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Frequent Detection of Pancreatic Lesions in Asymptomatic High-Risk Individuals:

Screening for Early Pancreatic Neoplasia (CAPS 3 Study)

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Abstract

BACKGROUND & AIMS—The risk of pancreatic cancer is increased in patients with a strong family history of pancreatic cancer or a predisposing germline mutation. Screening can detect curable, non-invasive pancreatic neoplasms, but the optimal imaging approach is not known. We determined the baseline prevalence and characteristics of pancreatic abnormalities using 3 imaging tests to screen asymptomatic, high-risk individuals (HRI).

METHODS—We screened 225 asymptomatic adult HRI at 5 academic US medical centers once, using computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). We compared results in a blinded, independent fashion.

RESULTS—Ninety-two of 216 HRI (42%) were found to have at least 1 pancreatic mass (84 cystic, 3 solid) or a dilated pancreatic duct (n=5) by any of the imaging modalities. Fifty-one of the 84 HRI with a cyst (60.7%) had multiple lesions, typically small (mean 0.55 cm, range 2–39 mm), in multiple locations. The prevalence of pancreatic lesions increased with age; they were detected in 14% of subjects <50 years old, 34% of subjects 50–59 years old, and 53% of subjects 60–69 years old (*P*<.0001). CT, MRI, and EUS detected a pancreatic abnormality in 11%, 33.3%, and 42.6% of the HRI, respectively. Among these abnormalities, proven or suspected neoplasms were identified in 85 HRI (82 intraductal papillary mucinous neoplasms [IPMN] and 3 pancreatic endocrine tumors). Three of 5 HRI who underwent pancreatic resection had high-grade dysplasia in <3 cm IPMNs and in multiple intraepithelial neoplasias.

CONCLUSIONS—Screening of asymptomatic HRI frequently detects small pancreatic cysts, including curable, non-invasive high-grade neoplasms. EUS and MRI detect pancreatic lesions better than CT.

Keywords

IPMN, PanIN; surveillance; familial pancreatic cancer

INTRODUCTION

Pancreatic ductal adenocarcinoma (PC) is one of the most lethal malignancies. Mortality rates have not significantly changed for decades. Interest in improving the outcomes of PC has led to the use of imaging tests to detect asymptomatic small cancers and pre-invasive lesions in high risk individuals (HRI) with an inherited predisposition, such as Peutz-Jeghers syndrome or PJS (132-fold increased risk[1]), hereditary pancreatitis (26.3-fold increased risk[2]), familial atypical mole multiple melanoma or FAMMM (p16 mutation,13-fold increased risk[3]), familial breast-ovarian cancer (FBOC) with *BRCA1 (breast related cancer 1,* 2.3-fold increased risk[4]), *BRCA2 (breast related cancer 2,* 3.5 to 5.9-fold increased risk[5-9]) or *PALB2 (partner and localizer of BRCA2*[10-12]) mutation, and hereditary nonpolyposis colorectal cancer or HNPCC[13]. Individuals from a family with a pair of affected first degree relatives (familial pancreatic cancer or FPC) also have a higher risk (6.4 to 32-fold) of PC [12, 1412, 15, 16].

The best approach for PC screening is not yet known. To date, multidisciplinary PC screening programs have screened HRI with one or more imaging tests using different equipment and imaging protocols, with variable diagnostic yield[17-20]. Five U.S. academic medical centers with pancreatic tumor registries and multidisciplinary PC screening programs formed the American Cancer of the Pancreas Screening (CAPS) Consortium and developed strict criteria for identifying and enrolling HRI, consensus terminology for radiologic and EUS abnormalities, and standardized methods of performing screening tests. We determined the diagnostic yield and concordance of initial screening by MRI, CT, and EUS for pancreatic lesions in screening-naive high risk individuals and calculated the prevalence of pancreatic and extra-pancreatic neoplasms detected by one-time screening. We also describe the factors associated with prevalent pancreatic neoplasia and the radiologic and pathologic correlates of pancreatic neoplasms in asymptomatic HRI who had operative treatment.

METHODS

Study Design and Patients

This was a multicenter prospective cohort study (CAPS 3 study) performed at tertiary care medical centers on an outpatient basis. HRI at the Johns Hopkins Hospital (Baltimore, Maryland), Mayo Clinic (Rochester, Minnesota), University of California (Los Angeles, California), Dana Farber Cancer Institute (Boston, Massachusetts), and M.D. Anderson Cancer Center (Houston, Texas) were identified by each site or through various websites (CAPS 3 study, Lustgarten Foundation, and the NIH clinicaltrials.gov). This study was approved by the institutional review boards of all participating sites. All subjects provided informed consent. The study was registered on the NIH clinicaltrials.gov website (NCT00438906).

Three groups of asymptomatic HRI were studied: PJS patients, FBOC patients with at least 1 affected first- or second-degree relative with PC, and relatives of patients with FPC with at least 1 affected first-degree relative. All participants were 40-80 years old (except for PJS subjects who could be as young as 30 years old) or 10 years younger than their youngest relative with PC. The selection of age 40 for initiation of screening FPC relatives was based upon the youngest age of FPC (age 45) and the age group with the highest risk for FPC (45-64.9 years) in a large FPC registry[14]. The initiation of screening at age of 30 years for PJS patients was based on the average age of onset of FPC 40.8 +/- 16.2)[1]. The selection of the age for initiation of screening was also influenced by our goal to potentially detect noninvasive precursor lesions [212223]. Patients were not eligible for screening if they were unable to provide informed consent, had prior pancreas screening, Karnofsky performance

status of < 60, any suspicion of pancreatic disease, prior pancreas surgery, severe medical illness, bleeding diathesis or thrombocytopenia, renal insufficiency, allergic reaction to radiographic contrast material, morbid obesity, and severe claustrophobia, and upper gastrointestinal tract obstruction.

Study Procedures

Highly experienced radiologists and gastroenterologists at the 5 tertiary academic medical centers participated in multiple conference calls and annual investigator's meetings to discuss the study protocol and promote adherence to study procedures.

MRI

Gadolinium and secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) was performed according to a standardized protocol. All MRI sequences were obtained at minimum 1.5 Tesla (GE or Siemens) using a phased array torso coil. Human synthetic secretin (0.2 ug/kg, ChiRhoClin Inc, Burtonsville, Maryland) was given intravenously. T2 weighted acquisitions for the MRCP were acquired in the coronal plane. Five post secretin MRCP images were acquired every minute starting 1 minute after secretin administration. The individual slices and reconstructed maximum-intensity projections before and after secretin were used for viewing the 3D MRCP. In addition, axial breath-hold unenhanced and dynamic contrast-enhanced (0.1 mmol per kilogram of body weight) T1-weighted three-dimensional fat-suppressed spoiled gradient-echo imaging were acquired in the arterial, portal venous and delayed phase (20 seconds, 70 seconds, and 3 minutes, respectively).

CT

Standardized pancreatic protocol CT scans were done on a Siemens Somatom Flash Dual Source scanner. Patients drank 1000 cc of water over a 30 minute period prior to the scan with the last 250 cc immediately prior to the study. Intravenous contrast was injected at 4-5 cc/sec using a volume of 100-120 cc of Omnipaque-350 or Visipaque-350 depending on patient renal function and/or age. Dual phase imaging at 30 sec and 60 seconds was routinely obtained. Scan parameters were 120 kVp, body quality reference mass of 320 mAs using Care Dose and .6 mm detectors. Images were reconstructed with thin and thick sections at .75 mm every .5 mm, and 3 mm every 3 mm respectively. Images were analyzed with post processing software including axial imaging, multi-planar reconstruction and 3D rendering. The 3D reconstruction was accomplished with both volume rendering and maximum intensity projection techniques.

Endoscopy

Gastroenterologists with expertise in EUS performed sedated upper endoscopy followed by EUS imaging using both a mechanical or electronic radial (GFUM20, GFUE160-AL5, Olympus Corporation) and linear echoendoscope (CFUC140P, SSD-Alpha5 or Alpha10, Olympus Corporation). EUS was scheduled as the last screening test after CT and MRI to potentially enable fine needle aspiration for any lesions detected by any of the 3 tests. The gastroenterologists performed EUS without prior knowledge of the results of CT and MRI. After EUS imaging was completed and results recorded, the findings of the prior MRI and CT were then disclosed to the endoscopist to allow correlation of radiologic findings, and tissue sampling of any clinically relevant lesions. Fine needle aspiration was performed during the same sedation according to standard medical care guidelines at each institution, with on-site cytopathology review of specimens for adequacy. When pancreatic cysts were aspirated, specimens were also submitted for carcinoembryonic antigen (CEA) testing, if aspirated cyst fluid volume was adequate for laboratory assay (1 ml or greater). Endoscopic

retrograde cholangiopancreatography (ERCP) was performed at the discretion of the clinical team to investigate ductal abnormalities.

Image Interpretation and Reporting

Participating gastroenterologists and radiologists were blinded to the results of the other imaging tests. Reporting of imaging findings was standardized across MRI, CT, and EUS using nomenclature developed at a prior 2004 CAPS consensus National Cancer Institute/ SPORE-sponsored workshop (Bethesda, MD). Main pancreatic duct dilation (duct diameter > 3 mm in the head, 2 mm in the body, and 1 mm in the tail) was considered abnormal. Pancreatic ductal and parenchymal abnormalities associated with chronic pancreatitis[24, 25] were noted. The final imaging diagnosis for the pancreas was given by the radiologist or gastroenterologist interpreting or performing each imaging test. The results of all imaging tests (including discrepancies) were communicated in writing to the patient by the site principal investigator. The determination of a pancreatic abnormality was made based on a positive result on any one of the 3 screening tests.

Final Diagnoses, Follow-up, Clinical Management

Patients were called by the study coordinator within 1 week from screening and seen by their primary physician/gastroenterologist as part of routine care. A follow-up clinical visit and abdominal imaging test one to three years from screening were recommended if a normal pancreas or nonspecific chronic pancreatitis-like abnormalities were seen at baseline, depending upon the patient's age and medical status according to local standard of care. Patients with lesions were managed according to the consensus of the clinical team. The final diagnosis for each screened patient was made at each site at study closure by the principal investigator based upon clinical judgement, repeat imaging, and cytology or surgical pathology.

Recommendations for treatment versus surveillance were individualized. Surgical treatment was offered for suspected prevalent pancreatic neoplasms (solid masses, suspected main duct or mixed intraductal papillary mucinous neoplasm (IPMN), branch duct IPMNs ≥ 2cm or with worrisome features for malignancy such as mural nodules), and/or abnormal cytology. If surgical resection was not imminently scheduled for these lesions, repeat imaging within 3 months was performed. Surveillance with MRI/EUS at 6-12 months was recommended for small cysts (suspected branch-duct IPMN) and other pancreatic lesions without worrisome features. When clinically appropriate, surgery was also offered for suspected extra-pancreatic neoplasms detected during screening.

Pancreatic surgery was performed by one expert pancreatico-biliary surgeon (RS) who had performed ≥ 500 pancreatic operations. One expert pathologist (RHH) provided a pathologic diagnosis using standard[26] and consensus international classification systems[27]. Final diagnoses were made for all patients at study closure by each site's gastroenterologist based upon consensus agreement between baseline imaging tests, repeat imaging, ERCP, cytology, and pathology (when applicable) and clinical follow-up for a minimum of 1 year from baseline.

Statistical Analysis and Sample Size Estimates

The chi-square, Fisher's exact test, t test, and Wilcoxon rank sum test were performed for categorical and numerical variables, where appropriate, to compare patient characteristics. Two-tailed p values < 0.05 were considered statistically significant. The kappa coefficient, Spearman's correlation coefficient, and Lin's concordance correlation coefficient were computed to analyze the agreement in imaging test results for categorical and continuous variables (presence or absence, size and total number of detected pancreatic lesions).

Univariate and multivariate logistic regression analyses were performed to evaluate possible and independent factors associated with pancreatic lesions. Analyses were performed using SAS (v. 9.2, SAS Institute, Cary, NC), R(v. 2.11.0), and Stata SE (Stata Corporation, Dallas, TX) software packages.

The study sample size was based upon the estimated population prevalence (reported prevalence 5-23%[18, 28, 29]) for a detectable pancreatic neoplasm in 15% of high risk individuals. A sample size of 200 would provide 30 detectable neoplasms with 95% confidence interval and precision of +/-5%.

RESULTS

Patients

Table 1 and Figure 1 summarize the characteristics of the high-risk individuals. Two hundred twenty-five asymptomatic HRI were enrolled. Nine of these were excluded from the analysis (due to prior recent screening imaging test, health reasons, failure to confirm the diagnosis of familial PC, and patient-initiated withdrawal) resulting in 216 evaluable patients (Johns Hopkins Hospital=112, Mayo Clinic=51, UCLA=16, MD Anderson Cancer Center = 20, Dana Farber Cancer Institute=17). Ninety percent of the participants were first degree relatives of patients with familial PC and the remaining were mutation carriers. The mean age of our patients was 56.1 years (range 28 – 79).

Diagnostic Yield

The overall prevalence of a focal pancreatic abnormality (lesion) in any of the 3 screening tests was 42.6% (92/216) (Figure 1). Five of the 92 (2.3%) patients with a pancreatic lesion had an isolated dilated main pancreatic duct (mean 3.3 mm, range 2.8-3.8 mm) without an associated mass. The remaining 87 patients (40.3% of all 216 subjects) had at least one cystic (84/216 or 38.8%) or solid lesion (3/216 or 1.4%) with or without associated pancreatic duct dilation.

The majority of the pancreatic mass lesions detected were small (mean size 0.55, range 0.2-3.9 cm), and cystic (84/87 or 96%). The majority of the patients with cysts had multiple lesions (51/84 or 60.7% of those with a cyst). The median number of cysts per patient with a cyst was 2 (range 1-20). Pancreatic cysts were multifocal (found in more than one region of the pancreas) in 46 of 84 (54.7%) patients with cysts. Three patients had 4 small solid pancreatic lesions, which were not concerning for malignancy by all imaging tests and EUS-guided fine needle aspiration (FNA).

EUS-FNA was performed in 12 patients with 16 lesions (4 solid lesions, 9 cysts, 4 peripancreatic lymph nodes) with size range 0.4 to 2.1 cm. Aspirates from the peripancreatic lymph nodes uniformly showed benign lymphocytes. Aspirates from solid lesions showed 3 pancreatic neuroendocrine tumors and one benign intra-pancreatic lymph node. Aspiration of pancreatic cysts was not routinely performed due to small size and absence of mural nodules. Only 4 of 9 cyst aspirates had diagnostic cytology for a mucinous cyst. Cyst fluid CEA was not analyzed when aspirated cyst fluid volume was < 1 cc, in which case only cytologic examination was performed. Cyst fluid aspirates from 3 patients (cyst size 15-18 mm) had elevated CEA levels diagnostic for mucinous cystic neoplasm (patient 1, Table 1)

Sixty two (28.7%) of HRI had one or more extra-pancreatic lesions detected by CT or MRI. The most common incidental lesions were kidney cysts (9.4%), liver cysts (7.5%), kidney stones (2.8%), and adrenal masses (1.9%).

Factors Associated with Prevalent Pancreatic Lesions

With univariate analyses, the prevalence of a pancreatic lesion (cyst, solid mass, or dilated pancreatic duct) was significantly associated with greater age (Table 1, Fishers exact, $p < 0.0001$). Pancreatic lesions were more common in patients aged 50-59 years and 60-69 years, than other age groups (Fishers exact, $p < 0.0001$). There were no differences in the prevalence of a pancreatic lesion in baseline screening tests according to risk group (familial PC versus mutation carrier), gender, race, ethnicity, Jewish ancestry, smoking, regular alcohol consumption, and personal history of type 2 diabetes (Table 1). With multivariate logistic regression analysis, patients older than 50 years were more likely to have a pancreatic lesion (odds ratio 4.4, 95% CI 2.2-9.1, $p < 0.0001$) after adjusting for male gender and cigarette smoking.

Concordance of CT, MRI, and EUS Pancreatic Abnormalities

The prevalence of pancreatic abnormalities detected in HRI varied by screening modality. A comparison of the detection rate of the CT, MRI, and EUS for any pancreatic lesion according to type of lesion is provided in Table 2.

A total of 283 cystic or solid lesions were detected in the 216 HRI by any screening modality. CT, MRI/MRCP, and EUS visualized a total of 39 (13.8%), 218 (77%), and 229 (79%) of all detected lesions, respectively. The concordance (percent agreement) for detection of any pancreatic lesion was higher between EUS and MRI (91%) than for EUS and CT (73%) (per patient analysis). There was also strong positive correlation between MRCP and EUS for the size (Spearman correlation coefficient=0.82) and moderate agreement for the number of pancreatic cystic or solid mass lesions (Lin's CCC=0.67). There was substantial agreement between EUS and MRI for the specific location (head or uncinate, body, or tail of the pancreas) of pancreatic mass lesions 1 cm and smaller (agreement 85.4%, kappa=0.79, $p< 0.0001$) and lesions more than 1 cm in size (agreement = 100%, kappa = 1.0).

CT, MRI, and EUS detected subcentimeter cysts in 11%, 33%, and 36% of 92 screened high risk individuals with a pancreatic lesion, respectively. Communication of cysts with the main pancreatic duct was seen by MRI in 53% of the 72 subjects with a cyst detected by MRI, which was superior to CT and EUS (Table 2). CT detected fewer suspected pancreatic cysts with size > 1 cm (n=12) (62.5%) than either MRI (90%) or EUS (100%) (p=0.007). EUS visualized subtle parenchymal and ductal abnormalities associated with chronic pancreatitis in 25% (5 or more out of 9 criteria present[25]) of HRI.

Both CT and EUS did not detect 5/72 (6.9%) patients with a cystic lesion seen by MRI. One of these 5 missed cysts was absent at 2 follow-up MRI examinations. The other 4 (5-8 mm) cysts located in head or tail were stable on follow-up imaging (final diagnoses 2 BD-IPMNs, 2 indeterminate cysts). In contrast, MRI and CT missed 19/92 lesions (22.3%) detected by EUS. Three of these 19 lesions were solid nodules (pancreatic neuroendocrine tumors size 1.3, 1,0, and 0.8 cm), 4 had dilated main pancreatic ducts without stricture or mass (stable on follow-up). The remaining 12 patients had cysts 2-11 mm in size (final diagnoses 3 BD-IPMNs, 9 indeterminate cysts).

Clinical and Pathologic Diagnoses

The mean follow-up time at study closure was 28.8 months (range 14-47.2). The final diagnoses for all subjects based upon clinical follow-up, repeat abdominal imaging, EUS/FNA, and/or surgery for were: confirmed or suspected branch duct IPMN (n=82), combined IPMN (n=2), pancreatic endocrine tumor (n=3), isolated main pancreatic duct dilation (n=4), indeterminate benign cyst (n=1), nonspecific chronic pancreatitis-like abnormalities (n=32),

and normal pancreas (n=92). No HRI was diagnosed with an invasive malignancy within the follow-up period after baseline screening.

Pancreatectomy was performed on 5 HRI (1 Whipple procedure, 3 distal, 1 total) with no major adverse events. The demographic, radiologic, and pathologic findings are summarized in Table 3. All patients had multiple and multifocal pancreatic neoplasms consisting of IPMN and pancreatic intraepithelial neoplasia (PanIN[27]). Three of the 5 patients had high-grade dysplasia involving the main duct and/or branch ducts as well as multifocal PanINs but no invasive PC. Patient 1 exemplifies a phenotype seen in high-risk patients characterized by multifocal IPMNs and PanINs involving the main and branch ducts. The CT and MRI detected a prominent main pancreatic duct and branch duct IPMNs but were not conclusive (Figure 2A). Endoscopy + EUS correctly predicted a mixed IPMN (Figure 2B, with video 1). The resected distal pancreas showed a remarkably large 11.5 cm intestinal-type IPMN extending into the branch ducts (Figure 3A) with 95% of the main duct epithelium showing high-grade dysplasia and synchronous multiple, multifocal PanINs (highest grade PanIN-3) (Figure 3B).

DISCUSSION

We report the first multicenter, prospective, blinded comparison of state-of-the-art clinical imaging tests for the first screening of a well-defined asymptomatic population of individuals with an increased risk for developing PC. The diagnostic yield for a pancreatic lesion (masses, cysts, or isolated dilated main pancreatic duct) was 92 of 216 HRI (42.6%). Single center studies using different approaches for imaging have reported variable diagnostic yields for one-time screening of heterogeneous groups of HRI. The prevalence of radiologic lesions in a study of American FPC relatives and mutation carriers was 16.5% (18/109) using an MRI-based screening approach[30]. In a Dutch study of *p16-Leiden* gene mutation carriers, MRI detected 3 PCs and 9 benign cysts (17.7%)[31]. Verna et al reported a baseline diagnostic yield for pancreatic lesions of 33% (11/33) for MRI screening and 45% (14/31) for EUS screening[32], similar to our current study.

The majority of lesions in the current study were cysts with typical characteristics of branch duct IPMNs, more commonly found in older individuals. MRI and CT may detect small incidental pancreatic cysts in 2.4%[33] and 2.8%[34] of asymptomatic individuals in the general population, respectively. An autopsy study reported a 24.3% prevalence of pancreatic cysts[35]. Our study results suggest that, compared to the general population, HRI have significantly more prevalent pancreatic cysts.

If pancreatic lesions are so common among asymptomatic HRI, which ones warrant surgical resection? Most of the lesions identified by screening pancreatic imaging tests in this and other screening studies[30-32, 36] were presumed BD-IPMNs based upon typical imaging characteristics. Most sporadic BD-IPMNs have a low risk for malignancy and can be safely observed if they do not meet standard internationally accepted consensus criteria for resection. These criteria include the presence of cyst features worrisome for malignancy (such as mural nodules, cyst size > 3 cm, or positive cyst fluid cytology), or a dilated main pancreatic duct of 1 cm or greater in diameter [37]. Because these criteria have been validated only in patients with sporadic pancreatic cysts, it is unclear if they are appropriate for high risk individuals. Individuals with a family history of PC undergoing pancreatic resection are significantly more likely to harbor widespread PC precursor lesions (IPMNs and PanINs)[3839] than those with sporadic PC. Furthermore, these PC precursors are more likely to contain higher grades of dysplasia, than are in pancreata from patients without a family history[39]. We detected and treated early pancreatic neoplasms associated with PC development. Three of the five asymptomatic patients that we detected and treated had high

grade neoplasia in an IPMN and/or multiple PanINs, similar to other screening studies involving HRI[18, 28]. Large long-term studies are needed to develop better criteria for surveillance and surgical resection of pancreatic lesions detected by screening. Such criteria should balance the morbidity of pancreas surgery with the opportunity to treat patients with a curable precursor lesion before they develop an incurable invasive cancer.

What age should we begin screening for pancreatic neoplasia in HRI? Age of onset is an important predictor of PC risk in familial kindreds[15]. However, despite their inherited predisposition, patients with familial PC develop their cancers at the same age as those with sporadic forms of the disease[40]. In the current study, we initiated screening at age 40 or 10 years younger than the youngest PC relative and found the likelihood of a prevalent pancreatic lesion to be much higher in individuals older than 50 years. Similarly, Ludwig and colleagues initiated screening at age 35 but found a higher baseline diagnostic yield in individuals older than 55 years[30]. Furthermore, all patients with resected high-grade neoplasia in PC precursor lesions in our study were all older than 60 years. Eleven of 14 reported prevalent screening-detected PC have been in patients 50 years or older[18-20, 28, 32]. Taken together, these results suggest that the age at which baseline pancreatic screening should be raised to at least 50 years, except in individuals with a relative with young-onset PC or known inherited predisposition to young-onset pancreatic cancer.

What might be an optimal method of screening individuals with an inherited increased risk for PC? We found that CT detected much fewer pancreatic lesions (mostly cysts) than MRI or EUS. Other single center studies support our conclusion that MRI and EUS are currently the best initial tests for detecting early pancreatic neoplasia[18, 29-32, 36]. The relative costs and effectiveness of MRI and EUS imaging for screening need further study. Coupled with the recent heightened concern about the increased risk of radiation-related cancers associated with CT, our study results suggest that routine CT using current technique might not be an optimal approach for screening HRI.

Multidisciplinary screening programs in the United States and Europe have detected 11 prevalent asymptomatic PCs (0.9-6.8%) at baseline evaluation in of 399 HRI [28,18, 30,32,31,29] and 4 incident PCs[31] in 79 HRI during surveillance with CT[18], MRI[303231], or EUS[28, 29, 32]. However, even with early detection, all but 4 were early stage T1N0 cancers. PC may develop from IPMNs (visualized as cysts and/or dilated ducts) or PanIN. The latter cannot be reliably identified by currently available imaging tests. Resected pancreata in this study and other studies[18, 28] had high-grade PanIN that could not be preoperatively diagnosed. This observation underscores a major limitation of using pancreatic imaging as a sole screening test.

Our study has several limitations. First, we used state-of-the-art radiologic and endoscopic imaging tests read/performed by experts in the field. Second, our study focused on one-time screening and prevalent neoplasia. Third, the final diagnoses of all lesions could not be verified by surgical pathology because most were not treated. Fourth, variability in the performance of EUS and interpretation of radiologic and EUS images among multiple physicians involved in this study may have influenced our study results. Finally, each site used standard-of-care for surveillance and treatment, which might result in differential follow-up and treatment. With no evidence-based practice guidelines for recommending surgery for asymptomatic pancreatic lesions detected by screening, each site used a multidisciplinary individualized approach to make decisions about operative treatment. Compared to earlier studies[18, 2841] where high risk individuals with suspected neoplasms (benign BD-IPMNs) were routinely offered surgery, the number of surgeries and pathologically-confirmed pancreatic neoplasms in this study were relatively low.

Since nearly all patients with symptomatic invasive PC and many of those with asymptomatic PC diagnosed in screening programs die of their malignancy, we suggest that the goal of a PC screening and surveillance program should be to detect and selectively treat asymptomatic high-grade precursor neoplasms, rather than focusing screening efforts to detect invasive cancers. Progress in the understanding of the genetic alterations in PC and associated precursors and development of biomarkers might help us improve the early detection and prevention of PC in asymptomatic individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PJS	Peutz-Jeghers Syndrome
PC	pancreatic cancer
EUS	endoscopic ultrasonography
FNA	fine needle aspiration
CT	computed tomography
ERCP	endoscopic retrograde cholangiopancreatography
IPMN	intraductal papillary mucinous neoplasm
BD	branch duct
PanIN	pancreatic intraepithelial neoplasia

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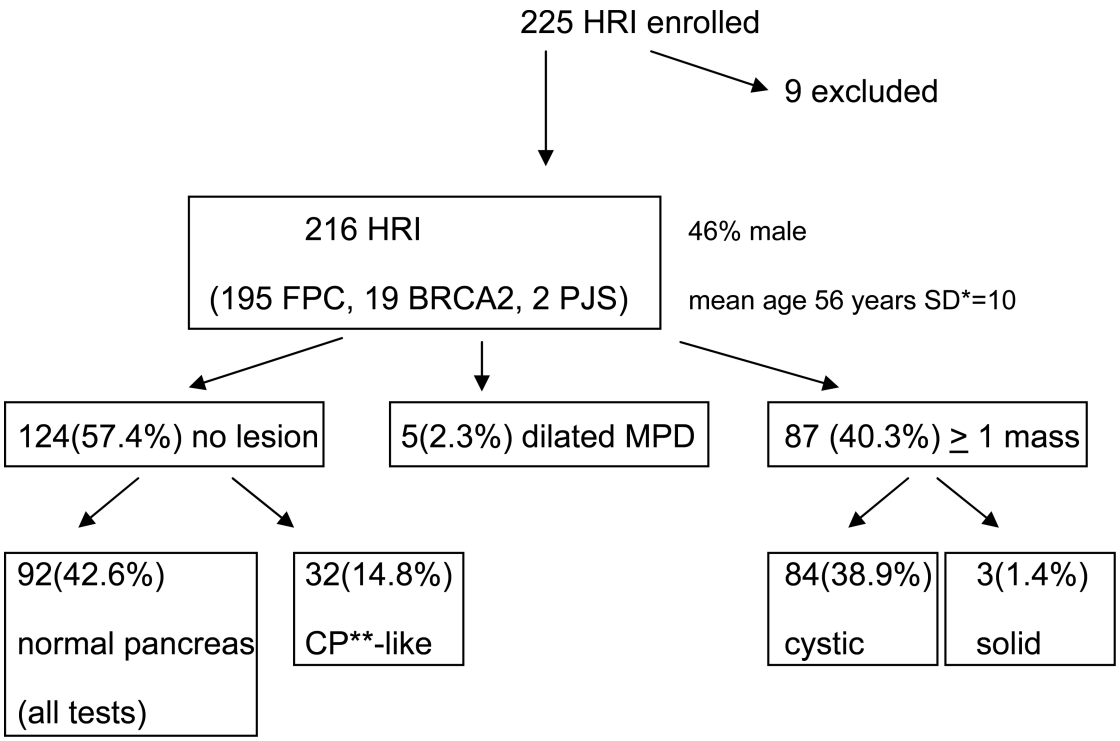
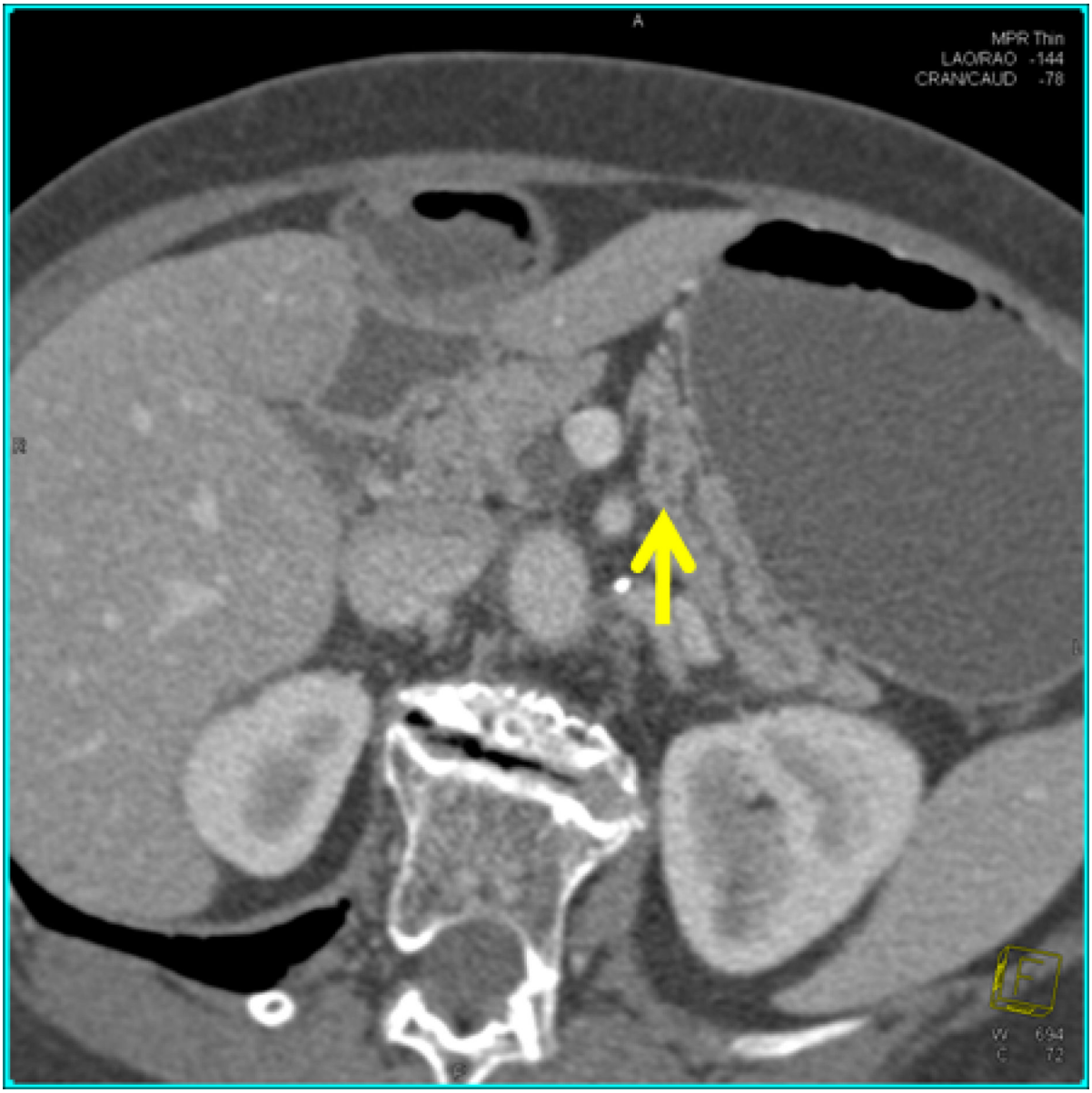
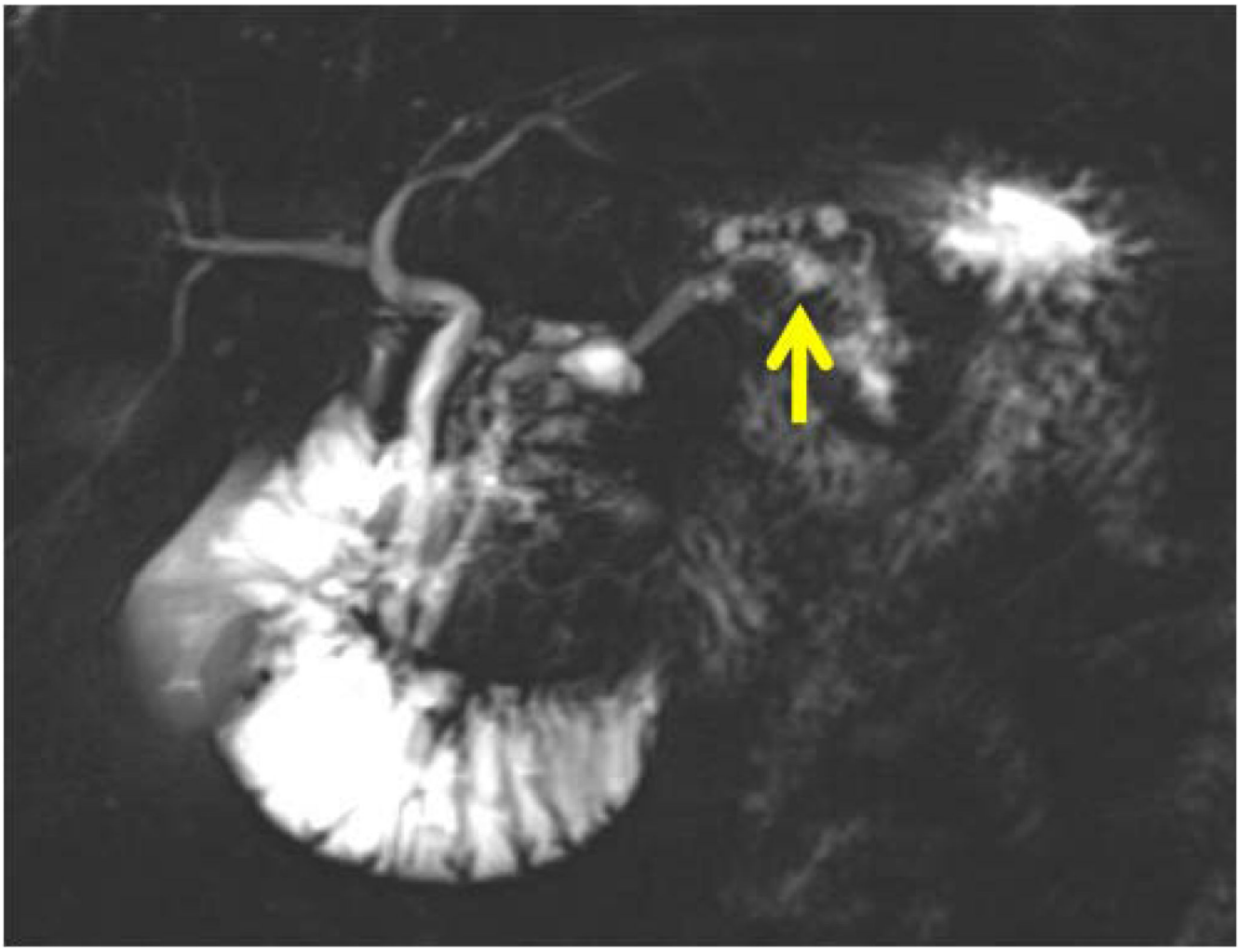


*SD= standard deviation

**CP=chronic pancreatitis

Figure 1.
Study Schema





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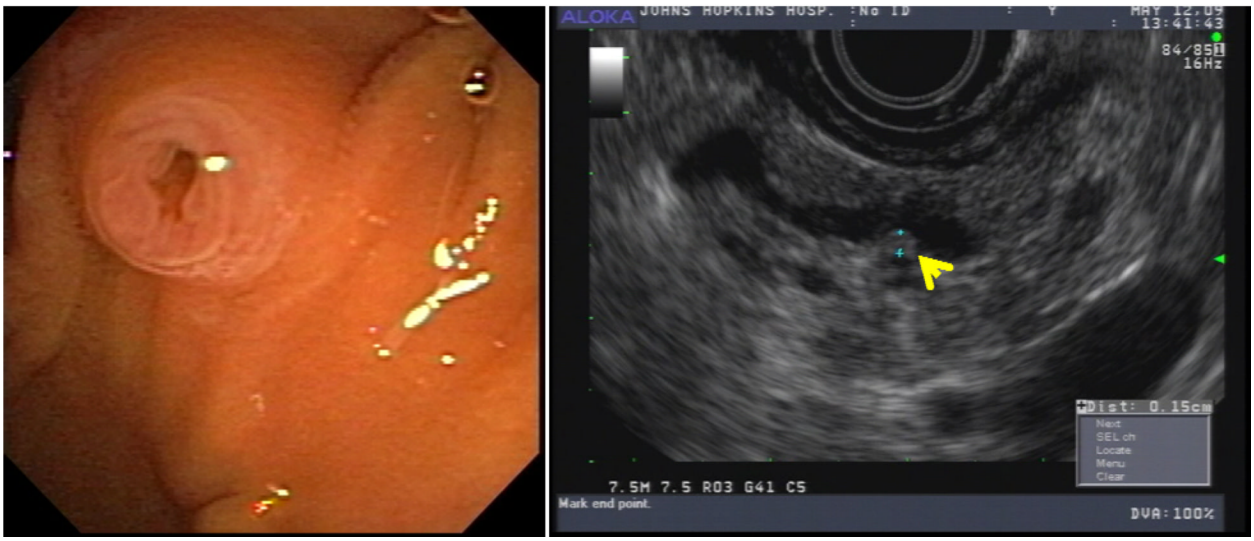
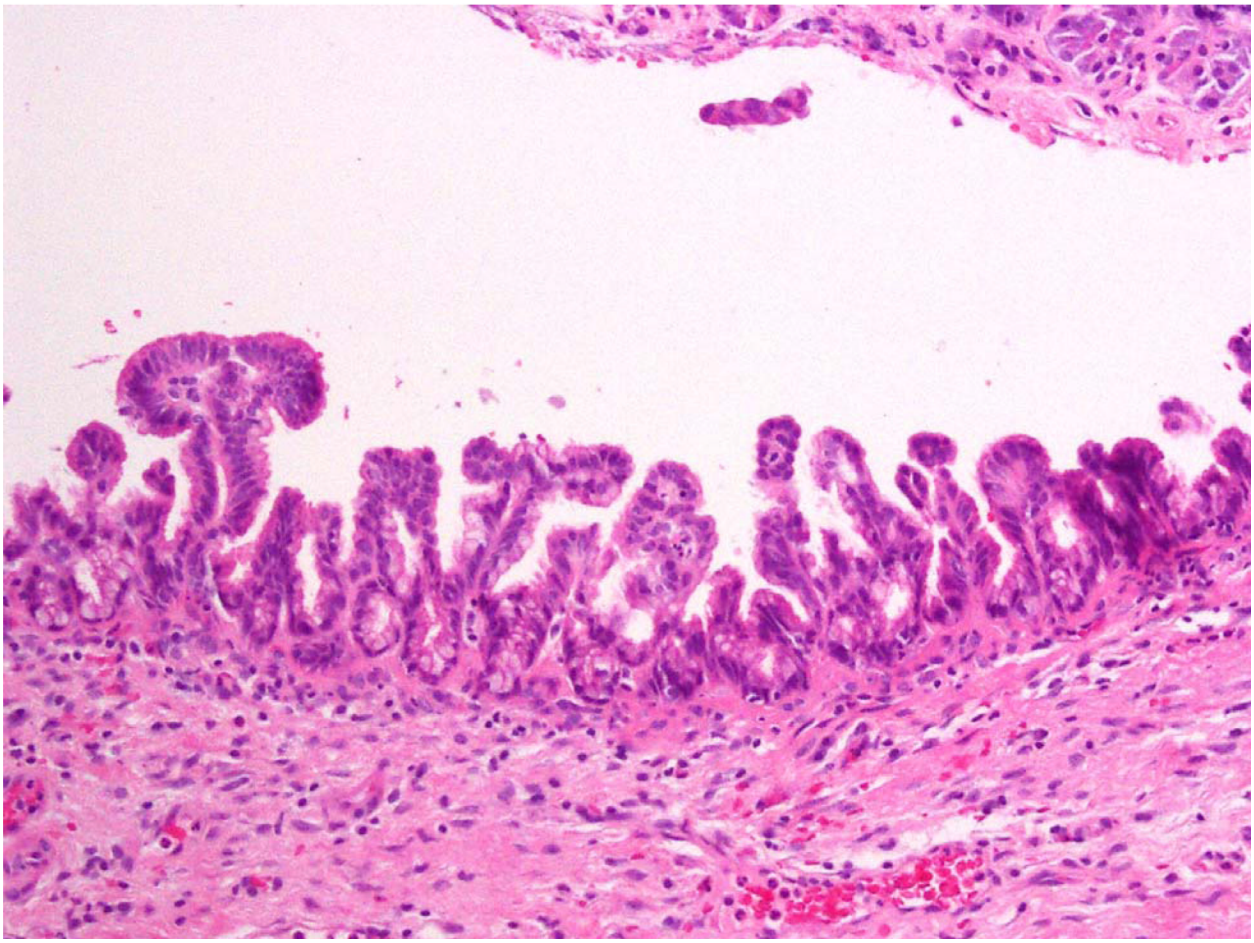


Figure 2.

Asymptomatic prevalent combined (main duct and multiple branch duct) IPMNs in a 74 year old healthy Ashkenazi Jewish woman with 2 affected first-degree and relatives; pancreatic protocol CT (3A, right image), MRI/MRCP (2A left image), and EUS (2B, right image) all showed multiple pancreatic cysts 3-15 mm (arrows indicate suspected BD-IPMNs) and a mildly dilated main pancreatic duct up to 3.8 mm. Endoscopic examination of the ampulla at the time of EUS showed a patulous pancreatic duct orifice with active mucin extrusion (2B, left image). EUS also showed echogenic mucin and polypoid mural nodules in the main duct and multiple cysts typical of mixed IPMN (2B, right image, arrow). See video (for online submission).

A



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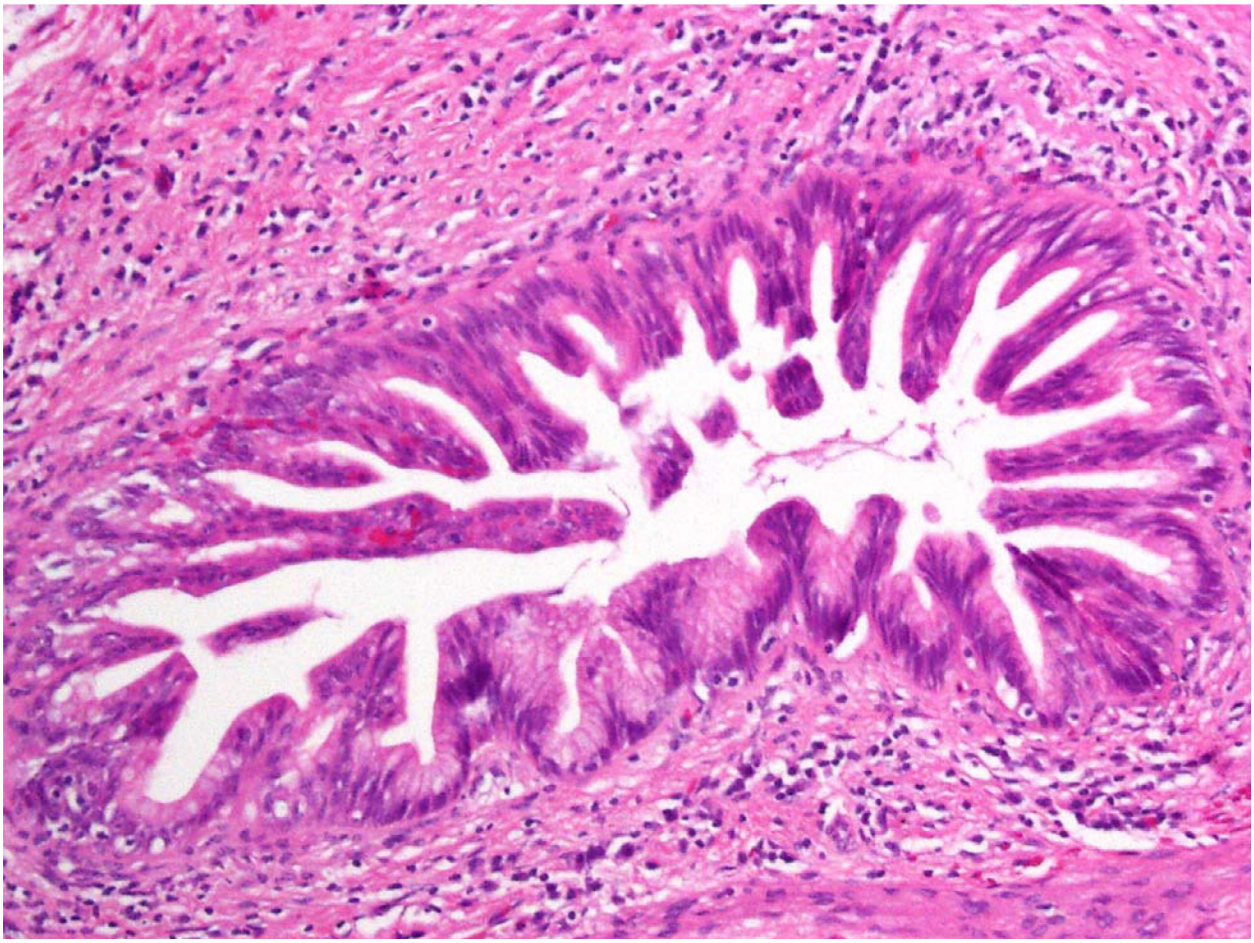

Figure 3.
Histologic sections from the distal pancreatectomy performed on Patient 1. The main duct intraductal papillary neoplasm (IPMN) harbored high-grade dysplasia (Figure 3A), and the adjacent pancreatic parenchyma pancreatic intraepithelial with high-grade dysplasia (PanIN-3) (Figure 3B).

Table 1

Patient Characteristics

	Patients without a Pancreatic Lesion N=124	Patients with a Pancreatic Lesion N=92	Total N=216
Familial PC	110 (89%)	85 (92%)	195(90%)
3 or more affected	70(56%)	50(54%)	120 (56%)
2 FDR affected	40 (32%)	35 (39%)	75 (35%)
BRCA2 + PC relative	13 (10%)	6 (7%)	19 (9%)
Peutz-Jeghers syndrome	1(0.8%)	1(1%)	2(0.9%)
Age*			
< 50 years	50 (40%)	12 (14%)	62(29%)
50-59 years	49 (39%)	31 (34%)	80 (37%)
60-69 years	18 (15%)	37 (53%)	55 (25%)
≥ 70 years	7 (6%)	12 (13%)	19 (8.8%)
Old (age > 50)*	74(48%)	80 (52%)	154 (71.3%)
Male gender	60 (48%)	40 (40%)	100 (46.4%)
Race and ethnicity			
Non-Hispanic white	124(98%)	88(98%)	212 (98%)
Hispanic white	1	0	1 (0.5%)
Black	0	1	2 (0.9%)
Native American	0	1	1(0.5%)
Jewish ancestry	16(13%)	12 (13%)	28 (13%)
Ever smoked (%)	11(9%)	7 (8%)	18 (8%)
Type II diabetes (%)	3(3)	6(6%)	9(4%)
Regular or heavy alcohol use	73(58%)	47 (52%)	120 (55%)

* chi square, $p < 0.0001$

Table 2

Comparison of CT, MRI, and EUS for Detection of Prevalent Pancreatic Lesions (Per Patient Analysis)

Lesion Detected	CT	MRI	EUS
Any pancreatic lesion* detected (in all 216 screened subjects)	24/216 (11%)	72/216 (33.3%)	92//216 (42.5%)
Pancreatic lesion type			
Solid mass (any size)	3/216(1.4%)	1/216 (0.4%)	3/216(1.4%)
Cystic mass (any size)	24/216(11%)	72/216(33%)	79/216(36%)
Cyst communication with MPD	8/24(36%)	38/72(53%)	21/79(27%)
Mural nodule	1/24(4.2%)	1/72(1.4%)	3/79 (3.8%)
Main pancreatic duct dilation	5/216(2.4%)	5/216(2.4%)	21/216(9.5%)
Branch duct dilation	10/216(4.6%)	29/216(14%)	37/216(17.1%)

Table 3

Pancreatic Radiologic and Pathologic Findings in 5 Surgically-Treated High Risk Patients

Patient/Age, Risk	CT	MRI/MRCP	EUS	Final Pathologic Diagnosis
Patient 1 73 year 2 FDR	4 cysts (0.6-1.5 cm, non-communicating), 1 cyst with mural nodule), normal MPD Diagnosis BD-IPMN	6 cysts (0.5-2.1 cm, 2 communicating), normal but prominent MPD, multiple dilated branch ducts Diagnosis: BD-IPMN	3 cysts (0.5- 1.5 cm, 2 communicating), multiple non-communicating cysts, focally dilated MPD 3.8 mm with mural nodules and echogenic mucin, multiple dilated branch ducts, EUS-FNA cyst fluid CEA >1000 Diagnosis: combined IPMN	Distal pancreatectomy: MD-IPMN (7 cm body and tail, intestinal type) with extensive HGD, involving multiple branch ducts, multiple PanIN (highest grade 3)
Patient 2 65 years 2 FDR	2 cysts (0.9-1.0 cm, non-communicating) Diagnosis: BD-IPMN	2 cysts (1.7, 1.4 cm, communicating); Diagnosis: BD-IPMN	Dilated MPD 2.8 mm with 2 cysts (0.9, 1.9 cm, communicating, 1 with 5.5 mm mural nodule), multiple dilated branch ducts, Diagnosis: BD-IPMN	Whipple: MD-IPMN (1.3 cm, head and neck, intestinal type) with LGD with BD-IPMN (1.0 with LGD, 1.5 cm with MGD), multifocal PanIN (highest grade 2)
Patient 3 67 years 2 FDR	One 1.2 cm non-communicating cyst (body) Diagnosis: BD-IPMN	2 communicating cysts (body 1.1-1.4 cm) Diagnosis: BD-IPMN	6 communicating cysts (0.5-1.2 cm head, body, tail), 1 cyst with mural nodule; 1 solid mass 0.7 cm (FNA:PNET) Diagnosis: multiple BD-IPMNs, PNET	Total pancreatectomy: Multiple BD-IPMN with LGD (head, body, tail); multifocal PanIN (highest grade 3); multiple PNET (0.6-1.5-cm)
Patient 4 72 years 2 FDR	1.4 cm non-communicating cyst Diagnosis: BD-IPMN	15 cysts (0.5-1.6 cm largest communicating), multiple dilated branch ducts Diagnosis: BD-IPMN	4 cysts (range 0.6 -1.8 cm, largest communicating), multiple dilated branch ducts Diagnosis: BD-IPMN	Distal pancreatectomy: BD-IPMN (1.9 cm, tail) with MGD, incipient IPMN + multifocal PanIN (highest grade 2)
Patient 5 61 years 1 FDR, 1SDR, BRCA2 FBOC	No lesion detected Diagnosis: normal pancreas	No lesion detected Diagnosis: normal pancreas	0.5 cm non-septated communicating cyst (enlarged on follow-up to 0.9 cm) Diagnosis: BD-IPMN	Distal pancreatectomy: Incipient IPMN* (0.9 cm, tail) with LGD + multifocal PanIN (highest grade 2)

• FDR = first degree relative

• SDR= second degree relative

• MD-IPMN = main duct intraductal papillary mucinous neoplasm

• BD-IPMN = branch duct intraductal papillary mucinous neoplasm

• HGD = high grade dysplasia

• MGD = moderate grade dysplasia

• LGD = low grade dysplasia

• FBOC= familial breast ovarian cancer syndrome

* incipient IPMN = pancreatic ductal neoplastic lesions with long finger-like papillae and extensive extracellular mucin