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Imaging, Diagnosis, Prognosis

Clinical Cancer Research

Pancreatic Cancer Screening in a Prospective Cohort of High-Risk Patients: A Comprehensive Strategy of Imaging and Genetics

Elizabeth C. Verna[1], Caroline Hwang[1], Peter D. Stevens[1], Heidrun Rotterdam[3], Stavros N. Stavropoulos[1], Carolyn D. Sy[1], Martin A. Prince[4], Wendy K. Chung[5], Robert L. Fine[6], John A. Chabot[2], and Harold Frucht[1]

Abstract

Purpose: Pancreatic cancer is a virtually uniformly fatal disease. We aimed to determine if screening to identify curable neoplasms is effective when offered to patients at high risk.

Experimental Design: Patients at high risk of pancreatic cancer were prospectively enrolled into a screening program. Endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and genetic testing were offered by a multidisciplinary team according to each patient's risk.

Results: Fifty-one patients in 43 families were enrolled, with mean age of 52 years, 35% of whom were male. Of these patients, 31 underwent EUS and 33 MRI. EUS revealed two patients with pancreatic cancer (one resectable, one metastatic), five with intraductal papillary mucinous neoplasms (IPMN), seven with cysts, and six with parenchymal changes. Five had pancreatic surgery (one total pancreatectomy for pancreatic cancer, three distal and one central pancreatectomy for pancreatic intraepithelial neoplasia 2 and IPMN). A total of 24 (47%) had genetic testing (19 for *BRCA1/2* mutations, 4 for *CDKN2A*, 1 for *MLH1/MSH2*) and 7 were positive for *BRCA1/2* mutations. Four extrapancreatic neoplasms were found: two ovarian cancers on prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy, one carcinoid, and one papillary thyroid carcinoma. Overall, 6 (12%) of the 51 patients had neoplastic lesions in the pancreas and 9 (18%) had neoplasms in any location. All were on the initial round of screening. All patients remain alive and without complications of screening.

Conclusions: Pancreatic cancer screening for high-risk patients with a comprehensive strategy of imaging and genetics is effective and identifies curable neoplasms that can be resected. Ongoing study will better define who will benefit from screening and what screening strategy will be the most effective. *Clin Cancer Res; 16(20); 5028–37. ©2010 AACR.*

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in most western countries (1). In 2009, there were approximately 42,470 new cases of pancreatic cancer diagnosed in the United States, and 35,240 cancer-related deaths (2). Due to the rapid progression and almost uniform fatality of the disease, early detection through screening will be essential to improve outcomes. As premalignant stages of disease, including pancreatic intraepithelial neoplasia (PanIN; refs. 3, 4) and intraductal papillary mucinous neoplasms (IPMN; refs. 5–7), have been identified, and the sensitivity of pancreatic imaging has improved with endoscopic ultrasound (EUS) and high-resolution magnetic resonance imaging (MRI), early detection of small curable pancreatic cancers and premalignant lesions now seems possible. It has been shown that early-stage pancreatic cancer may be resected for cure, as evidenced by a series from Japan where 100% of patients were cured when the pancreatic cancer was <1 cm (8). Unfortunately, no current screening strategy is adequately safe, sensitive, and cost effective to be implemented in the general population, even in those with significant risk factors such as tobacco exposure or advanced age.

Pancreatic cancer screening, however, is under investigation in individuals with the highest risk of pancreatic cancer due to a hereditary predisposition (9–14). About 3% to 16% of pancreatic cancer is thought to be either syndromic or familial (15–22), due to multiorgan cancer syndromes, other genetically driven chronic diseases, or familial groupings of pancreatic cancer with yet unidentified genetic abnormalities (familial pancreatic cancer; ref. 23). The cancer syndromes known to increase the risk

Authors' Affiliations: [1]Division of Digestive and Liver Diseases, Department of Medicine, and [2]Department of Surgery, Muzzi Mirza Pancreatic Cancer Prevention and Genetics Program, Departments of [3]Pathology, [4]Radiology, and [5]Pediatrics and Molecular Genetics, and [6]Division of Hematology and Oncology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York

Corresponding Author: Harold Frucht, Columbia University College of Physicians & Surgeons, New York-Presbyterian Hospital, 622 West 168th Street, Box 83, New York, NY 10032-3784. Phone: 212-305-9337; E-mail: hf2011@columbia.edu.

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Translational Relevance

This article shows the efficacy of cancer screening in individuals assessed to be at high risk for pancreas cancer. Patients underwent genetic testing, imaging, and pancreas lesion resection as appropriate. This comprehensive strategy of imaging and genetic evaluation resulted in the identification of preneoplastic pancreas lesions, as well as pancreas and extrapancreatic cancers that could be resected. The study is an incremental contribution to the growing and important field of pancreas cancer risk evaluation and screening. Ongoing research will better define genetic and environmental risk factors for pancreas cancer, and improve risk stratification and identification of at-risk individuals. It will also allow us to better understand which testing modalities are most useful, and at what frequency.

of pancreatic cancer include Peutz-Jeghers syndrome (PJS; ~132- fold increased risk; ref. 24), familial atypical multiple mole melanoma (FAMMM; ~9- to 22-fold increased risk; refs. 25–28), hereditary nonpolyposis colorectal cancer (HNPCC; up to 8.6-fold increased risk; refs. 29–31), and familial breast-ovarian cancer (*BRCA1* mutations with a ~2-fold increased risk and *BRCA2* mutations with ~5% lifetime risk; refs. 32–36). Other high-risk genetic diseases that increase the risk of pancreatic cancer include most prominently hereditary pancreatitis, with a 40% cumulative lifetime risk of pancreatic cancer (37, 38). Finally, familial pancreatic cancer includes groups of patients with a strong family history of pancreatic cancer but without an identified genetic syndrome. Although the definition of familial pancreatic cancer is debated, it is generally defined as at least two first-degree relatives with pancreatic cancer, without meeting criteria for one of the above syndromes. The National Familial Pancreas Tumor Registry at Johns Hopkins University showed a 4.6-, 6.4-, and 32-fold increased risk of pancreatic cancer in individuals with 1, 2, and ≥3 affected first-degree relatives, respectively (although the increased risk in those with one first-degree relative was not statistically significant; ref. 39). Careful study of these patients has led to the discovery of candidate pancreatic cancer susceptibility genes, for example the partner and localizer of *BRCA2* (*PALB2*) gene that encodes a protein that colocalizes with and stabilizes the BRCA2 protein (40–42). The *Palladin* gene that encodes a cytoskeletal protein and is prevalent in one well-characterized high-risk family was also thought to be a pancreatic cancer susceptibility gene (43, 44). It has recently been found to be overexpressed in tumor-associated fibroblasts and may play a role in pancreatic cancer tumor microenvironment and metastatic potential (45). *Palladin* may therefore be useful as a biomarker for early pancreatic cancer.

In general, screening programs involve multidisciplinary teams of specialists and a combination of imaging techniques, usually with a focus on EUS (9–14, 46, 47). However, data are preliminary and there is no widely accepted screening protocol. Consensus practice recommendations (9), based largely upon expert opinion, suggest a threshold of a >10-fold increased risk of developing pancreatic cancer to select individuals who may benefit from screening, but this threshold is not validated and excludes patients at significant risk (5- to 10-fold increased). Outcomes and cost-effectiveness analyses are also not currently possible given the lack of uniform screening practices. Although genetic counseling and testing have been recommended as part of the care of select patients (9), there is little information published on the impact of genetic testing in these patients.

We therefore developed a high-risk pancreatic cancer screening program at our multidisciplinary pancreas center starting in 2005 and enrolled all patients with a family history of pancreatic cancer who were interested in screening. All patients were risk-stratified into high-, moderate-, and average-risk groups based on family history, and screened with imaging and genetic testing when appropriate. We herein report our initial experience.

Materials and Methods

Patients and protocol

All patients who were referred to the Pancreas Cancer Prevention and Genetics Program at Columbia University Medical Center/NewYork Presbyterian Hospital with a family history of pancreatic cancer and interest in their risk of disease were offered enrollment in this prospective cohort. The protocol included a detailed history and physical exam, collection of family history by a genetic counselor, a personal and family health history questionnaire completed by the patient, results of all imaging and blood testing, and storage of frozen serum and any surgically resected tissue. Blood was processed for DNA extraction and EBV immortalization. This protocol was approved by the Columbia University Medical Center Institutional Review Board and all participants provided informed consent.

Screening

This study focuses on the yield of initial screening exams for the patients in this cohort, and does not include the results of surveillance exams. Upon presentation, patients were assessed for their level of risk based upon the number of family members affected and age of onset, and whether the family history was suggestive of a known genetic cancer syndrome (Fig. 1). Patients were classified as average risk if they had only one family member affected at an age >55 years. These patients were generally not recommended for screening, but some patients were tested if significant psychological stress led them to prefer to be screened. Patients were classified as moderate risk if they had more than one family member with pancreatic cancer or one first-degree family member with the onset of disease at <55 years of age, but did not meet the

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criteria for high-risk classification. Depending on their age relative to the youngest affected family member, these patients were offered MRI or EUS of the pancreas as well as an oral glucose tolerance test (OGTT) and serum cancer antigen 19-9 (CA 19-9). The high-risk patients were classified based upon a family history and/or genetic testing consistent with one of the genetic cancer syndromes (PJS, HNPCC, BRCA1/2, FAMMM, hereditary pancreatitis) or who met our definition of familial pancreatic cancer (any three affected relatives, two first-degree relatives with pancreatic cancer, or one first-degree and at least one second-degree relative, one with onset at age <55). *BRCA1/2* mutation carriers were placed in this group if they had at least one first- or second-degree relative with pancreatic cancer. These patients were offered EUS and MRI, as well as the OGTT and CA 19-9 testing.

Genetic testing

Genetic testing was recommended at the discretion of the clinician and genetic counselor. The approach was to first test the youngest affected family member available, or the proband if the proband had a personal history of cancer. An exception to this approach was made in the case of suspected *BRCA1/2* mutations in patients of Ashkenazi Jewish descent. In this group, patients interested in *BRCA1/2* testing were offered multisite *BRCA* testing, even if they themselves did not have a personal history of cancer. Genetic testing for *BRCA* (BRCAnalysis

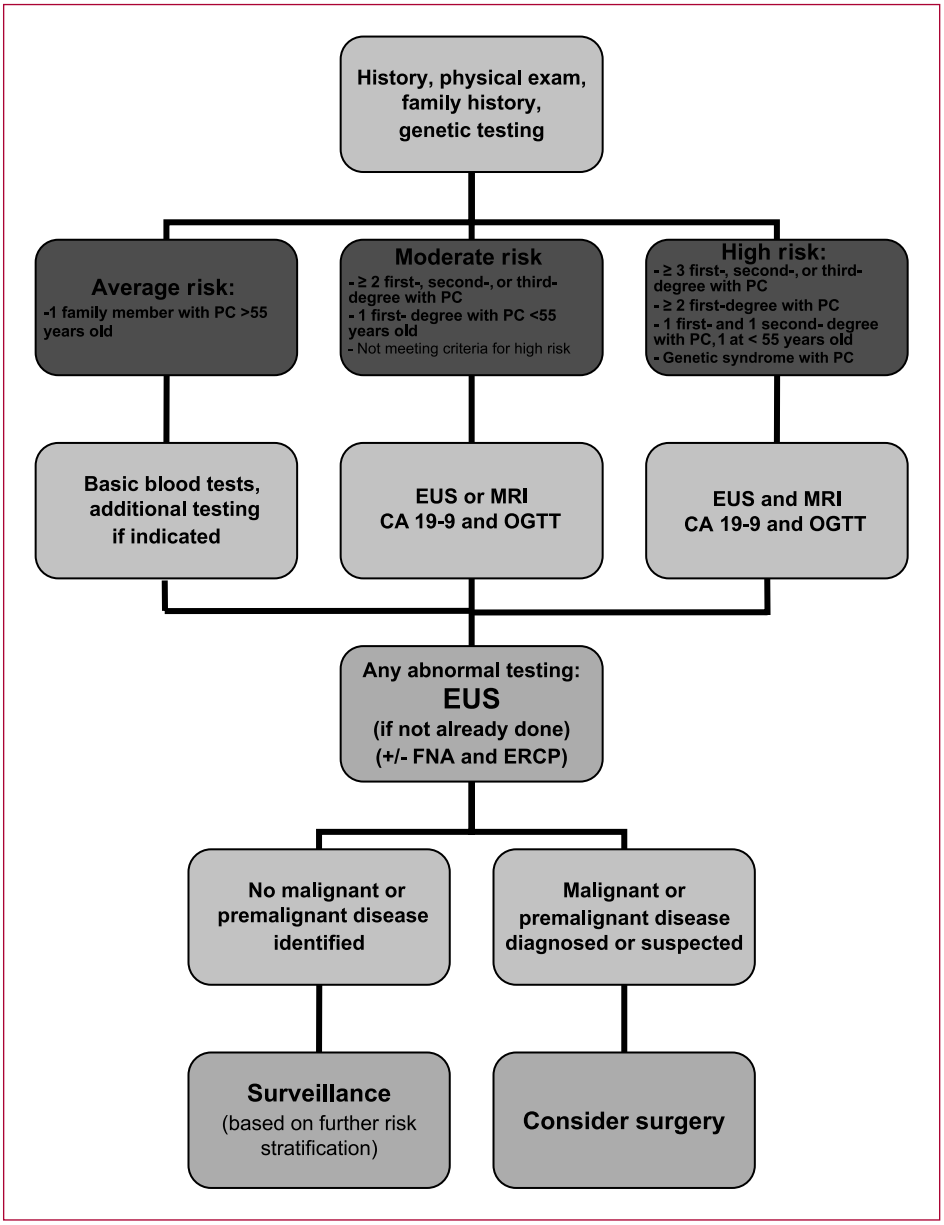

Fig. 1. Pancreatic cancer screening general algorithm used in this cohort. PC, pancreatic cancer.

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or Multisite 3 BRCAnalysis), HNPCC (Comprehensive Colaris), and *CDKN2A* (Comprehensive Melaris) were commercially done through Myriad Genetic Laboratories (Salt Lake City, UT). Genetic counseling before and after testing was provided by a genetic counselor or clinician with specific expertise in pancreatic cancer genetics, and informed consent was obtained. Patients who tested positive for a germline mutation underwent multiorgan cancer screening as appropriate. In the case of documented *BRCA1/2* mutations, prophylactic mastectomy and oophorectomy, chemoprevention, and enhanced screening were discussed.

Pancreatic imaging

EUS. Standard upper endoscopy was done, followed by EUS imaging with a curvilinear echoendoscope and processor (GFUC140P and SSD-Alpha 5, Olympus Corporation). Abnormalities of interest included mass lesions, IPMNs, cysts, and chronic pancreatitis-like parenchymal changes. Fine needle aspiration (FNA) under EUS guidance was done with a linear array echoendoscope when mass lesions, cysts, or suspicious lymph nodes were encountered. In general, FNA specimens were evaluated for abnormal cells by an onsite cytopathologist, and the fluid removed from cyst aspiration was sent for carcinoembryonic antigen (CEA) and amylase. Endoscopic retrograde cholangiopancreatography (ERCP) was done at the discretion of the interventional endoscopist, generally when ductal irregularities or changes consistent with IPMN required additional assessment.

MRI and magnetic resonance cholangiopancreatography. All MRI images were obtained at 1.5 Tesla (GE HD EXCITE 14.0 m4) using a body coil for signal transmission and an 8-channel body array coil for reception. Abdominal organs were localized on T2-weighted single-shot fast spin echo images obtained in three cardinal planes. The pancreatic duct was imaged on a 40-mm-thick slab single-shot fast spin echo sequence positioned to cover the pancreatic duct in the coronal-oblique plane using an echo time = 900 ms and also on a three-dimensional magnetic resonance cholangiopancreatography (MRCP) including the entire pancreas and duodenum. Detailed images of pancreatic architecture, liver, and abdominal vasculature were obtained using dynamic three-dimensional liver accelerated volume acquisition (LAVA) before, during, and following injection of 20 mL of gadodiamide or gadobenate dimeglumine contrast in individuals with glomerular filtration rate >30 mL/minute as estimated from serum creatinine. Images were analyzed by a radiologist experienced in pancreatic imaging, but blinded to the patient's pancreatic cancer risk factors.

Follow-up

After completion of the first series of genetic, radiologic, and blood testing, patients were discussed at a weekly multidisciplinary Pancreas Center conference attended by surgeons, gastroenterologists, oncologists, radiologists, and geneticists. All patients with any abnormal test who had not undergone EUS as part of the initial screening were recommended for EUS. The possibility of surgical intervention was discussed by the team for patients with abnormal EUS exams for neoplastic or preneoplastic lesions in patients with high or moderate risk of pancreatic cancer. Findings such as resectable mass lesions, a high suspicion for main-duct IPMN (IPMN-M), or abnormal cytology on FNA were among those considered for surgery. Patients who did not undergo surgery were again risk-stratified based upon history and testing, and entered surveillance. Patients thought to be at highest risk due to family history or imaging findings and who were within 10 years of the youngest onset of pancreatic cancer in their family, as well as patients who underwent partial pancreatectomies, were then screened every six months with alternating MRI and EUS. Patients at moderate risk underwent annual imaging, and those at average risk returned for annual visits and further testing if they developed symptoms or new onset diabetes mellitus. The results of surveillance exams are not included in this article.

Results

Patients

Fifty-one patients from 43 unique families were enrolled and underwent initial screening from 2005 to 2008. The mean age at presentation was 52 years (range, 29-77), 35% were male, 35% had some previous tobacco exposure, and 6% reported previous heavy alcohol use (Table 1). The majority (90%) were non-Hispanic white and 25 (49%) patients were of Ashkenazi Jewish ancestry. Fifteen patients (29%) had a personal history of cancer other than pancreatic cancer (Table 1), most commonly breast cancer (14% of the cohort).

Family history and risk stratification

Fifteen (29%) patients had at least two first-degree relatives with pancreatic cancer and 35 (69%) had at least two first-, second-, or third-degree relatives with pancreatic cancer (Table 2). Thirty-one (61%) patients had two or more first-, second-, or third-degree relatives with a nonpancreatic cancer. Breast cancer was the most common extrapancreatic cancer (35% of patients), followed by prostate cancer, lung cancer, and melanoma (Table 2).

All patients evaluated were risk-stratified into average, moderate, or high risk of pancreatic cancer, based on the criteria developed for this cohort (Fig. 1). Thirty-two (63%) patients were classified as high risk, 14 (27%) as moderate risk, and 5 (10%) as average risk (Table 2).

Genetic testing

Twenty-one patients (41%) consented to genetic testing (Table 3): 16 for *BRCA1/2* mutations, 1 for *CDKN2A* mutations (for FAMMM syndrome), 3 for both *BRCA1/2* and *CDKN2A* mutations, and 1 for *MLH1/MSH2* (for HNPCC, the patient opted not to have testing for *MSH6*). Of those patients tested, seven were positive for *BRCA1/2* mutations (one in comprehensive testing and six with multisite testing).

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Table 1. Patient characteristics

Number of patients	51
Number of unique families	43
Mean age (SD), years	52 (12.3)
Male gender (%)	18 (35)
Race and ethnicity (%)	
Non-Hispanic white	46 (90)
Hispanic white	3 (6)
Black	1 (2)
Native American	1 (2)
Ashkenazi Jewish ancestry	25 (49)
Ever smoked (%)	17 (35)
Alcohol use (%)	
Previous heavy use	3 (6)
Social or occasional use	39 (76)
No use	9 (18)
Type 2 diabetes mellitus (%)	2 (4)
Number of patients with a personal history of nonpancreatic cancer (%)	15 (29)
Breast cancer	7
Malignant melanoma	4
Cervical cancer	1
Endometrial cancer	1
Lung cancer	1
Squamous cell carcinoma of the face	1
Lymphoma	1

Of the seven patients with *BRCA1/2* mutations, one had resectable pancreatic cancer on initial screening. Two patients with *BRCA1/2* mutations and personal histories of breast cancer underwent prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). The pathology of both of these patients was abnormal, one with ovarian papillary serous adenocarcinoma (*BRCA1*) and one with tubal intraepithelial carcinoma (*BRCA2*).

Pancreatic cancer screening

Of the 51 patients in the protocol, 31 (61%) underwent EUS and 33 (65%) underwent MRI-MRCP (Table 4). Of the 10 patients who had neither EUS nor MRI, two were in the average-risk category and were not tested. Of the three high-risk patients who did not have testing, two were very young at enrollment (>10 years younger than their youngest affected family member) and one is currently in therapy for breast and ovarian cancers and deferred further screening. Five of the moderate-risk patients did not have any imaging, four due to patient preference and one due to young age compared with affected family members.

The most common abnormal findings on EUS were parenchymal changes seen in chronic pancreatitis (hyperechoic foci, echogenic strands, lobularity, cysts, hyperechoic duct margins, dilated pancreatic duct, duct irregularity, visible side branches and stones). Of the 31 patients who underwent EUS, 6 (19%) had at least three of these changes, whereas 3 (10%) had at least five of these changes (Table 4). Two patients (both high risk) had mass lesions on EUS, each with adenocarcinoma on FNA (one metastatic to the liver and treated with systemic chemotherapy, the other localized and resected). FNA was also done on one patient with abnormal-appearing parenchyma (nondiagnostic) and three patients with cystic lesions (all nondiagnostic on cytology, one with a CEA of 1,169 units/mL). ERCP was done in seven patients, two of which confirmed changes consistent with branch-duct IPMN (IPMN-B). No main-duct IPMN-M lesions were found and all IPMN-B lesions were <3 cm in greatest diameter. MRI was done in 33 (65%) of the cohort, and was normal in 22 of 33 (67%; Table 4). The two masses seen on EUS were also observed on MRI. No procedural complications were encountered during the screening process.

Pancreatic surgical procedures and pathologic diagnoses

Six patients had pancreas pathology by resection or FNA available for review (Table 5). One high-risk patient had stage IV metastatic adenocarcinoma with three liver lesions at the time of presentation and underwent palliative chemotherapy. This patient had one first-degree relative with pancreatic cancer at the age of 53 and one affected second-degree relative. One high-risk patient was also diagnosed with resectable pancreatic cancer when a mass was seen on EUS, and FNA was diagnostic for adenocarcinoma. This patient underwent a total pancreatectomy, revealing a 2-cm moderately differentiated adenocarcinoma arising from IPMN-M. He had a *BRCA2* mutation and two first-degree relatives with pancreatic cancer, the youngest at 46 years of age.

Four other patients had partial pancreatectomies (three distal and one central; Table 5). All four of these had IPMN-B with moderate dysplasia and multifocal PanIN2 lesions on pathology. None had definitive PanIN3 or "carcinoma *in situ*." Therefore, a total of 12% of the 51 patients in this cohort (10% of high-risk and 14% of the moderate-risk patients) were found to have malignant or possibly premalignant lesions of the pancreas on pathology. All of these patients are alive and all but the patient with stage IV adenocarcinoma are in surveillance without additional pathology identified.

Nonpancreatic pathology

The testing done for the purposes of this protocol to screen for pancreatic cancer also revealed lesions arising from organs other than the pancreas (Table 5). One patient had a retroperitoneal carcinoid seen on MRI, which was resected. One patient had an elevated CA 19-9 on study enrollment, and a cyst in the pancreas with an elevated CEA on fluid aspiration. This patient underwent central pancreatectomy but no pancreatic cancer was identified and the CA 19-9 remained elevated (Table 5). A positron emission tomography scan then revealed increased uptake in a thyroid nodule, which led to the

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diagnosis of papillary carcinoma of the thyroid. The patient underwent partial thyroidectomy, which confirmed this pathology. In addition, as mentioned above, two *BRCA1/2*-positive patients underwent prophylactic TAH-BSO, each revealing early cancers on pathology: one tubal intraepithelial carcinoma (*BRCA2*) and one ovarian papillary serous adenocarcinoma (*BRCA1*). Both are without evidence of metastatic disease at follow-up.

Therefore, a total of 10 preneoplastic or neoplastic lesions (pancreatic and extrapancreatic) were discovered in 9 (18%) patients through this pancreatic cancer screening program, each treated with curative intent except for one case of metastatic pancreatic cancer.

Discussion

We describe the results of initial screening exams in a prospective cohort of patients with a family history of pancreatic cancer. Overall, 12% of our patients were diagnosed with malignant or premalignant disease of the pancreas, and 18% were diagnosed with malignant or premalignant diseases of any organ. All patients who

Table 2. Family cancer risk profile for the patients in our cohort

Median youngest age (range) of PC onset in family, years	61 (30-82)
Number of patients with:	
≥3 first-degree relatives with PC	3
2 first-degree relatives with PC	12
1 first-degree relative with PC	29
0 first-degree relatives with PC	7
Number of patients with:	
≥3 first-, second-, and third-degree relatives with PC	13
2 first-, second-, and third-degree relatives with PC	22
1 first-, second-, and third-degree relative with PC	16
Number of patients with:	
≥5 first-, second-, and third-degree relatives with non-PC	8
4 first-, second-, and third-degree relatives with non-PC	8
3 first-, second-, and third-degree relatives with non-PC	4
2 first-, second-, and third-degree relatives with non-PC	11
1 first-, second-, and third-degree relative with non-PC	16
0 first-, second-, and third-degree relatives with non-PC	4
Number of patients with first- or second-degree relatives with:	
Breast cancer	18
Prostate cancer	10
Lung cancer	8
Malignant melanoma	6
Ovarian cancer	5
Endometrial cancer	5
Colon cancer	5
Gastric cancer	4
Head and neck cancers	4
Glioblastoma	3
Hepatocellular carcinoma	1
Cervical cancer	1
Number of patients with family history suggestive of:*	
Familial pancreatic cancer	34
BRCA1/2	17
HNPCC	3
FAMMM	3
Risk category, number (%)	
High risk	32 (63)
Moderate risk	14 (27)
Average risk	5 (10)

Abbreviation: PC, pancreatic cancer.
*Some patients had family histories suggestive of more than one syndrome.

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Table 3. Genetic testing done

Suspected cancer syndrome	Gene tested	Positive tests (%)*
BRCA1/2	*BRCA1/2*	7/19 (37)
FAMMM	*CDKN2A*	0/4 (0)
HNPCC	*MLH1/MSH2*	0/1 (0)

*Three patients were tested for both *BRCA1/2* and *CDKN2A*.

underwent pancreas surgery were in the moderate- or high-risk groups, and all had pathologic changes that correlated with imaging findings. No patient suffered significant complications of the screening process or surgical interventions.

Pancreas cancer has the poorest survival of any common solid malignancy, and presentation with advanced disease due to a lack of early symptoms or screening remains a major impediment to successful treatment. Although pancreatic cancer screening at a population level remains impractical at this time, screening of individuals at high risk of pancreatic cancer has begun at several centers (9–14, 46). Our series confirms data from these other cohorts that malignant and premalignant lesions can be identified through screening EUS and pancreas surgery may be undertaken with the goal of preventing disease progression.

The major limitation of our protocol is that it remains an observational cohort and not a controlled trial. Therefore, comparisons of imaging findings between these patients and those without known elevated risk of pancreatic cancer are not possible. We believe that it remains unknown what type of patient would represent an adequate control in this setting, and we did not expand enrollment for patients undergoing pancreatic EUS or genetic testing for other reasons. Our protocol also recruited patients more broadly than many others in the literature. For this reason, we also used a cutoff of 55 years at age of onset in affected family members to identify patients at risk. The consensus guidelines were not published at the time of study design, and

Table 4. Diagnostic findings in the pancreas for those patients who underwent imaging

	Overall (*n* = 51)	Average risk (*n* = 5)	Moderate risk (*n* = 14)	High risk (*n* = 32)
EUS	31 (61%)	2 (40%)	5 (36%)	24 (75%)
Normal*	4	0	1	3
Changes of chronic pancreatitis†				
≥3 of the 9 findings	6	1	0	5
≥5 of the 9 findings	3	0	0	3
IPMN-B	5	0	2	3
Other cysts	7	0	4	3
Solid mass lesion	2	0	0	2
FNA	6 (18%)	0 (0%)	3 (21%)	3 (9%)
Of mass or parenchyma	3	0	0	3
Of cysts or IPMN lesions	3	0	3	0
ERCP	7 (14%)	1 (20%)	1 (7%)	5 (16%)
Normal	4	0	1	3
IPMN-B	2	1	0	1
PD irregularities	2	1	0	1
MRI/MRCP	33 (65%)	3 (60%)	7 (50%)	23 (72%)
Normal	22	2	4	16
IPMN	1	0	1	0
Other cysts	6	0	2	4
Solid mass lesion	3	1	0	2
Isolated PD irregularities	1	0	0	1
No EUS or MRI	10 (20%)	2 (40%)	5 (36%)	3 (9%)
Pancreas surgery	5 (10%)	0 (0%)	2 (14%)	3 (10%)

Abbreviation: PD, pancreatic duct.

*Normal examinations included those with no abnormalities as well as those with only age-related changes such as mild atrophy or fatty infiltration.

†The changes associated with chronic pancreatitis include hyperechoic foci, hyperechoic strands, lobularity, cysts, hyperechoic duct margins, dilated pancreatic duct, duct irregularity, visible side branches, and stones.

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Table 5. Pathologic diagnoses rendered

Location	Age	Risk category	Indication	Procedure	Pathologic diagnosis
Pancreas	58	High	Mass in the HOP with liver lesions on EUS/MRI	FNA	Stage IV PC
	61	High	2 cm mass in HOP on EUS	Total pancreatectomy	PC with adjacent IPMN and multifocal PanIN2
	47	High	IPMN-B, irregular PD on EUS/ERCP	Distal pancreatectomy	IPMN-B with moderate dysplasia and multifocal PanIN2
	56	High	IPMN-B on EUS/ERCP		
	40	Moderate	IPMN-B on EUS/MRI		
	45*	Moderate	1 cm cyst BOP with elevated cyst fluid CEA (1,169) on EUS	Central pancreatectomy	Cyst remnant, IPMN-B with moderate dysplasia, focal PanIN2
Ovary	52	High	Prophylactic, *BRCA1/2* positive and personal history of breast cancer	TAH-BSO	Tubal intraepithelial carcinoma
	60	High			Ovarian papillary serous adenocarcinoma
Retroperitoneal	43	High	Retroperitoneal mass on MRI	Resection	Carcinoid
Thyroid	45*	Moderate	PET thyroid uptake, FNA papillary carcinoma	Thyroidectomy	Papillary thyroid carcinoma

Abbreviations: HOP, head of pancreas; BOP, body of pancreas; PET, positron emission tomography.
*One patient had both pancreas and thyroid surgery.

as little is known about the pancreatic cancer risk in patients with a family history but without a known germline mutation, we were less stringent than other centers in the criteria needed to enter this cohort. Our strategy was to subsequently risk-stratify each participant with the criteria above, most of which are in line with the criteria for low, moderate, and high risk from the consensus conference (9). Our testing recommendations were based upon this risk stratification, with more invasive and frequent testing done in the patients at the highest risk. It is possible, however, that our rate of pancreatic pathology and germline mutations was diluted by our average and moderate risk patients. Although the two adenocarcinomas seen were in the high-risk group, it is interesting to note that a similar percentage of patients in the moderate-risk group went to surgery with preneoplastic lesions.

We stressed a multidisciplinary approach for these patients to ensure that patients and their families were evaluated for patterns of multiorgan cancer syndromes and were educated on testing. Genetic testing was used as an adjunct to imaging, and revealed *BRCA1/2* germline mutations in seven patients, two of whom underwent prophylactic salpingo-oopherectomy with early ovarian malignancies. We believe this comprehensive approach is essential to any screening program as these syndromes are associated with cancers outside the pancreas. It is likely that given our predominantly non-Hispanic white population with a high proportion of individuals of Ashkenazi Jewish decent, we detected a higher proportion of *BRCA1/2* mutations than will be seen in other populations, possibly limiting the generalizability of this finding.

Our cohort underwent screening with a combination of EUS and MRI imaging. It is unknown whether EUS or MRI is the best initial screening modality, or even whether radial or linear echoendoscopes are superior (47). EUS offers high sensitivity and the possibility of tissue sampling, and is therefore central to pancreatic cancer screening in most centers. The relevance of subtle EUS parenchymal findings (such as those seen in chronic pancreatitis), however, is unknown. Although some authors propose that they can correlate these parenchymal abnormalities with PanIN lesions on pathology (48), these data must be carefully assessed, and no patients in this cohort went to surgery for these findings alone. MRI has not been as widely reported in other cohorts, but permits the identification of lesions outside the purview of EUS without the radiation exposure associated with computed tomography. In this cohort, all solid and cystic lesions that went to surgery were seen on both MRI and EUS. In addition, one retroperitoneal carcinoid was seen on MRI, and given the multiorgan cancer susceptibilities in many of these syndromes, cross-sectional imaging may play an important role.

The significance of each imaging finding and the natural history of many pathologic lesions (such as IPMN and PanIN) are also not known. Therefore, there is an important and significant risk of overdiagnosis and overtreatment in people who undergo pancreatic cancer screening.

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Indeed, several patients in published cohorts have gone to surgery with benign findings on pathology and none of the patients in our cohort who had partial pancreatectomies had high-grade dysplasia associated with their PanIN or IPMN lesions. In addition, pancreas surgery (unlike polypectomy in colorectal cancer screening) carries significant risk of morbidity and mortality, and at least one patient cited in the literature has died as the result of prophylactic pancreas surgery (47). Therefore, although it is accepted that mass lesions found in patients at high risk should be resected when possible, the optimal management of other lesions is unknown. The natural history of IPMN remains poorly defined. The categorization is evolving, the preoperative diagnosis is often incorrect, and the management continues to be controversial. The incidence of invasive cancer in IPMN lesions is approximately 11% for IPMN-B, compared with 48% for IPMN-M, with a 5-year survival >50% for both (49). Although prognosis and survival can be affected by the number of involved lymph nodes, and familial predisposition, this is also poorly understood. Those with IPMN-M perhaps should be considered for resection given the higher malignant potential, but IPMN-B lesions that were more common in our cohort are generally managed conservatively. In the early experience with these patients, some centers did laparoscopic distal pancreatectomies to further risk-stratify these patients, and in patients with multifocal high-grade dysplasia, total pancreatectomy was considered. As the genetic susceptibility likely confers a risk throughout the entire pancreas, or a "field effect," it was thought that the abnormalities in the distal pancreatectomy specimen likely reflect changes seen throughout the entire gland. This approach is no longer widely used, and in our cohort, none of the patients who underwent distal pancreatectomy had surgery for this reason (all were done to evaluate focal abnormalities). In those patients who go to surgery for focal lesions, it is possible that multifocal PanIN lesions seen on pathology have prognostic implications for the unresected pancreas (50), and all of these patients are in surveillance.

Pancreatic cancer remains an important, deadly disease. Although premalignant lesions such as IPMN and PanIN have been characterized, efficient screening and resection of high-risk lesions is currently not possible. Although screening in the general population is therefore not feasible, it may benefit patients with the highest risk. As there is not yet, and may not be an autosomal dominant gene mutation identified for familial pancreatic cancer, this population should clinically be approached as having a multigenic predisposition. A comprehensive, multidisciplinary approach that combines imaging with genetic risk assessment should be stressed. Given the limited data available, however, screening should occur in experienced centers with prospective cohorts whenever possible.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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