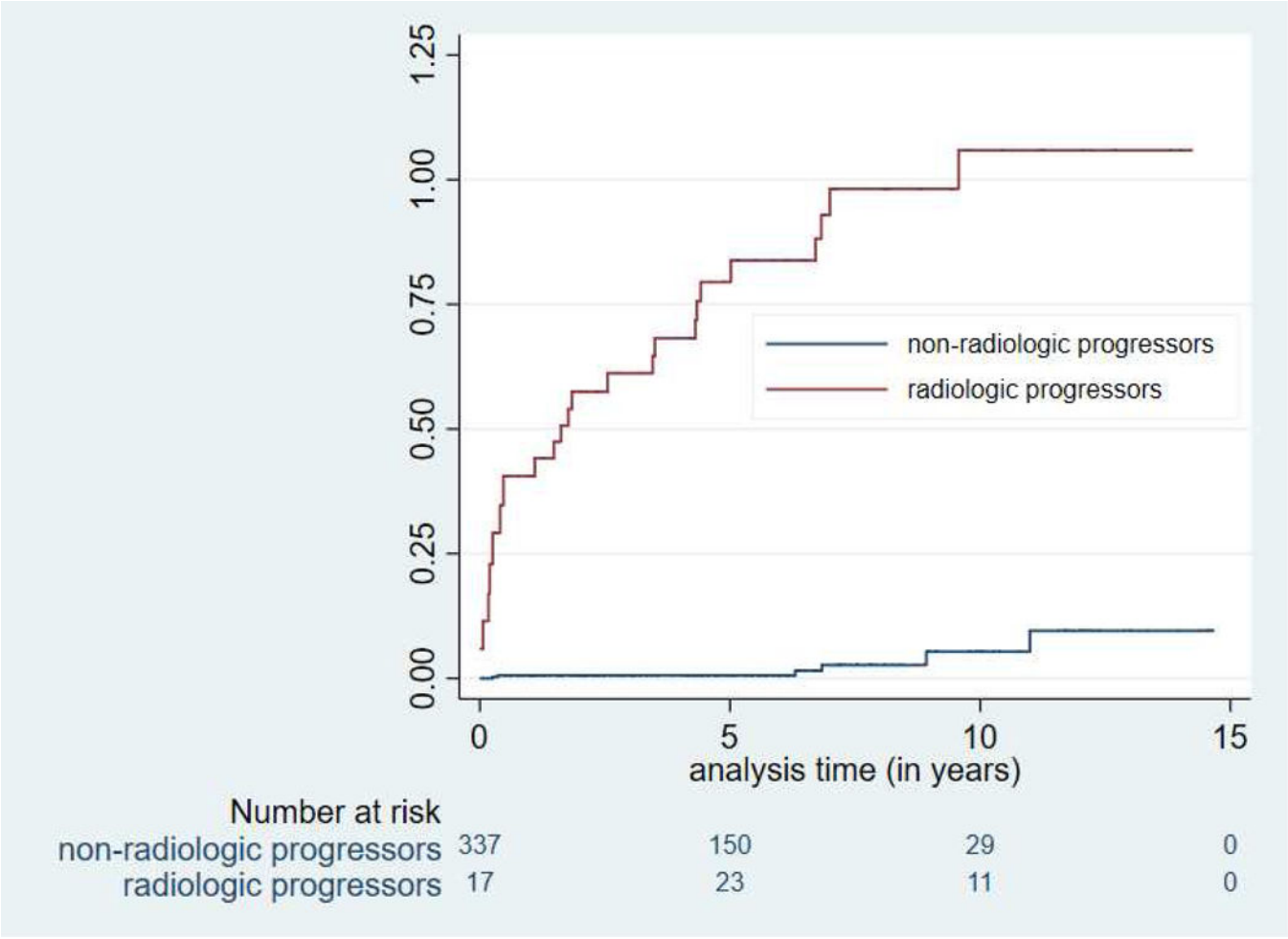


Figure 1.

Cumulative risk (hazard) for neoplastic progression (PDAC, IPMN-HGD, or PanIN-3) for high risk individuals after baseline screening. Overall neoplastic progression rate was 1.6% per year.



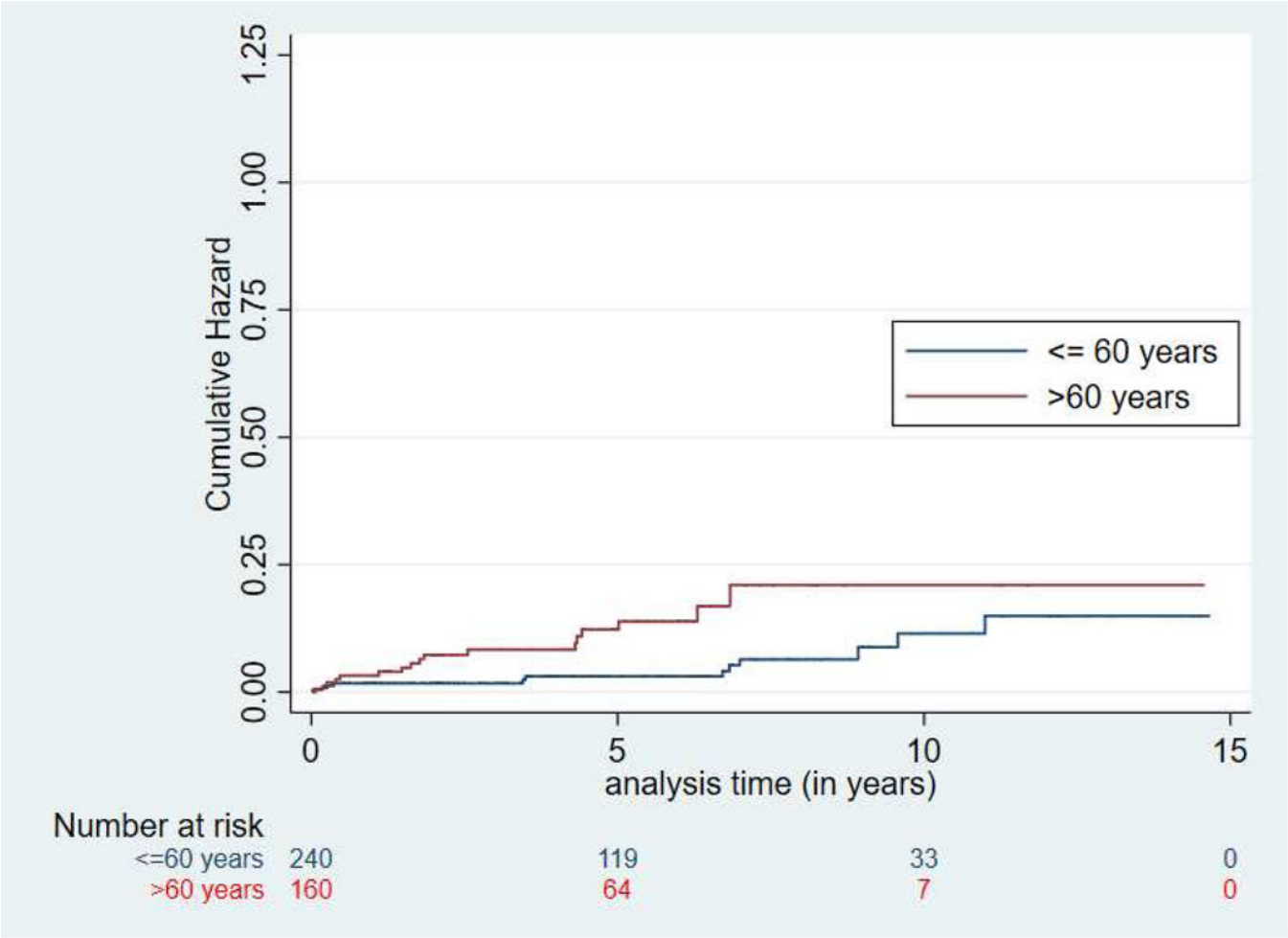


Figure 2.

Risk for neoplastic progression was significantly increased in HRI with worrisome features (radiologic progression) ($p < 0.0001$) (2A) and those beginning screening at age > 60 (2B).

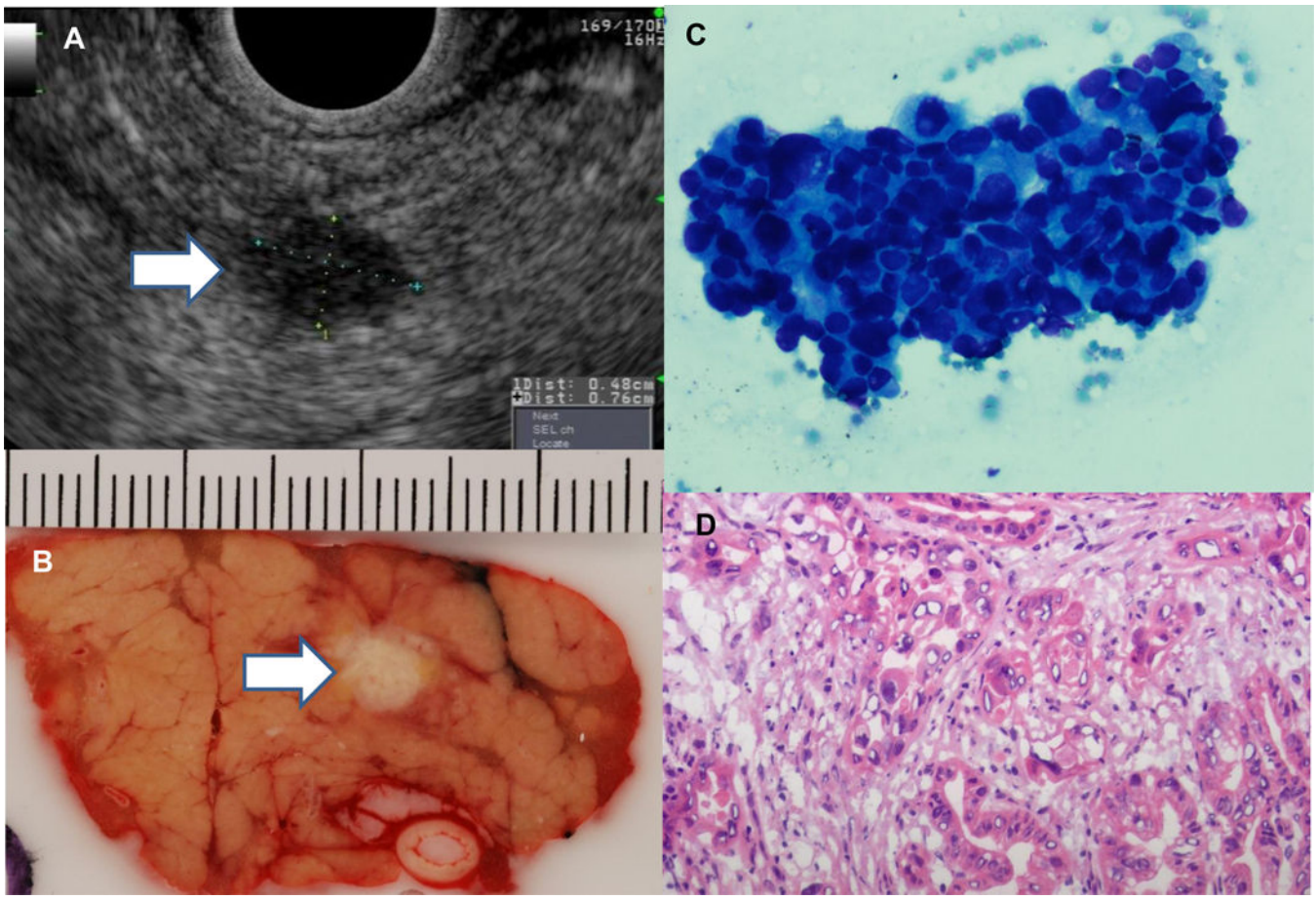
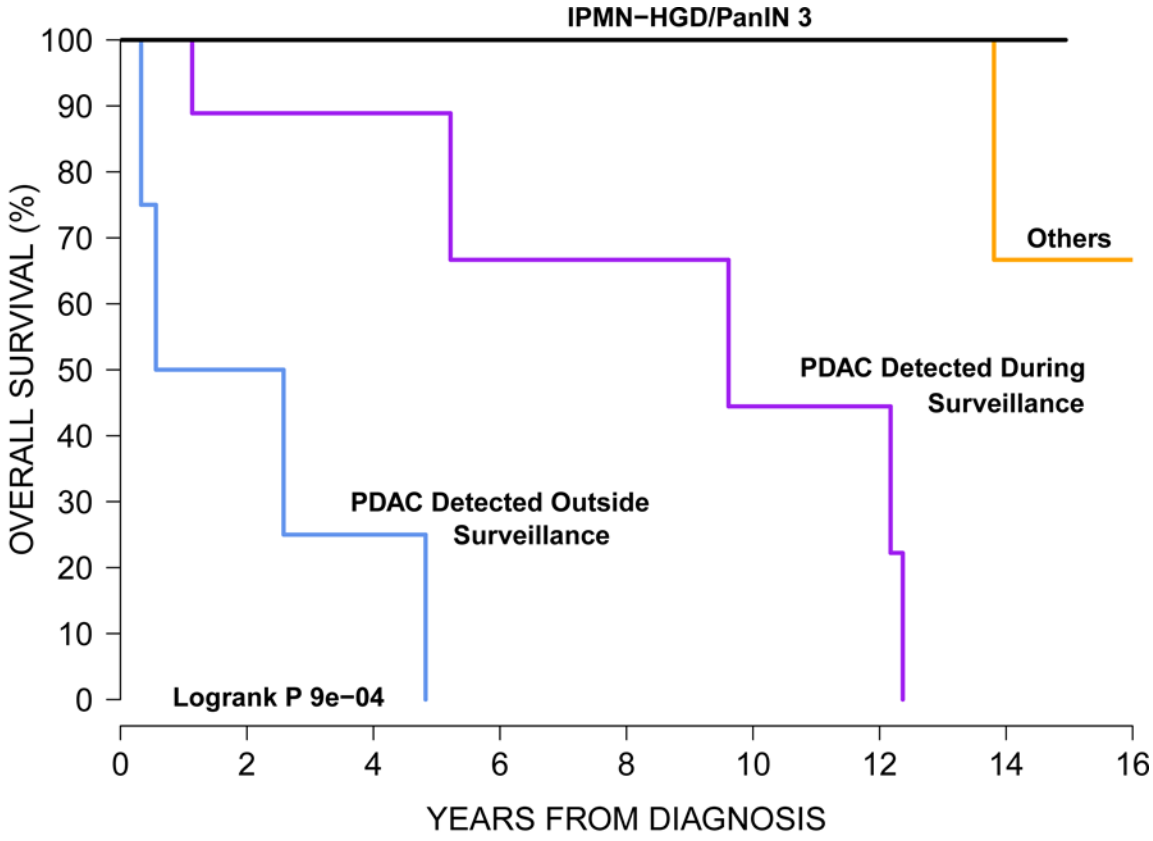


Figure 3.

Incident asymptomatic 7 mm pancreatic cancer detected after 10 years of surveillance, shown by arrows in endoscopic ultrasound (EUS) image (A) and gross pathology section of the pancreatic body (B). Final pathologic diagnosis was stage T1N0 moderately differentiated adenocarcinoma with negative margins (cytology smear from EUS-guided fine needle aspiration) C; hematoxylin and eosin stain, venous and perineural invasion were not identified (D).



No. at risk

PDAC (Outside Surveillance)	4	2	1	0	0	0	0	0	0
PDAC (During Surveillance)	10	7	6	3	3	2	2	0	0
IPMN−HGD/PanIN 3	10	10	9	7	6	3	2	1	0
Others	28	22	20	10	8	6	4	2	1

Figure 4.

Kaplan-Meier curves for overall survival for high risk individuals diagnosed with pancreatic neoplasms diagnosed by surgery or endoscopic ultrasound guided fine needle aspiration. The group “Others” includes pathologically-proven lower grade pancreatic neoplasms that were not PDAC, IPMN-HGD, or PanIN-3 (IPMN with LGD or MGD, PanIN-2, PanNET, serous cystadenoma, pseudocyst).

Table 1

Baseline Patient Characteristics

	Progressor (n = 24)		Non-Progressor (n = 330)	Total (n = 354)	*P*-value
	PDAC (n = 14)	**High Grade Precursor Neoplasm[1] (n = 10)**			
Mean age (range)	62.5(45-75)	64.4(47-78)	55.8(29-81)	56.4 (29-81)	<0.0001
Age > 60 years	9(70%)	7(64%)	117(35%)	133(38%)	0.009
Male	7 (50%)	1(10%)	160 (48%)	168 (48%)	0.052
Race and Ethnicity					1.0
Black	0	0	8(2.4%)	8 (2.2%)	
White	14(100%)	10(100%)	308 (93%)	332 (94%)	
Asian	0	0	4(1%)	4 (1.1%)	
More than one race	0	0	9(3%)	9 (2.5%)	
Hispanic	0	0	1(0.3%)	1 (0.2%)	
Familial PC	14(100%)	8(80%)	322(94%)	344 (97%)	0.043
3 or more FDR with PDAC	3(21%)	0	26(8%)	29(8%)	0.167
3 or more relatives with PDAC	11(79%)	5(50%)	179(54%)	195(55%)	0.178
Mutation carrier	1(7%)	3(30%)	53(16%)	57 (16%)	0.327
Peutz-Jeghers syndrome	0	2 (20%)	8(2%)	10(3%)	0.043
CDKN2A	0	0	4(1%)	4 (1%)	1.0
BRCA1/BRCA2/PALB2	1(7%)	1(10%)	39(12%)	41(12%)	1.0
Lynch syndrome	0	0	1(0.3%)	1(0.3%)	1.0
PRSS1	0	0	1(0.3%)	1(0.3%)	1.0
Current smoking	1(7%)	3(30%)	25(86%)	29(8%)	0.07
Ever smoked	5(36%)	5(50%)	119(36%)	129 (36%)	0.702
Personal history of other cancer	4(29%)	3(30%)	64(19%)	71 (20%)	0.419
Type II diabetes	1(7%)	0	27(8%)	28 (8%)	1.0
BMI ≥30	2(14%)	3(30%)	82(24%)	87(25%)	0.694
Dilated MPD at baseline[2]	9(64%)	5(50%)	62(19%)	76 (21%)	<0.0001

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	Progressor (n = 24)		Non-Progressor (n = 330)	Total (n = 354)	*P*-value
	PDAC (n = 14)	High Grade Precursor Neoplasm[1] (n = 10)			
Three or more cysts at baseline	5(36%)	8(80%)	36(11%)	49(14%)	<0.0001

Familial PC (pancreatic cancer) = kindred with at least one pair of affected relatives with pancreatic ductal adenocarcinoma (PDAC)

FDR = first-degree relatives; MPD = main pancreatic duct

[1]High grade precursor neoplasm = intraductal papillary mucinous neoplasm (IPMN) with high grade dysplasia or pancreatic intraepithelial neoplasia (PanIN)-3

[2]Dilated MPD defined by Rosemont criteria (≥ 3.5 mm in the head, ≥ 2.5 mm in the body, and/or ≥ 1.5 mm in the tail), < 5 mm

Table 2

Description of 24 High Risk Individuals with Neoplastic Progression

Patient No.	Age at Diagnosis (years)/Gender	HRI Category	Time to Detection of Tumor (years)	Tumor Type/Size (mm)	Management	TNM stage	Outcome/ Survival time from Diagnosis (years)	Cause of Death
PDACs Detected and Operated During Surveillance								
1	72/F	FPC	0.2	PDAC/2	Distal pancreatectomy	T1N1M1	Alive/10.9	NA
2	46/F	FPC	0.6	PDAC/28	Whipple	T2N1M0	Died/12.3	Gastric cancer surgery complications
3	66/M	FPC	2.2	PDAC/28	Distal pancreatectomy	T2N1M0	Died/1.1	PDAC
4	79/F	FPC	4.4	PDAC/25	Whipple	T3N1M0	Alive/1.8	NA
5	73/F	FPC	4.4	PDAC/15	Whipple	T3N0M0	Alive/3.9	NA
6	70/M	FPC	5.2	PDAC/45	No surgery; metachronous PDAC 5 years after Whipple formain duct IPMN	T4N1M1	Died/0.2	PDAC
7	51/F	FPC	6.8	PDAC/35	Distal pancreatectomy	T2N1M0	Alive/7.2	NA
8	55/M	FPC	9.7	PDAC/27	Distal pancreatectomy 8 years after Whipple for IPMN-adenoma	T3N0M0	Died/1.1	PDAC
9	70/M	FPC	9.1	PDAC/7	Total pancreatectomy	T1NM0	Alive/3.7	NA
10	74/M	FPC	9.9	PDAC/36	Distal pancreatectomy	T3N1M0	Died/3.7	PDAC
High Grade Precursor Neoplasms Detected and Treated During Surveillance								
11	67/F	FPC	0.3	PanIN3	Total pancreatectomy	NA	Alive/10.2	NA
12	56/F	FPC	0.3	Combined IPMN-HGD	Total pancreatectomy	NA	Alive/8.6	NA
13	53/F	FPC	0.4	PanIN3	Total pancreatectomy	NA	Alive/4.4	NA
14	67/F	FPC	2.0	IPMN-HGD/10; IPMN-HGD/5	Distal pancreatectomy followed by completion Whipple	NA	Alive/4.8	NA
15	58/F	FPC	2.5	IPMN-HGD; PanIN-3	Whipple	NA	Alive/9.9	NA
16	66/F	PJS	2.5	IPMN-HGD	Distal pancreatectomy[1]	NA	Alive/4.1	NA
17	76/F	FPC	2.0	PanIN3	Whipple	NA	Alive/7.2	NA
18	56/F	FPC	1.5	PanIN3 in MPD	Whipple	NA	Alive/8.1	NA
19	72/M	FPC	1.9	IPMN-HGD	Distal pancreatectomy[2]	NA	Alive/7.2	NA

Patient No.	Age at Diagnosis (years)/Gender	HRI Category	Time to Detection of Tumor (years)	Tumor Type/Size (mm)	Management	TNM stage	Outcome/ Survival time from Diagnosis (years)	Cause of Death
20	47/M	PJS	0.3	IPMN-HGD	Whipple	NA	Alive/14.7	NA
Tumors Detected Outside Surveillance (Late or Stopped Surveillance)								
21	77/M	FPC	1.6	PDAC/25	No surgery	T2N1M1	Dead/2.2	PDAC
22	68/M	FPC	4.5	PDAC/22	No surgery	T2N1M1	Dead/0.3	PDAC
23	59/M	FPC	9.0	PDAC/25	Total pancreatectomy	T2N1M0	Dead/4.0	PDAC
24	82/F	FPC	6.9	PDAC/*	No surgery	TxNxM1	Dead/0.5	PDAC

PDAC = pancreatic ductal adenocarcinoma,

^ first-degree relatives diagnosed with PDAC at <55 years

* Patient reported diagnosis of an unresectable cancer, tumor size unknown.

Table 3

Cox Proportional Hazards Regression Model for Neoplastic Progression after Adjusting for Time Varying Radiologic Progression and the Type of Radiological Progression

	Adjusted Model		
	Hazard Ratio	**p-value**	**95% CI**
Any radiologic progression	23.96	<0.0001	9.43, 60.87
Type of radiologic progression			
Cyst or duct changes	41.20	<0.0001	12.52, 135.53
Solid mass	422.60	<0.0001	102.42, 1743.74
Age at baseline > 60 years	1.64	0.29	0.65, 4.14
Mutation positive	0.66	0.53	0.18, 2.41
Total lesions at baseline ≥ 3	4.85	<0.0001	2.02, 11.64
Dilated MPD at baseline[1]	1.68	0.25	0.70, 4.06

[*] Dilated MPD defined by Rosemont criteria[1] (≥ 3.5 mm in the head, ≥ 2.5 mm in the body, and/or ≥ 1.5 mm in the tail), < 5 mm

[1] Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc 2009;69:1251-61.