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ORIGINAL ARTICLE

The role of family history in predicting germline pathogenic variant carriers who develop pancreatic cancer: Results of a multicenter collaboration

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) surveillance is recommended for some individuals with a pathogenic or likely pathogenic variant (PV/LPV) in a PDAC susceptibility gene; the recommendation is often dependent on family history of PDAC. This study aimed to describe PDAC family history in individuals with PDAC who underwent genetic testing to determine the appropriateness of including a family history requirement in these recommendations.

Methods: Individuals with PDAC with a germline heterozygous PV/LPV in *ATM*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, or *PMS2* (PV/LPV carriers) were assessed for family history of PDAC in first-degree relatives (FDRs) or second-degree relatives (SDRs) from nine institutions. A control group of individuals with PDAC without a germline PV/LPV was also assessed.

Results: The study included 196 PV/LPV carriers and 1184 controls. In the PV/LPV carriers, 25.5% had an affected FDR and/or SDR compared to 16.9% in the control group ($p = .004$). PV/LPV carriers were more likely to have an affected FDR compared to the controls ($p = .003$) but there was no statistical difference when assessing only affected SDRs ($p = .344$).

Conclusions: Most PV/LPV carriers who developed PDAC did not have a close family history of PDAC and would not have met most current professional societies'

recommendations for consideration of PDAC surveillance before diagnosis. However, PV/LPV carriers were significantly more likely to have a family history of PDAC, particularly an affected FDR. These findings support family history as a risk modifier in PV/LPV carriers, and highlight the need to identify other risk factors.

KEYWORDS
genetic testing, germline mutation, pancreatic cancer, risk factors

INTRODUCTION

In the United States, approximately 1.7% of the population is diagnosed with pancreatic ductal adenocarcinoma (PDAC) during their lifetime, and approximately 10% of PDAC diagnoses are due to a hereditary predisposition.[1,2] There are several hereditary cancer syndromes known to increase the risk for PDAC, including familial atypical multiple mole melanoma (*CDKN2A*), hereditary breast and ovarian cancer (*BRCA1* and *BRCA2*), Li–Fraumeni syndrome (*TP53*), Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*), and Peutz–Jeghers syndrome (*STK11*), as well as pathogenic variants in *ATM* and *PALB2*.[3–10]

Multiple professional societies have established guidelines or recommendations for PDAC surveillance. Most of these recommendations include a family history requirement in their surveillance criteria for "moderate risk" genes such as *ATM*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, and *PMS2*; no family history of PDAC is required to meet surveillance criteria for *CDKN2A* and *STK11* carriers given their association with the highest increase in PDAC risk. Given the high risk for multiple cancer types in *TP53* carriers, annual whole-body magnetic resonance imaging (MRI), which is able to evaluate the pancreas, is included in surveillance recommendations, and therefore dedicated imaging of the pancreas is not typically recommended.

The current National Comprehensive Cancer Network (NCCN) guidelines titled "Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic" indicate that PDAC surveillance can be considered for individuals with a known heterozygous pathogenic or likely pathogenic variant (PV/LPV) in *ATM*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, or *TP53* and a first-degree relative (FDR) or second-degree relative (SDR) with PDAC from the same side of the family as the known PV/LPV.[11]

The updated recommendation from the International Cancer of the Pancreas Screening (CAPS) Consortium reached consensus to consider PDAC surveillance for individuals with a PV/LPV in *ATM*, *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, or *PALB2* and at least one PDAC-affected FDR. For individuals with a *BRCA2* PV/LPV, consensus was also reached to consider PDAC surveillance if there were at least two PDAC-affected relatives of any degree.[12]

The American College of Gastroenterology (ACG) recommends that PDAC surveillance for individuals with an *ATM*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, or *PMS2* PV/LPV should be limited to those with a PDAC-affected FDR or SDR,[13] whereas the American Gastroenterological Association (AGA) and the American Society of Clinical Oncology (ASCO) state that PDAC surveillance should be considered for individuals with an *ATM*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, or *PMS2* PV/LPV who have one or more PDAC-affected FDRs.[14,15]

Because most professional societies only recommend consideration for PDAC surveillance for individuals with a germline PV/LPV in a moderate risk PDAC susceptibility gene (*ATM*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, or *PMS2*) if there is also a family history, our study aimed to assess family history data for individuals who were diagnosed with PDAC with a PV/LPV in one of the aforementioned genes to determine the benefits and limitations of using family history as part of the eligibility for PDAC surveillance.

MATERIALS AND METHODS

In this retrospective study, we assessed individuals who were diagnosed with PDAC for a family history of PDAC in FDRs or SDRs. The study population included individuals who had a germline PV/LPV in a moderate risk PDAC susceptibility gene, henceforth referred to as "PV/LPV carriers." Inclusion criteria for PV/LPV carriers included a histologically verified exocrine pancreatic cancer diagnosis, germline PV/LPV in *ATM*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, or *PMS2*, and availability of a three-generation family history (ascertained by a genetic professional or via electronic medical records). Although the NCCN and CAPS do not include *PMS2* carriers for consideration for PDAC surveillance, we opted to include them in our analyses because the ACG, AGA, and ASCO do include *PMS2* carriers. Exclusion criteria for PV/LPV carriers included pancreatic neuroendocrine tumors, a clinical diagnosis of PDAC without histological verification, or the presence of a germline PV/LPV in *CDKN2A*, *STK11*, or *TP53*; these genes were excluded because current guidelines do not require family history for surveillance eligibility.

PV/LPV carriers were compared to individuals who were diagnosed with PDAC who had no PV/LPV identified via multigene panel genetic testing, now to be referred to as "controls." Inclusion criteria for the controls included a histologically verified exocrine pancreatic cancer diagnosis, genetic testing that included *APC*, *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *STK11*, and *TP53*, no known germline PV/LPV in any cancer susceptibility gene, and availability of a three-generation family history (ascertained by a genetic professional or via electronic medical records).

Exclusion criteria for the controls included pancreatic neuroendocrine tumors, a clinical diagnosis of PDAC without histological verification, genetic testing that did not include the minimum required 13 PDAC susceptibility genes, or the presence of a germline PV/LPV in any known cancer susceptibility gene. Individuals who only had variants of uncertain significance identified via genetic testing were included in the control group.

Data were collected from nine institutions with PDAC registries at tertiary medical centers, which included the University of Pittsburgh, University of California San Francisco, New York University Langone Health, Columbia University Irving Medical Center, Corewell Health William Beaumont University Hospital, Ohio State University Wexner Medical Center, Providence, University of Chicago, and IRCCS San Raffaele Scientific Institute. Institutional review board approval was obtained at the University of Pittsburgh, and data use agreements were established between each institution and the University of Pittsburgh, which was the receiving site of the data.

χ^2 and *t*-tests were used to evaluate differences between the PV/LPV carriers and the controls. *p* values of <.05 were considered significant. Statistical analyses were performed with the SAS statistical software package (version 9.4; SAS Institute, Cary, North Carolina).

RESULTS

The total study population consisted of 196 PV/LPV carriers and 1184 controls. Characteristics of the study population stratified by PV/LPV carrier status are presented in Table 1. There was no statistically significant difference in age at diagnosis, sex, ethnicity, Ashkenazi Jewish ancestry, or smoking status at diagnosis between PV/LPV carriers and controls. PV/LPV carriers were significantly more likely to be White ($p = .02$) and to have a personal history of another cancer compared to the subjects in the control group ($p < .001$). The majority of the PV/LPV carriers had a PV/LPV in *ATM* ($n = 59$; 30.1%) or *BRCA2* ($n = 74$; 37.8%). Other affected genes included 25 *BRCA1* (12.8%), one *MLH1* (0.5%), three *MSH2* (1.5%), 10 *MSH6* (5.1%), 18 *PALB2* (9.2%), and six *PMS2* (3.1%). No individuals with an *EPCAM* PV/LPV met criteria for the analysis.

Table 2 presents information on family history for the total study population and stratified by PV/LPV carrier status. Among the PV/LPV carriers, 18.9% of individuals had at least one FDR who had been diagnosed with PDAC compared to only 11.4% of the subjects in the control group ($p = .003$). In addition, 14.6% of the PV/LPV carriers had a PDAC-affected SDR or a PDAC-affected SDR *and* a PDAC-affected FDR versus only 8.1% of the controls ($p = .006$). Evaluation of the family history of only PDAC-affected SDRs (i.e., excluding those also with a PDAC-affected FDR) showed that 8.2% of the PV/LPV carriers had an SDR with PDAC compared to 6.2% of the controls ($p = .344$). Additionally, 25.5% of the PV/LPV carriers had an FDR and/or SDR who had been diagnosed with PDAC compared to 16.9% of the controls ($p = .004$).

Stratified by gene, individuals with an *MSH6* PV/LPV were most likely to have a PDAC-affected FDR or SDR (40.0%), followed closely by an *ATM* or *PALB2* PV/LPV (33.9% and 33.3%, respectively). None of the individuals with an *MLH1*, *MSH2*, or *PMS2* PV/LPV had a PDAC-affected FDR or SDR, but they also represented the fewest numbers of individuals in our study population (see Table 3).

DISCUSSION

Our data show that the majority of individuals with a germline PV/LPV in a moderate risk PDAC susceptibility gene who develop PDAC do not meet current NCCN, CAPS, ACG, AGA, or ASCO recommendations for PDAC surveillance because they do not have a PDAC-affected FDR or SDR. These findings suggest that family history alone is not sufficient for identifying most individuals with a PV/LPV in these genes who are at risk of developing PDAC. Although the majority of affected PV/LPV carriers do not have a PDAC-affected FDR or SDR, they are significantly more likely to have a family history of PDAC than affected individuals who do not have an identified PV/LPV, which suggests that family history of PDAC, particularly in an FDR, could still play a role in helping to define PDAC risk in PV/LPV carriers and in enriching the surveillance population, which remains necessary until noninvasive and more cost-effective surveillance strategies are developed.

Until noninvasive and more cost-effective PDAC surveillance is available, our data highlight the importance of ensuring that individuals with a germline PV/LPV in a moderate risk PDAC susceptibility gene understand and discuss symptoms of PDAC, such as new-onset diabetes, unexplained weight loss, persistent and unexplained abdominal discomfort, and jaundice, with their health care providers. In order to assess for new-onset diabetes, it is imperative that individuals with a germline PV/LPV in a moderate risk PDAC susceptibility gene follow the American Diabetes Association's recommendations for screening for diabetes.[17] These recommendations indicate that HbA1c screening should be conducted in all individuals beginning at age 35 years. Screening may need to begin earlier for individuals who are overweight or obese with at least one additional risk factor and for individuals with a history of gestational diabetes. If via screening, individuals are found to have prediabetes, then screening should continue annually; if HbA1c is normal, then screening should continue at a minimum of 3-year intervals.[16] At this time, other blood markers are not used for PDAC surveillance because none have been demonstrated to be effective in the clinical setting in high-risk patients.[17] It is also important to discuss lifestyle modifications to avoid other risk factors for PDAC with individuals with a germline PV/LPV in a moderate risk PDAC susceptibility gene, including avoidance of smoking,[18] maintaining a healthy weight,[19] getting regular physical activity,[19] and eating a healthy diet.[20]

Some experts in the field advocate for discarding the requirement for family history when creating surveillance recommendations as a way to expand surveillance. Roch et al. reported on 83 of 204 *BRCA1* or *BRCA2* PV/LPV carriers at their institution who had

TABLE 1 Demographic information stratified by PV/LPV carrier status.

	Total study population (*N* = 1380)	PV/LPV carriers (*n* = 196)	Controls (no PV/LPV) (*n* = 1184)	*p*
Age at diagnosis, mean ± SD, years	65.7 ± 11.2	65.2 ± 12.2	65.7 ± 11.0	.58
Sex, No. (%)				.58
Female	694 (50.3)	95 (48.5)	599 (50.6)	
Male	686 (49.7)	101 (51.5)	585 (49.4)	
Race, No. (%)				.02
Asian	103 (7.5)	11 (5.6)	92 (7.8)	
Black	84 (6.1)	7 (3.6)	77 (6.5)	
Mixed	44 (3.2)	2 (1.0)	42 (3.6)	
Other	71 (5.1)	6 (3.1)	65 (5.5)	
White	1051 (76.1)	170 (86.7)	881 (74.4)	
Unknown	27 (2.0)	0	27 (2.3)	
Ethnicity, No. (%)				.06
Non-Hispanic	1237 (89.6)	185 (94.4)	1052 (88.9)	
Hispanic	99 (7.2)	8 (4.1)	91 (7.7)	
Unknown	44 (3.2)	3 (1.5)	41 (3.5)	
Ashkenazi Jewish, No. (%)				.07
No	1042 (75.5)	155 (79.1)	887 (74.9)	
Yes	155 (11.2)	25 (12.7)	130 (11.0)	
Unknown	183 (13.3)	16 (8.2)	167 (14.1)	
Smoking status at diagnosis, No. (%)				.39
Current	120 (8.7)	19 (9.7)	101 (8.5)	
Never	665 (48.2)	103 (52.5)	562 (47.5)	
Past	466 (33.8)	56 (28.6)	410 (34.6)	
Unknown	129 (9.3)	18 (9.2)	111 (9.4)	
Personal history of other cancer, No. (%)[a]				<.0001
No	1127 (81.7)	128 (65.3)	999 (84.4)	
Yes	252 (18.3)	68 (34.7)	184 (15.5)	
Unknown	1 (0.0)	0 (0.0)	1 (0.1)	

Abbreviation: PV/LPV, pathogenic/likely pathogenic variant.

[a]Excludes basal cell and squamous cell carcinomas of the skin.

undergone diagnostic imaging. Of the 83 with abdominal imaging or endoscopic evaluation of the pancreas, two (2.4%) were found to have PDAC (both *BRCA2* PV/LPV carriers) and 11 (13.3%) were found to have intraductal papillary mucinous neoplasms (three *BRCA1* PV/LPV carriers and eight *BRCA2* PV/LPV carriers).[21] Shah et al. found in their study that only one of 10 individuals with a *BRCA1* or *BRCA2* PV/LPV who were diagnosed with PDAC had an FDR with PDAC.[22] Katona et al. also recently described findings from 64 individuals with a PV/LPV in *BRCA1*, *BRCA2*, *PALB2*, or *ATM* and no family history of PDAC who underwent at least one endoscopic ultrasound (EUS) for PDAC surveillance. They identified pancreatic cysts or masses in 22% of their population, with two of 64 diagnosed with PDAC (both *BRCA2* PV/LPV carriers).[23] Additionally, the American Society for Gastrointestinal Endoscopy (ASGE) recently published recommendations on screening for PDAC in individuals with genetic susceptibility. In these recommendations, the ASGE suggests screening for all individuals with a *BRCA1* or *BRCA2* PV/LPV, regardless of family history, but this was on the basis of a very low quality of evidence.[24]

Evidence that PDAC surveillance improves outcomes in the hereditary setting is mounting. In published data from the multicenter Cancer of the Pancreas Screening (CAPS5) study, Dbouk et al. illustrated that seven of nine high-risk individuals with surveillance-detected PDAC had stage I disease and that 5-year survival in

TABLE 2 Family history of PDAC in PV/LPV carriers with PDAC compared to individuals with PDAC and no PV/LPV.

	Total study population	PV/LPV carriers	Controls (no PV/LPV)	*p*
PDAC-affected FDRs, No. (%)	*N* = 1380	*n* = 196	*n* = 1184	.003
No	1208 (87.5)	159 (81.1)	1049 (88.6)	
Yes	172 (12.5)	37 (18.9)	135 (11.4)	
PDAC-affected SDRs, No. (%)[a]	*N* = 1242	*n* = 171	*n* = 1071	.006
No	1130 (91.0)	146 (85.4)	984 (91.9)	
Yes	112 (9.0)	25 (14.6)	87 (8.1)	
PDAC-affected SDRs only, No. (%)[b]	*N* = 1208	*n* = 159	*n* = 1049	.344
No	1130 (93.5)	146 (91.8)	984 (93.8)	
Yes	78 (6.5)	13 (8.2)	65 (6.2)	
PDAC-affected FDRs and/or SDRs, No. (%)	*N* = 1380	*n* = 196	*n* = 1184	.004
No	1130 (81.9)	146 (74.5)	984 (83.1)	
Yes	250 (18.1)	50 (25.5)	200 (16.9)	

Abbreviations: FDR, first-degree relative; PDAC, pancreatic ductal adenocarcinoma; PV/LPV, pathogenic/likely pathogenic variant; SDR, second-degree relative.

[a]Includes patients who have PDAC-affected SDRs only and patients who have both PDAC-affected FDRs and SDRs; patients who have PDAC-affected FDRs only are not included this group.

[b]Includes patients who have PDAC-affected SDRs only; patients who have a PDAC-affected FDR only or a PDAC-affected FDR in addition to a PDAC-affected SDR are not included in this group.

TABLE 3 Family history of PDAC in PV/LPV carriers stratified by gene.

	ATM	*BRCA1*	*BRCA2*	*MLH1*	*MSH2*	*MSH6*	*PALB2*	*PMS2*
PDAC-affected FDRs, No. (%)	*n* = 59	*n* = 25	*n* = 74	*n* = 1	*n* = 3	*n* = 10	*n* = 18	*n* = 6
No	43 (72.9)	21 (84.0)	63 (85.1)	1 (100)	3 (100)	9 (90.0)	13 (72.2)	6 (100)
Yes	16 (27.1)	4 (16.0)	11 (14.9)	0 (0)	0 (0)	1 (10.0)	5 (27.8)	0 (0)
PDAC-affected SDRs, No. (%)[a]	*n* = 50	*n* = 21	*n* = 67	*n* = 1	*n* = 3	*n* = 9	*n* = 14	*n* = 6
No	39 (78.0)	20 (95.2)	59 (88.0)	1 (100)	3 (100)	6 (66.7)	12 (85.7)	6 (100)
Yes	11 (22.0)	1 (4.8)	8 (12.0)	0 (0)	0 (0)	3 (33.3)	2 (14.3)	0 (0)
PDAC-affected SDRs only, No. (%)[b]	*n* = 43	*n* = 21	*n* = 63	*n* = 1	*n* = 3	*n* = 9	*n* = 13	*n* = 6
No	39 (90.7)	20 (95.2)	59 (93.7)	1 (100)	3 (100)	6 (66.7)	12 (92.3)	6 (100)
Yes	4 (9.3)	1 (4.8)	4 (6.7)	0 (0)	0 (0)	3 (33.3)	1 (8.3)	0 (0)
PDAC-affected FDRs and/or SDRs, No. (%)	*n* = 59	*n* = 25	*n* = 74	*n* = 1	*n* = 3	*n* = 10	*n* = 18	*n* = 6
No	39 (66.1)	20 (80.0)	59 (79.7)	1 (100)	3 (100)	6 (60.0)	12 (66.7)	6 (100)
Yes	20 (33.9)	5 (20.0)	15 (20.3)	0 (0)	0 (0)	4 (40.0)	6 (33.3)	0 (0)

Abbreviations: FDR, first-degree relative; PDAC, pancreatic ductal adenocarcinoma; PV/LPV, pathogenic/likely pathogenic variant; SDR, second-degree relative.

[a]Includes patients who have PDAC-affected SDRs only and patients who have both PDAC-affected FDRs and SDRs; patients who have PDAC-affected FDRs only are not included this group.

[b]Includes patients who have PDAC-affected SDRs only; patients who have a PDAC-affected FDR only or a PDAC-affected FDR in addition to a PDAC-affected SDR are not included in this group.

screening-detected PV/LPV carriers is 73.3%.[25] In the general US population, fewer than 10% of PDACs are stage I, and the 5-year overall survival for individuals with PDAC is only 12.8%.[1] These encouraging data by Dbouk et al.[25] support the role of surveillance with annual EUS and/or MRI in individuals with an increased risk for PDAC.

Current surveillance options for pancreatic cancer are imaging-based procedures, such as EUS and MRI, which are costly. Kumar et al. showed that screening with an index EUS was cost-effective when the lifetime risk for PDAC is greater than 10.8%, but for lower risks other factors had to be met. Because this study only evaluated index EUS, it could not comment on the cost-effectiveness of annual EUS

surveillance.[26] Corral et al. showed that surveillance with EUS was cost-effective for individuals with a relative risk for PDAC 20-fold higher than the general population.[27] The findings of these studies suggest that surveillance with EUS may not be cost-effective for individuals with a PV/LPV in a moderate risk PDAC susceptibility gene in the absence of a family history because their risk would not meet the proposed thresholds on the basis of currently available data regarding risk associated with a PV/LPV in these genes.

Additionally, the yield for PDAC surveillance in these high-risk individuals is quite low, at less than 2% annually for an advanced precursor lesion or an invasive cancer,[28] and some individuals who undergo PDAC surveillance eventually undergo surgery for lesions that prove to be low grade. For example, in the CAPS5 study, only three of eight individuals who underwent surgery for worrisome lesions had high-grade dysplasia identified,[25] which raises the potential for increased morbidity associated with unnecessary surgery as well as additional secondary comorbidities such as diabetes and the unnecessary use of health care dollars.

Because family history alone is not an adequate risk predictor and because the current parameters of surveillance require an enriched population, we attempted to identify other possible modifiers to risk in the PV/LPV carriers. There was no statistically significant difference in smoking status between our PV/LPV carriers and the individuals without a PV/LPV, which suggests that smoking history would not help further enrich carriers for surveillance. PV/LPV carriers were more likely to have a personal history of another cancer than the controls ($p < .0001$) but this is likely because of the nature of having a genetic cancer predisposition rather than a predictor of developing PDAC. We were not able to assess other known or proposed risk factors for PDAC, such as alcohol use, obesity, non-O blood types, diabetes, and diet, because of a lack of data.

There were several limitations to our study. This was a retrospective study, and data on known or proposed PDAC risk factors such as alcohol use, obesity, and diabetes were not available. Family histories were self-reported, and some family histories were obtained via electronic medical record review, rather than elicited by a genetic counselor or geneticist, and therefore could be inaccurate or incomplete. Not all individuals in the study population were tested via a universal testing program for patients with PDAC, and therefore there could be ascertainment bias based on family history.

Because of the aforementioned limitations, a future prospective study is needed to validate our findings. Additionally, further studies are needed to determine risk factors other than family history that will help enrich the group of individuals with a hereditary predisposition for PDAC who will benefit from PDAC surveillance. Future studies should not only compare PDAC-affected individuals with and without a PV/LPV in a known PDAC susceptibility gene but also individuals who have not been diagnosed with PDAC. By comparing individuals with a PV/LPV in a PDAC susceptibility gene with and without a PDAC diagnosis, lifestyle, demographic, and medical risk factors as well as other genetic modifiers can be better assessed for their role in the development of PDAC in a setting of a known hereditary syndrome. Larger studies are also needed to be able to assess each gene individually to determine the differences in how family history of PDAC and other factors affect risk. Future larger studies with a design that will allow for penetrance calculations is of particular interest for *ATM*, *MSH6*, and *PALB2* because a PV/LPV in these genes had the highest rates of family history of PDAC in our study.

In conclusion, our study showed that 74.5% of individuals with a germline PV/LPV in *ATM*, *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, or *PMS2* who develop PDAC do not have a family history of PDAC, and therefore do not meet most published recommendations for consideration of PDAC surveillance. Family history of PDAC, particularly an affected FDR, was significantly more likely within PV/LPV carriers than controls, which shows that family history has some impact on risk stratification and may continue to have a role in PDAC surveillance recommendations. Given that the requirement of a family history of PDAC excludes the majority of PV/LPV carriers who develop PDAC from prediagnosis surveillance, the identification of other risk factors in the setting of a hereditary cancer syndrome is paramount to determining which carriers will most benefit from surveillance and to limiting the amount of overscreening until a noninvasive, low-cost option becomes available. At a minimum, our data support current guidelines for PDAC surveillance in individuals with a PV/LPV in a moderate risk PDAC susceptibility gene and an affected FDR or SDR. Our data are a starting point to consider expanding PDAC surveillance to all carriers of a PV/LPV in a moderate risk PDAC susceptibility gene regardless of family history but also demonstrate the need for identification of additional risk modifiers via larger prospective studies.

AUTHOR CONTRIBUTIONS

Eve Karloski: Conceptualization, methodology, formal analysis, investigation, data curation, writing–original draft, visualization, and project administration. **Beth Dudley**: Conceptualization, methodology, investigation, writing–review and editing, and visualization. **Brenda Diergaarde**: Formal analysis and writing–review and editing. **Amie Blanco**: Investigation and writing–review and editing. **Jessica N. Everett**: Investigation and writing–review and editing. **Elana Levinson**: Investigation and writing–review and editing. **Tara Rangarajan**: Investigation and writing–review and editing. **Peter P. Stanich**: Investigation, resources, and writing–review and editing. **Kimberly Childers**: Writing–review and editing and investigation. **Sandra Brown**: Writing–review and editing and investigation. **Christine Drogan**: Writing–review and editing and investigation. **Giulia Martina Cavestro**: Investigation, resources, and writing–review and editing. **Kelly Gordon**: Investigation and writing–review and editing. **Aparajita Singh**: Resources and writing–review and editing. **Diane M. Simeone**: Writing–review and editing and resources. **Hannah Reich**: Writing–review and editing and investigation. **Fay Kastrinos**: Writing–review and editing and resources. **Dana Zakalik**: Resources and writing–review and editing. **Heather Hampel**: Resources and writing–review and editing. **Rachel Pearlman**: Resources and writing–review and editing. **Ora K. Gordon**: Resources and writing–review and editing. **Sonia S. Kupfer**: Resources and writing–review and editing. **Marta Puzzono**: Resources and writing–review and editing. **Raffaella Alessia**

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

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REFERENCES

1. *Cancer Stat Facts: Pancreatic Cancer*. Surveillance, Epidemiology, and End Results Program, National Cancer Institute. Accessed May 23, 2024. https://seer.cancer.gov/statfacts/html/pancreas.html
2. Rulyak SJ, Brentnall TA. Inherited pancreatic cancer: improvements in our understanding of genetics and screening. *Int J Biochem Cell Biol*. 2004;36(8):1386-1392. doi:10.1016/j.biocel.2004.02.010
3. Goldstein AM, Fraser MC, Struewing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med*. 1995;333(15):970-974. doi:10.1056/nejm199510123331504
4. Thompson D, Easton DF, Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. *J Natl Cancer Inst*. 2002;94(18):1358-1365. doi:10.1093/jnci/94.18.1358
5. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. *J Natl Cancer Inst*. 1999;91(15):1310-1316. doi:10.1093/jnci/91.15.1310
6. Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. *Oncogene*. 2001;20(34):4621-4628. doi:10.1038/sj.onc.1204621
7. Aarnio M, Mecklin JP, Aaltonen LA, Nyström-Lahti M, Järvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. *Int J Cancer*. 1995;64(6):430-433. doi:10.1002/ijc.2910640613
8. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res*. 2006;12(10):3209-3215. doi:10.1158/1078-0432.ccr-06-0083
9. Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. *Cancer Discov*. 2012;2(1):41-46. doi:10.1158/2159-8290.cd-11-0194
10. Jones S, Hruban RH, Kamiyami M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science*. 2009;324(5924):217. doi:10.1126/science.1171202
11. Daly MB, Pal T, AlHilli Z, et al. NCCN clinical practice guidelines in oncology (NCCN guidelines): genetic/familial high-risk assessment: breast, ovarian, and pancreatic version 3.2024. Accessed February 23, 2024. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
12. Goggin M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut*. 2020;69(1):7-17. doi:10.1136/gutjnl-2019-319352
13. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guidelines: genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110(2):223-262. doi:10.1038/ajg.2014.435
14. Aslanian HR, Lee JH, Canto MI. AGA clinical practice update on pancreas cancer screening high-risk individuals: expert review. *Gastroenterology*. 2020;159(1):358-362. doi:10.1053/j.gastro.2020.03.088

15. Stoffel EM, McKernin SE, Brand R, et al. Evaluating susceptibility to pancreatic cancer: ASCO provisional clinical opinion. *J Clin Oncol*. 2018;37(2):153-164. doi:10.1200/jco.18.01489
16. ElSayed NA, Aleppo G, Aroda VR, et al. Classification and diagnosis of diabetes: standards of care in diabetes—2023. *Diabetes Care*. 2023;46(suppl 1):S19-S40. doi:10.2337/dc23-s002
17. Katona BW, Worthington C, Clay D, et al. Outcomes of the IMMray PanCan-d test in high-risk individuals undergoing pancreatic surveillance: pragmatic data and lessons learned. *JCO Precis Oncol*. 2023;7:e2300445. doi:10.1200/po.23.00445
18. Maisonneuve P, Lowefels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol*. 2015;44(1):186-198. doi:10.1093/ije/dyu240
19. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA*. 2001;286(8):921-929. doi:10.1001/jama.286.8.921
20. Arem H, Reedy J, Sampson J, et al. The Health Eating Index 2005 and risk for pancreatic cancer in the NIH-AARP study. *J Natl Cancer Inst*. 2013;105(17)1298-1305. doi:10.1093/jnci/djt185
21. Roch AM, Schneider J, Carr RA, et al. Are BRCA1 and BRCA2 gene mutation patients underscreened for pancreatic adenocarcinoma? *J Surg Oncol*. 2019;119(6):777-783. doi:10.1002/jso.25376
22. Shah I, Silva-Santisteban A, Germansky KA, et al. Association between family history and risk of pancreatic cancer in patients with BRCA1 and BRCA2 pathogenic variants. *Pancreas*. 2022;51(7):733-738. doi:10.1097/mpa.0000000000002104
23. Katona BW, Long JM, Ahmad NA, et al. EUS-based pancreatic cancer surveillance in BRCA1/BRCA2/PALB2/ATM carriers without a family history of pancreatic cancer. *Cancer Prev Res*. 2021;14(11):1033-1040. doi:10.1158/1940-6207.capr-21-0161
24. Sawhney MS, Calderwood AH, Thosani NC, et al. ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations. *Gastrointest Endosc*. 2022;95(5):817-826. doi:10.1016/j.gie.2021.12.001
25. Dbouk M, Katona BW, Brand RE, et al. The multicenter Cancer of Pancreas Screening study: impact on stage and survival. *J Clin Oncol*. 2022;40(28):3257-3266. doi:10.1200/jco.22.00298
26. Kumar S, Saumoy M, Oh A, et al. Threshold analysis of the cost-effectiveness of endoscopic ultrasound in patients at high risk for pancreatic ductal adenocarcinoma. *Pancreas*. 2021;50(6):807-814. doi:10.1097/mpa.0000000000001835
27. Corral JE, Das A, Bruno MJ, Wallace MB. Cost-effectiveness of pancreatic cancer surveillance in high-risk individuals. *Pancreas*. 2019;48(4):526-536. doi:10.1097/mpa.0000000000001268
28. Canto MI, Almario JA, Schulick RD, et al. Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. *Gastroenterology*. 2018;155(3):740-751. doi:10.1053/j.gastro.2018.05.035

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