Original Research

Endoscopic Ultrasound

OPEN

New-onset diabetes is a predictive risk factor for pancreatic lesions in high-risk individuals: An observational cohort study

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ABSTRACT

Background and Objectives: Pancreatic cancer (PC) is the third cause of cancer-related deaths. Early detection and interception of premalignant pancreatic lesions represent a promising strategy to improve outcomes. We evaluated risk factors of focal pancreatic lesions (FPLs) in asymptomatic individuals at hereditary high risk for PC.

Methods: This is an observational single-institution cohort study conducted over a period of 5 years. Surveillance was performed through imaging studies (EUS or magnetic resonance imaging/magnetic resonance cholangiopancreatography) and serum biomarkers. We collected demographic characteristics and used univariate and multivariate logistic regression models to evaluate associations between potential risk factors and odd ratios (ORs) for FPL development.

Results: A total of 205 patients completed baseline screening. Patients were followed up to 53 months. We detected FPL in 37 patients (18%) at baseline; 2 patients had lesions progression during follow-up period, 1 of them to PC. Furthermore, 13 patients developed new FPLs during the follow-up period. Univariate and multivariate analyses revealed that new-onset diabetes (NOD) is strongly associated with the presence of FPL (OR, 10.94 [95% confidence interval, 3.01–51.79; $P < 0.001$]; OR, 9.98 [95% confidence interval, 2.15–46.33; $P = 0.003$]). Follow-up data analysis revealed that NOD is also predictive of lesions progression or development of new lesions during screening (26.7% *vs.* 2.6%; $P = 0.005$).

Conclusions: In a PC high-risk cohort, NOD is significantly associated with presence of FPL at baseline and predictive of lesions progression or new lesions during surveillance.

Key words: Early detection; New-onset diabetes; Focal pancreatic lesions; Germline mutations; EUS; MRI/MRCP

INTRODUCTION

Pancreatic cancer (PC) is one of the most lethal solid malignancies. According to the National Cancer Institute, the estimated number of new PC cases in 2022 is 62,210, with 49,830 predicted deaths.[1] Most PC patients present with local invasion or metastatic disease at diagnosis. Only 11% of the cases are diagnosed in the localized stage, for which the 5-year survival rate is 39%. When all stages are considered, only 10% of patients with PC survive for 5 years or longer from the date of diagnosis.[2,3]

Previous studies suggest a window of opportunity for early detection of PC. A period greater than 10 years is estimated from tumor initiation to acquisition of metastatic capacity.[4] Current screening strategies have many challenges in effectively detecting PC at early stages because of limitations of imaging and serum biomarkers.[5–7] Recent studies have reported an overall survival benefit of routine surveillance in patients diagnosed with PC during active surveillance

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Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Web site (www.eusjournal.com).

Endoscopic Ultrasound (2024) 13:2

Received: 1 June 2023; **Accepted**: 13 December 2023.

Published online: 10 April 2024

http://dx.doi.org/10.1097/eus.0000000000000057

versus those individuals who were lost to surveillance (85% *vs.* 25% survival at 3 years; $P < 0.0001$).[8]

This article reports the observations of the first 5 years of screening from a high-risk cohort followed at MD Anderson Cancer Center. We aimed to identify factors associated with focal pancreatic lesion (FPL) at baseline and predict the development of new lesions during follow-up with the goal of finding biomarkers to guide future screening strategies.

MATERIALS AND METHODS

Patient selection and enrollment

Asymptomatic adults (>18 years old) have been enrolled into a pancreatic cancer high risk cohort since January 2015. This study was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board. The following 2 categories of patients were considered to have hereditary high risk and were therefore eligible for screening: (1) patients with 2 first-degree relatives with PC or 1 first-degree relative plus 1 second-degree relative with PC on the same side of the family, and (2) patients with germline mutations in genes associated with higher susceptibility for PC (*BRCA1*, *BRCA2*, *PALB2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *ATM*, *TP53*, *CDKN2A*, *APC*, *STK11*, and *PRSS1*), many of whom also had relatives affected with PC.

Screening procedures

A multidisciplinary team agreed on the imaging methodology and follow-up timing based on each patient's initial imaging and laboratory testing results. The multidisciplinary team consisted of a gastrointestinal medical oncologist, a gastroenterologist, a gastrointestinal surgeon, and a magnetic resonance imaging (MRI) expert radiologist. The screening methods used were the following: (A) Laboratory testing: serum CA19-9, plasma fasting or random blood glucose levels, hemoglobin A_{1c} (HbA_{1c}), serum lipase, and amylase levels. (B) MRI/magnetic resonance cholangiopancreatography (MRCP): performed using a pancreas-dedicated protocol, including multiple-pulse sequences and T1 weighting combined with T2-weighted sequences. Intravenous gadolinium was used as a contrast agent, and MRCP reconstruction was performed. (C) EUS: performed using upper endoscopes (Olympus America, Center Valley, PA), linear array echoendoscopes (Olympus America), and ultrasound processors (Hitachi Aloka Medical, Wallingford, CT). At each screening, patients had either MRI/MRCP or EUS plus laboratory testing. Depending on testing results, patients were followed annually or every 6 months.

Data collection

Data variables collected included sex and race/ethnicity of the patients, history of smoking and alcohol use, history of chronic diabetes, new-onset diabetes (NOD within the first 3 years of their diabetes diagnosis.), history of pancreatitis, family history of cancer, personal history of cancer, presence of germline mutations, laboratory values, and imaging results at the first clinical visit (baseline) and during a 5-year follow-up period.

Description of pancreatic lesions detected during screening

Lesions were categorized as FPL or diffuse changes for improved characterization of the results. Two types of FPLs were included: solid and cystic lesions. Solid lesions were defined in the MRI/MRCP radiology report as areas of hypointensity relative to the regular pancreatic parenchyma on fat-suppressed T1-weighted pregadolinium and dynamic postcontrast T1-weighted imaging.[9,10] Cystic lesions were T1 hypointense and T2 bright and well defined on the radiology report. Diffuse changes in the pancreas are nonspecific changes such as lobularity, septations, dilated side branches, and heterogeneity of the parenchyma.

Statistical methods

We reported frequencies and percentages for categorical variables. Summary statistics, such as means, medians, SDs, and minimum and maximum values, were calculated for continuous data. χ^2 and Fisher exact tests were used to evaluate associations between the groups. Wilcoxon rank sum test was used to compare the distributions of continuous variables between 2 different groups. Univariate and multivariate logistic regression models were performed to identify any risk factors associated with FPL. The clinically and statistically important risk factors (age, alcohol consumption, NOD, PC family history, and presence of any germline mutation) were included in the models. Odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression models were calculated. Thirteen patients with unknown genetics data were excluded from the multivariate logistic analysis. *P* values less than 0.05 were considered significant. All statistical analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Patient demographics and characteristics

Two hundred five patients completed baseline screening with laboratory testing and imaging studies between January 2015 and January 2020. The median age of the participants was 52 years (27–81 years), and 161 patients (78.5%) were female. Most patients (78%) were White, 13.7% were Hispanic, 5.9% were African American, and 2.4% were Asian. The cohort included 73.7% never smokers, 21.9% former smokers, and 4.4% current smokers. Sixty-six percent of patients reported occasional alcohol intake, whereas 34% had no alcohol intake history. Fifty-six percent of the patients had a personal cancer history, 60.5% had a family history of PC, and 79% were carriers of a germline mutation. The most common germline mutation detected was *BRCA2* (42.9%), followed by *BRCA1* (8.8%) and *TP53* (8.8%) mutations. Eighty-two patients (40%) had a family history of PC in addition to carrying a germline mutation [Table 1]. Ninety-three patients completed at least 1 follow-up screening during the 5-year period (2015–2020). Demographic characteristics of the subgroup who had follow-up screening can also be found in Table 1.

Screening outcomes

From 205 patients eligible for analysis with baseline screening completed, 51 had findings on imaging studies: 37 patients (18%) with FPL and 14 patients (6.8%) with diffuse findings. Specifically, from the 37 patients with FPL, 33 had cystic lesions, and 4 had solid lesions (2%): 2 of them were diagnosed with a pancreatic neuroendocrine tumor, and 2 patients had fine-needle aspiration reporting no malignant cells content. The patients with cystic lesions included 27 (13.2%) with sub-cm cystic lesions with no malignant suspicious features, 5 patients (2.4%) with cystic lesions larger than 1 cm, and 1 patient (0.5%) with a serous cystadenoma [Figure 1].

Table 1

Demographic, medical and family history factors in PCHRC

Characteristics	Patients With Baseline Screening (*n* = 205)	Patients With Follow-Up Screening (*n* = 93)
Age, y		
Mean (SD)	52.88 (±12.4)	55.28 (±13.3)
Median (min–max)	52 (27–81)	56 (28–81)
Sex		
Female	161 (78.5%)	69 (74.2%)
Male	44 (21.5%)	24 (25.8%)
Race and ethnicity		
White	160 (78%)	75 (80.6%)
Hispanic	28 (13.7%)	11 (11.8%)
African American	12 (5.9%)	4 (4.3%)
Asian	5 (2.4%)	3 (3.3%)
Smoking		
Never	151 (73.7%)	75 (80.6%)
Past	45 (21.9%)	18 (19.4%)
Current	9 (4.4%)	—
Alcohol		
Nondrinker	70 (34%)	32 (34.4%)
Drinker	135 (66%)	61 (65.6%)
Personal history of cancer		
Yes	115 (56%)	55 (59.1%)
No	90 (44%)	38 (40.9%)
Family history of pancreatic cancer		
Yes	124 (60.5%)	60 (64.5%)
No	81 (39.5%)	33 (35.5%)
Presence of germline mutation		
Yes	162 (79%)	77 (82.8%)
No	30 (14.6%)	12 (12.9%)
Unknown	13 (6.4%)	4 (4.3%)
BRCA2	88 (42.9%)	41 (44.5%)
BRCA1	18 (8.8%)	11 (11.9%)
P53	18 (8.8%)	10 (10.8%)
PALB2	16 (7.8%)	7 (7.5%)
CDKN2A	10 (4.9%)	5 (5.4%)
ATM	9 (4.4%)	4 (4.4%)
STK11	3 (1.5%)	3 (3.3%)
MLH1	2 (1%)	1 (1.1%)
APC	1 (0.5%)	—
CFTR	2 (1%)	—
PRSS1	1 (0.5%)	—
Presence of germline mutation and family history	82 (40%)	45 (49%)

PCHRC: pancreatic cancer high risk cohort.

A total of 93 patients completed at least 1 follow-up cycle during the 5 years of the study observation, with the following outcomes: 13 patients developed new pancreatic focal lesions (14%), 4 of whom already had lesions at baseline, and 2 patients (2.1%) had progression of lesions detected at baseline: 1 with progression to PDAC and 1 with a solid lesion developed over an existing cyst without atypia on fine-needle aspiration biopsy. Also, 1 patient had diffuse pancreatic changes during follow-up. Twenty patients (21.5%) had stable lesions from baseline, whereas 57 (61.3%) continued to have negative screening [Figure 1].

Risk factors associated with FPLs at baseline

When we assessed for factors associated with the presence of FPL (including cystic and solid lesions), we found that patients with FPL were much more likely to have NOD compared with the patients with negative findings (18.9% *vs.* 1.9%; $P = 0.0005$; Table 2). As previously reported, patients with FPL were older than those with negative findings (median age, 61 *vs.* 50.5 years; $P > 0.00001$; Table 2). Family history of PC and the presence of germline mutations were not associated with FPL detection. When we separately assessed risk factors for the development of diffuse pancreatic lesions, we found that smoking history ($P = 0.01$) and male sex ($P = 0.0009$) were significantly enriched in patients with diffuse lesions compared with patients with negative findings (Supplementary Table 1, http://links.lww.com/ENUS/A358).

Risk factors predictive of new or progressing pancreatic lesions during follow-up

As expected, we found that patients with new or progressing lesions were older than those with stable or negative findings (median age, 66 *vs.* 55 years; $P = 0.01$). Similar to baseline, patients with NOD also had a higher risk for developing new or progressing lesions than those without NOD (26.7% *vs.* 2.6%; $P = 0.005$) during follow-up. From 15 patients who developed new or progressing lesions during follow-up, 4 had NOD (26.7%), whereas 2 patients (2.6%) with stable or negative findings had NOD [Table 3].

NOD is the main risk factor associated with FPL at baseline and during follow-up

Univariate and multivariate logistic regression analyses were performed to explore the predictive value of clinically and statistically important risk factors (NOD, alcohol consumption, PC family history, and presence of any germline mutation) in patients with FPL. In the univariate analysis, the odds of having FPL were significantly higher in patients with NOD (OR, 10.94; 95% CI, 3.01–0.79; $P < 0.001$), and this finding was still significant in the multivariate analysis (OR, 9.98; 95% CI, 2.15–46.33; $P = 0.003$) when accounting for other clinically relevant factors like age, alcohol, PC family history, and presence of germline mutations [Table 4].

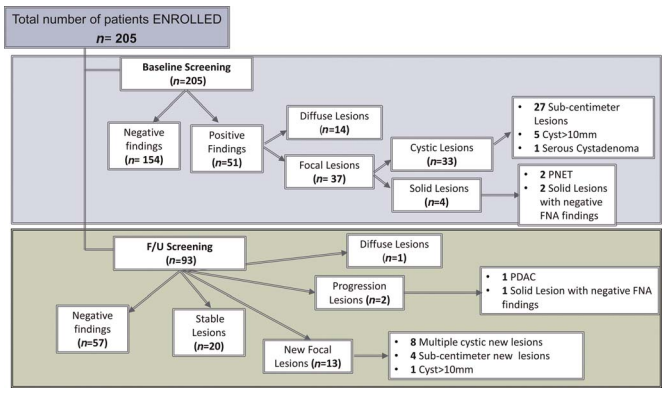

Figure 1. Screening results based on imaging findings. FNA: fine-needle aspiration; PC: pancreatic cancer; PNET: pancreatic neuroendocrine tumor.

DISCUSSION

National Comprehensive Cancer Network guidelines recommend PC screening for high-risk individuals at experienced high-volume centers with appropriate expertise, using a multidisciplinary approach.[11] Individuals get risk assessment, and screening is discussed after being identified as high risk.[12] We presented baseline results and 5-year follow-up of our PC high-risk cohort. Overall, our study found that the prevalence of pancreatic abnormalities in high-risk patients was 22%, consistent with the other screening programs.[13–15] Studies have shown survival improvement with detection of PC at early stages.[16] Furthermore, reports from long-standing high-risk

Table 2

Factors associated with FPL at baseline

Variables	Negative Results (*n* = 154)	Focal Pancreatic Lesions (*n* = 37)	*P**
Age, y			
Mean (SD)	51 (±12.3)	60.95 (±10.1)	**<0.0001**
Median (min–max)	50.5 (27–79)	61 (38–81)	
Sex			
Female	125 (81.2%)	30 (81.1%)	>0.99
Male	29 (18.8%)	7 (18.9%)	
Race/ethnicity			
White	114 (74%)	33 (89.2%)	
Hispanic	23 (15%)	4 (10.8%)	0.14
African American	12 (7.8%)	—	
Asian	5 (3.2%)	—	
Smoking			
Never	118 (76.6%)	26 (70.3%)	0.21
Past	30 (19.5%)	11 (29.7%)	
Current	6 (3.9%)	—	
Alcohol consumption			
Nondrinker	59 (38.3%)	9 (24.3%)	0.12
Drinker	95 (61.7%)	28 (75.7%)	
Personal medical history			
Personal history of cancer	86 (55.8%)	23 (62.2%)	0.58
New-onset diabetes	2 (1.9%)	8 (18.9%)	**0.0005**
New-onset diabetes and prediabetes	6 (3.9%)	9 (24.3%)	**0.0003**
Chronic diabetes	8 (5.2%)	1 (2.7%)	>0.99
Episodes of pancreatitis	5 (3.2%)	3 (8.1%)	0.18
Family history of PC	90 (58.4%)	23 (62.2%)	0.71
Presence of germline mutation			
Yes	129 (83.8%)	26 (70.3%)	0.14
No	16 (10.4%)	8 (21.6%)	
Unknown	9 (5.8%)	3 (8.1)	
Germline mutations			
BRCA2	67 (45.9%)	17 (43.5%)	0.70
BRCA1	16 (10.4%)†	2 (5.4%)	0.53
P53	15 (9.7%)	2 (5.4%)	0.53
PALB2	15 (9.7%)	1 (2.7%)	0.31
CDKN2A	9 (5.8%)	—	0.21
ATM	5 (3.2%)‡	3 (8.1%)	0.17
STK11	3 (1.9%)	—	>0.99
MLH1	2 (1.3%)	—	>0.99
APC	1 (0.6%)	—	>0.99
CFTR	2 (1.3%)§	—	>0.99
PRSS1	—	1 (2.7%)	>0.99

**P* value compares the focal pancreatic lesions to negative results.

†Two patients also have *CDKN2A* mutation, and 1 patient also has a *BRCA2* mutation.

‡One patient also has *P53* mutation, and 1 patient also has *PALB2* mutation.

§One patient also has *APC* mutation.

Table 3

Factors predictive of new or progressing pancreatic lesions during follow-up

Variables	Negative Results or Stable Lesions (*n* = 77)	New Lesions or Progression (*n* = 15)	*P**
Age, y			
Mean (SD)	53.8 (±13.5)	63.1 (±9.3)	**0.01**
Median (min–max)	55 (28–81)	66 (48–73)	
Sex			
Female	59 (76.6%)	13 (86.7%)	0.5
Male	18 (23.4%)	2 (13.3%)	
Race/ethnicity			
White	62 (80.5%)	12 (80%)	
Hispanic	10 (13%)	1 (6.7%)	0.73
African American	3 (3.9%)	1 (6.6%)	
Asian	2 (2.6%)	1 (6.7%)	
Smoking			
Never	61 (79.2%)	13 (86.7%)	0.72
Past	16 (20.8%)	2 (13.3%)	
Current	—	—	
Alcohol consumption			
Nondrinker	28 (36.3%)	3 (20%)	0.37
Drinker	49 (63.7%)	12 (80%)	
Personal medical history			
Personal history of cancer	45 (58.4%)	9 (60%)	>0.99
New-onset diabetes	2 (2.6%)	4 (26.7%)	**0.005**
New-onset diabetes and prediabetes	2 (2.6%)	5 (33.3%)	**0.001**
Chronic diabetes	4 (5.2%)	1 (6.7%)	>0.99
Episodes of pancreatitis	1 (1.3%)	1 (6.7%)	0.3
Family history of PC	46 (59.7%)	13 (86.7%)	0.07
Presence of germline mutation			
Yes	66 (85.7%)	11 (73.3%)	0.46
No	9 (11.7%)	3 (20%)	
Unknown	2 (2.6%)	1 (6.7%)	
Germline mutations			
BRCA2	35 (45.4%)	6 (40%)	>0.99
BRCA1	9 (11.7%)†	2 (13.3%)	0.68
P53	10 (12.9%)	—	0.35
PALB2	6 (7.8%)	1 (6.7%)	>0.99
CKN2A	4 (5.2%)	1 (6.7%)	0.58
ATM	3 (3.9%)‡	1 (6.7%)	0.5
STK11	2 (2.6%)	—	>0.99
MLH1	1 (1.3%)	—	>0.99
APC	—	—	
CFTR	—	—	
PRSS1	—	—	

**P* value compares the new lesions or progression lesions to negative results or stable lesions.

†Two patients also have *CDKN2A* mutation.

‡One patient also has *PALB2* mutation, and 1 patient also has *P53* mutation.

Bold values represent the statistically significant results.

Table 4

Logistic regression analysis for predictive risk factors of focal pancreatic lesions

Variable (Level)	Univariate Analysis, OR (95% CI)	*P*	Multivariate Analysis, OR (95% CI)	*P*
Age	1.08 (1.04–1.11)	**<0.001***	1.08 (1.04–1.12)	**<0.001***
Alcohol	1.87 (0.91–4.13)	0.089	2.28 (0.92–5.6)	0.072
New-onset diabetes	10.94 (3.01–51.79)	**<0.001***	9.98 (2.15–46.33)	**0.003***
Pancreatic cancer family history	1.46 (0.74–2.99)	0.27	1.18 (0.49–2.88)	0.708
Presence of any germline mutation	0.51 (0.22–1.23)	0.13	0.79 (0.29–2.15)	0.65

* marks statistically significance.

programs have shown survival benefit in patients enrolled in surveillance.[17]

Recent studies have demonstrated that age older than 60 years, multiple cysts, and dilated main ducts at baseline were robust predictors of the radiologic and neoplastic progression of pancreatic lesions.[8] Age of onset is an important predictor of PC risk in familial kindreds. Similarly, we found that the incidence of FPL was higher in older individuals. Only 6 patients (2.7%) with FPL in our study were younger than 50 years. Furthermore, all patients detected with solid lesions in our study were older than 64 years.

Increasing evidence suggests that NOD precedes PC diagnosis,[18–20] and 85% of patients with PC can have hyperglycemia, which manifests as early as 3 years before the cancer diagnosis.[21–23] Shah et al. [24] noticed a similar trend in a cohort of high-risk individuals undergoing PC screening, where 20% of high-risk individuals had abnormal fasting blood sugars, of which only 1 patient was diagnosed with NOD; however, it did not statistically correlate with the presence of focal lesions. Similarly, another retrospective study of high-risk individuals found an HbA_{1c} >5.7% associated with the presence of pancreatic cysts but not with diabetes (HbA_{1c} ≥6.5%) because of a small number of patients (n = 4).[25] In our high-risk cohort, the most robust clinical risk factor for detecting pancreatic lesions was NOD diagnosis, which maintained statistical significance after multivariate analyses. Moreover, our study is the first one to show that NOD is predictive of the development of new pancreatic lesions and the progression of lesions during follow-up.

Our study had several limitations: relatively small size, young cohort, single institution, and a short follow-up time. This was likely the reason for only 1 patient in our cohort developing PC, compared with previous reports.[8,26] Although some FPL may progress to malignancy, some could regress or stay stable. Whether these focal lesions predict a more substantial field defect with a greater chance of malignancy in another region of the pancreas compared with the ones who did not have an FPL can only be determined with longer-term follow-up. More extended surveillance will give us more data to make more definitive conclusions. Our population had more female individuals and was enriched with Whites, so this disparity may also influence the study's findings.

In conclusion, NOD is a significant risk factor for the presence of FPL and is also predictive development of new or progressing pancreatic lesions in a high-risk cohort during 5-year follow-up. More extensive studies with a more diverse population are needed to validate these findings further and understand their clinical implications.

Conflicts of Interest

A.M. receives royalties from Cosmos Wisdom Biotechnology and Thrive Earlier Detection, an Exact Sciences Company, and is a consultant for Freenome and Tezcat. F.M. is an SAB Member at Neological Biosciences. Dr Bhutani is Walter H Wriston Distinguished Professor for Pancreatic Cancer Research.
Manoop S. Bhutani is a senior associate editor of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

Financial Support and Sponsorship

Dr F. McAllister received support from the National Cancer Institute (1R37CA237384), Cancer Prevention Research Institute of Texas (RP200173), Shelby Levine Pancreatic Scholar Program, V Foundation (Translational Award), Sabin Family Foundation, Robert L. Fine Cancer Research Foundation, and MD Anderson Moonshot Philanthropic Funds.

Author Contributions

S.B., C.H., and F.M. designed, extracted data, performed analysis, and wrote the manuscript. F.M. and M.S.B. supervised the study. W.D. and L.F performed statistical analysis. S.B. and M.H had worked on data tabulation and extraction. M.H., M.M, P.Q., I.C., A.A.L.C., M.M, Y.N.Y., B.A., E.V., P.B, M.H.G.K, S.T.C., A.M., E.P.T., M.P.K., M.S.B., and F.M. contributed with patients' data, study revision, analysis, and writing revision. S.B., C.H., F.M. and M.S.B contributed by the critical analysis of manuscript and contribution in resubmission write up.

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