Research Article

Cancer Prevention Research

Outcome of Pancreatic Cancer Surveillance Among High-Risk Individuals Tested for Germline Mutations in *BRCA1* and *BRCA2*

Amethyst Saldia[1], Sara H. Olson[1], Pamela Nunes[1], Xiaolin Liang[1], Marguerite L. Samson[1], Erin Salo-Mullen[2], Vanessa Marcell[2], Zsofia K. Stadler[2], Peter J. Allen[3,4], Kenneth Offit[2], and Robert C. Kurtz[2]

Abstract

Germline mutations in *BRCA1/2* are risk factors for pancreatic ductal adenocarcinoma (PDAC). The aim of this study was to evaluate whether results of surveillance for PDAC in high risk individuals (HRI) differ between those with and without a pathogenic *BRCA1/2* mutation. This prospective study was conducted within the Pancreatic Tumor Registry at a major cancer center. There were 83 HRIs with $\geq$1 first-degree relative with PDAC who underwent surveillance and testing for pathogenic germline mutations in *BRCA1/2*. A secondary analysis includes 18 HRIs with known mutations in *BRCA1/2* but with weaker family history. HRIs were evaluated over time using magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound when indicated by MRCP findings. We reviewed imaging results, blinded to mutation status. Demographic information was obtained from interviewer-administered questionnaires. The outcome was the proportion with any pancreatic abnormality identified at initial or follow-up surveillance. Among the 83 HRIs in the main analysis, 48 had a mutation in *BRCA1/2* and 35 did not. Overall, 16 of 48 (33%) *BRCA1/2*-positive and 13 of 35 (37%) *BRCA1/2*-negative participants had pancreatic abnormalities on imaging; in each group, all but one finding was an intraductal papillary mucinous neoplasm. Among those with pathogenic mutations but weaker family history, results were similar: 7 of 18 (39%) with pancreatic abnormalities. Results of surveillance for pancreatic abnormalities on imaging are similar regardless of *BRCA1/2* mutation status. While the results from this small study need confirmation in other studies, at present there does not appear to be increased yield from targeting individuals with *BRCA1/2* mutations for surveillance.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a highly lethal disease and is the third leading cause of cancer-related death in the United States (1). SEER data placed the age-adjusted incidence rate at 12.5 per 100,000 in 2010–2014, with the mortality rate nearing that at 10.9 per 100,000 (2). This poor outcome is attributed to the advanced stage of this disease that is almost always present when patients present with symptoms of PDAC such as abdominal pain or jaundice. Screening for some other gastrointestinal cancers can be effective in improving cancer mortality, as has been shown for colorectal cancer. While the approximately 30% reduction in colorectal cancer mortality over the last several decades is attributable to several factors, there is little doubt that screening programs have made a significant impact (3).

There is some evidence that when PDAC is found incidentally, before symptoms develop, survival can be dramatically improved. Patients with small (<2 cm) pancreatic cancers or those without nodal disease have demonstrated improved 5-year survival rates following resection of PDAC (4). Recent studies on long-term surveillance programs show higher resectability rates for asymptomatic screen-detected PDAC compared with symptomatic PDAC and improved 3-year and 5-year survival rates (5, 6).

The detection of PDAC precursor lesions is an area of interest in preventing the development of pancreatic cancer

[1]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York. [2]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York. [3]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York. [4]Department of Surgery, Duke University, Durham, North Carolina.

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Corresponding Author: Amethyst Saldia, Memorial Sloan Kettering Cancer Center, 485 Lexington Ave, 2nd floor, New York, NY 10017. Phone: 646-888-8310; Fax: 929-321-1517; E-mail: saldiac@mskcc.org

Cancer Prev Res 2019;12:599–608

doi: 10.1158/1940-6207.CAPR-18-0272

in high risk individuals (HRI). These lesions include intraductal papillary mucinous neoplasms (IPMN) and pancreatic intraepithelial neoplasia (Pan-IN). IPMNs can be observed with cross-sectional imaging such as magnetic resonance cholangiopancreatography (MRCP), and endoscopy such as endoscopic ultrasound, while Pan-IN lesions cannot (7). Family history is an established risk factor for PDAC (8), as are smoking (9), obesity (10, 11), diabetes (12), chronic pancreatitis (13), and pathogenic mutations in several genes, including *BRCA1/2* (14–16).

Mutations in *BRCA2* are the most common germline mutations influencing risk of PDAC with prevalence estimates ranging from approximately 2% to 19% (17, 18). *BRCA1* mutations also contribute, albeit less, to overall prevalence of inherited predisposition to PDAC (18, 19). The relative risk of pancreatic cancer for carriers of *BRCA1* mutations has ranged from 0.8 to 4.7 (14, 18, 20–26). In studies of carriers of *BRCA2* mutations, the reported range is somewhat higher, from 2.0 to 21, with most results around 3–6 (14, 18, 20–24, 27, 28).

Hoping to identify precursor lesions such as IPMN or early PDAC in individuals at higher risk for development of PDAC, we began a surveillance program within the framework of our larger familial pancreatic tumor registry study at Memorial Sloan Kettering Cancer Center (MSKCC, New York, NY) in 2002. The MSKCC Pancreatic Tumor Registry (29) includes both patients with PDAC and at-risk family members, including those with germline mutations known to increase PDAC risk.

The question leading to this study was whether, among healthy individuals with positive family history of PDAC, those with known pathogenic mutations in *BRCA1/2* would have more pancreatic abnormalities compared with individuals who have undergone germline genetic testing with no mutations in *BRCA1/2* identified.

Materials and Methods

HRIs

The MSKCC Pancreatic Tumor Registry opened enrollment in May 2003. As of June 30, 2017, the Registry had enrolled 554 relatives of patients with pancreatic cancer. Of these, 243 HRIs agreed to take part in surveillance with MRCP, with some participants undergoing CT in select circumstances. Regarding germline genetic test results, 190 of the 554 HRIs have known *BRCA1/2* mutation status. This analysis is based on individuals who have both undergone surveillance and have known *BRCA1/2* mutation status (Fig. 1).

The eligibility criteria for HRIs changed over the course of the Registry study, reflecting what we and others learned about conducting surveillance in this population. In general, changes resulted in requiring stronger family history and older age at beginning surveillance. Other changes reflected the growing numbers of HRIs undergoing genetic testing for mutations in *BRCA1/2* and genes involved in other rare cancer syndromes. When enrollment began in May 2003, we included relatives with $\geq$1 first-degree relative (FDR) and $\geq$ 1 other affected relative. In 2011, we changed eligibility requirements to require HRIs to have $\geq$2 affected FDRs, while individuals with known genetic syndromes were required to have $\geq$1 FDR or $\geq$1 SDR (second-degree relative) with PDAC. The main analysis in this article is based on those individuals who had $\geq$1 FDR with pancreatic cancer, had surveillance at age $\geq$45 years, and had testing for pathogenic mutations in *BRCA1/2* ($n = 83$). We also report separately on a group of 18 HRIs with known *BRCA1/2* mutations and second-degree, but not first-degree, relatives with pancreatic cancer who underwent surveillance at age $\geq$45.

HRIs in this article were not tested for all PDAC susceptibility genes. However, any HRIs with known pathogenic mutations in other PDAC susceptibility genes were excluded from this analysis.

HRIs are identified in several ways: by study or clinical staff if they are related to a patient with pancreatic cancer; by referral from the MSKCC Clinical Genetics Service; or by self-referral after finding our Registry on the internet. HRIs identified by study and clinical staff are referred to the Clinical Genetics Service for genetic counseling if they have not been seen there previously.

Data collection

All aspects of the study were performed after approval by the MSKCC Institutional Review Board and conducted in accordance with the U.S. Common Rule. After providing informed written consent, all participants in the Registry are personally interviewed by a trained research study assistant. The interview covers established and potential risk factors for PDAC. Respondents also complete a detailed questionnaire to ascertain personal and family history of cancer. The family history questionnaire includes questions on the birthplace and religion of each grandparent to assess genetically high risk populations such as individuals with Ashkenazi Jewish ancestry. Alternatively, if a participant was already seen by the MSKCC Clinical Genetics Service, the pedigree created during that consultation by a board-certified genetic counselor is used. Follow-up questionnaires are administered approximately every 2 years to update information on lifestyle exposures [such as smoking, body mass index (BMI), and diabetes] and family history of pancreatic and other cancers. For this analysis, we used data from the baseline questionnaire, except for personal and family history of cancer, which was from updated family history questionnaires.

Surveillance

HRIs are offered surveillance with MRCP/CT at enrollment and at 1-year intervals. Those with cysts and/or

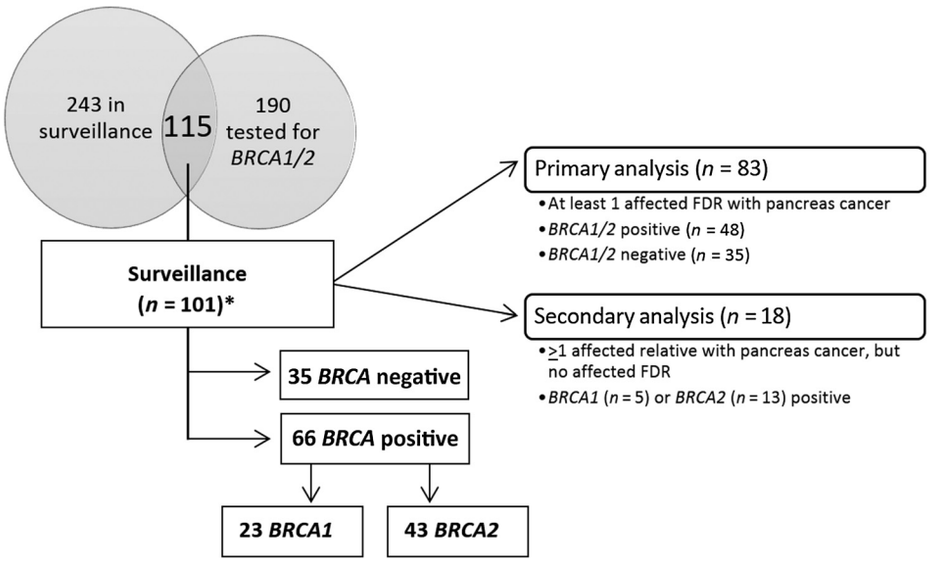

Figure 1.
Overview of subjects in analysis.

pancreatic lesions identified on screening may undergo follow-up imaging every 6–9 months at the discretion of the treating physician. We utilize MRCP as the primary surveillance tool because of its sensitivity and because there is no associated radiation exposure. By choice, per treating physician's recommendation, or as follow-up for other medical issues, some participants also had abdominal and pelvic CT scans during the period of surveillance ($n = 13/83$ in main analysis; 5/18 in secondary analysis). Endoscopic ultrasound and/or surgery are recommended if the MRCP indicates an abnormal finding in the pancreas, such as a large or enlarging pancreatic cyst size ≥ 3 cm, cyst size that increases over surveillance intervals, a dilated main pancreatic duct, or the presence of a solid component in the pancreas on imaging. In December 2012, the surveillance protocol was updated to recommend that HRIs with pathogenic germline mutations in *BRCA1/2* undergo annual endoscopic ultrasound evaluations scheduled approximately 6 months after MRCP.

Data analysis

We compared the characteristics of HRIs with and without pathogenic mutations in the *BRCA1/2* genes, separately and together; Table 1 summarizes these results with *P* values from χ^2 tests. We determined the proportion with an abnormality on MRCP/CT within those groups and whether abnormalities noted were prevalent or incident. We further compared the characteristics of those HRIs with and without findings of IPMN, the most common lesions observed. We described the lesions found and the outcome of follow-up for those with screen-detected IPMNs. We used logistic regression to estimate ORs to evaluate the independent influence of *BRCA1/2* mutation status and characteristics associated with presence of IPMNs.

Results

Characteristics of HRIs

As shown in Table 1, the median age of HRIs with at least one FDR was 54 (range 45–69) and 75% (62/83) of participants were women. Nearly all were white (77/83, 93%) and non-Hispanic (80/83, 96%), and over half (45/83, 54%) had 2 or more Ashkenazi Jewish grandparents. Most participants were college educated (79/83, 95%). Most were of normal weight or were underweight (57/83, 69%), 35% (29/83) had ever smoked cigarettes (only 4% were current smokers), and 6% (5/83) had been diagnosed with diabetes. Nearly half (39/83, 47%) had a personal history of cancer. Most of the reported cancers were breast cancer in women ($n = 25$). Overall, 20% (17/83) had ≥ 2 FDRs with pancreatic cancer and 36% (30/83) had 1 FDR and ≥ 1 SDR. The median length of total time in surveillance for the 83 HRIs was 48 months (range 0–149). Most participants (77%) had three or more screening events (i.e., MRCP, CT, or endoscopic ultrasound) over the course of surveillance.

As shown in Table 1, HRIs who tested positive for pathogenic mutations in *BRCA1/2* were more likely to be of Ashkenazi Jewish descent (65% vs. 40%; $P = 0.03$). They were also more likely to be male (33% vs. 14%; $P = 0.05$) and to be non-Hispanic (100% vs. 91%; $P = 0.04$). Those who were *BRCA1/2* negative had stronger family history, with 88% having at least 1 FDR and another first- or second-degree relative affected, compared with 34% of those who were *BRCA1/2* positive ($P < 0.0001$); this reflects differences in eligibility requirements as described above.

Table 1. Characteristics of HRIs tested for *BRCA1* and *BRCA2* mutations

	Total (83; *n*, %)	*BRCA* positive (48; *n*, %)	*BRCA* negative (35; *n*, %)	*P*
Age at first surveillance				
45–49	24 (29)	10 (21)	14 (40)	0.15
50–59	39 (47)	26 (54)	13 (37)	
60–69	20 (24)	12 (25)	8 (23)	
Median age (range)	54 (45–69)	55 (45–67)	53 (45–69)	
Sex				
Male	21 (25)	16 (33)	5 (14)	0.05
Female	62 (75)	32 (67)	30 (86)	
Race				
White	77 (93)	46 (96)	31 (89)	0.23
African American, Other	6 (7)	2 (4)	4 (11)	
Ethnicity				
Non-Hispanic	80 (96)	48 (100)	32 (91)	0.04
Hispanic	3 (4)	0	3 (9)	
Ancestry[a]				
≥2 Ashkenazi Jewish grandparents	45 (54)	31 (65)	14 (40)	0.03
No Ashkenazi Jewish grandparents	38 (46)	17 (35)	21 (60)	
Years of education				
High school or less	4 (5)	2 (4)	2 (6)	0.93
College	23 (28)	13 (27)	10 (29)	
Graduate school	56 (67)	33 (69)	23 (66)	
Smoking				
Never	54 (65)	34 (71)	20 (57)	0.20
Past or current	29 (35)	14 (29)	15 (43)	
BMI				
Normal or underweight (<25)	57 (69)	30 (63)	27 (77)	0.16
Overweight or obese (≥25)	26 (31)	18 (38)	8 (23)	
Diabetes				
No	78 (94)	46 (96)	32 (91)	0.40
Yes	5 (6)	2 (4)	3 (9)	
Personal history of cancer				
None	44 (53)	22 (46)	22 (63)	0.12
≥1 diagnosis	39 (47)	26 (54)	13 (37)	
Family history of PDAC				
≥2 FDR	17 (20)	6 (13)	11 (31)	<0.0001
1 FDR and ≥1 SDR	30 (36)	10 (21)	20 (57)	
1 FDR only[b]	36 (43)	32 (67)	4 (11)	
BRCA mutation status				
BRCA positive	48 (58)	48 (100)	NA	NA
BRCA1	18 (22)	18 (38)	NA	
BRCA2	30 (36)	38 (62)	NA	
*BRCA*1/2 negative	35 (42)	NA	35 (100)	

Abbreviation: NA, not applicable.

[a]There were no HRIs with only 1 Ashkenazi Jewish grandparent.

[b]Includes 1 HRI whose FDR had early-onset PDAC, and 3 HRIs with 1 affected FDR and an additional affected relative (not SDR).

BRCA2 mutations were more common ($n = 30$) than *BRCA1* mutations ($n = 18$; Table 1). Most mutations (29/48) were the Ashkenazi Jewish founder mutations: c.68_69delAG ($n = 6$) and c.5266dupC ($n = 5$) in *BRCA1* and c.5946delT ($n = 18$) in *BRCA2*. Median length in surveillance was longer for *BRCA1/2*-negative HRIs (median 60 months; range 0–149) than for *BRCA1/2* positive (median 36 months; range 0–127), again reflecting changes in eligibility over time.

Our article focuses on the findings and follow-up of HRIs with presumed IPMN. For the remaining 54 HRIs in the main cohort without identified pancreatic lesions, the median months of follow up was 36 months (35 for the *BRCA1/2* positive and 66.5 for the *BRCA1/2* negative) and the median number of screening events was 5 (3.5 for the *BRCA1/2* positive and 5.5 for the *BRCA1/2* negative).

Abnormalities found on MRCP/CT

Overall, about one-third (29/83, 35%) of HRIs with known *BRCA1/2* mutation status were found to have an abnormality on MRCP/CT (Table 2); nearly all of these (27/83, 33%) were interpreted as branch-duct IPMN. The proportion with IPMN was similar for those with (31%) and without (34%) any pathogenic *BRCA* mutation and for those with mutations in *BRCA1* (33%) and in *BRCA2* (30%). Most IPMN (overall, 21/27, 78%) were prevalent lesions, found on initial surveillance, and this did not vary by presence or absence of *BRCA1/2* mutations.

For the remaining 2 HRIs with abnormalities found on surveillance, 1, with a *BRCA2* mutation, was identified as having chronic pancreatitis (confirmed by endoscopic ultrasound); the other, with no mutations in *BRCA1/2*, was found to have a pancreatic mass that was confirmed to

Table 2. Pancreatic abnormalities identified in HRIs testing positive or negative for *BRCA* mutations

	***BRCA* positive**			
	Total (48; *n*, %)	***BRCA1* (18; *n*, %)**	***BRCA2* (30; *n*, %)**	***BRCA* negative (35; *n*, %)**
Any abnormality on MRCP/CT	16 (33)			13 (37)
Abnormality identified as IPMN	15 (31)	6 (33)	9 (30)	12 (34)
Prevalent (found on first MRCP/CT)	11 (23)	5 (28)	6 (20)	10 (29)
Incident (found on subsequent MRCP/CT)	4 (8)	1 (6)	3 (10)	2 (6)

NOTE: Abnormalities other than branch-duct IPMNs were 1 *BRCA*-positive patient with chronic pancreatitis and 1 *BRCA*-negative patient with metastatic serous carcinoma of mullerian origin to pancreas.

be metastases of high-grade serous carcinoma of mullerian origin.

Secondary analysis in *BRCA1/2*-positive HRIs with weaker family history

The 18 HRIs in this additional group had at least one affected SDR, but no affected FDR; most (14/18, 78%) had only one SDR. Overall, these HRIs were similar demographically to the *BRCA1/2*-positive HRIs with stronger family history, described above, except that a nonstatistically significant higher proportion were aged $\geq$60 (45% vs. 25%; $P = 0.28$). The proportion of this subgroup who were found to have abnormalities was 39%; all were considered to be IPMNs. Median length in surveillance was longer for those with negative findings (median 39 months, range 21–110) than those with positive (median 1 month, range 0–102). Five of the 11 HRIs with negative findings were recently recruited and had only one screen.

Follow-up of presumed IPMNs

Our follow-up of the 27 HRIs with presumed branch-duct IPMN in the main analysis is summarized in Supplementary Table S1. Endoscopic ultrasound was recommended and undertaken for 19 (12 *BRCA1/2* positive and 7 *BRCA1/2* negative) and confirmed pancreatic lesions in 12 of these cases (7 in *BRCA1/2*-positive and 5 in *BRCA1/2*-negative individuals; Fig. 2). Endoscopic ultrasound did not visualize the pancreatic lesions initially identified on imaging for 7 HRIs, likely due to the small size of these pancreatic cysts, which ranged from 0.3 to 1.4 cm on imaging. These small cysts were again noted on follow-up MRCP for all 7 patients, and they continue to be monitored with MRCP for any changes.

Surgery was recommended for 4 HRIs. Patient 1, with a mutation in *BRCA*2, underwent surgery due to increasing size cystic lesions throughout the pancreas. Surgical pathology showed IPMN with low grade dysplasia and chronic pancreatitis in the remaining pancreas. This patient presented approximately 9 months later with jaundice and metastatic cancer in her liver; liver biopsy was consistent with pancreaticobiliary origin. Cross-sectional imaging of the remaining pancreas showed no pancreatic mass to account for this metastatic disease. The patient is now deceased.

Baseline MRCP for Patient 2, *BRCA1/2* negative, identified cystic lesions in the pancreatic head and neck.

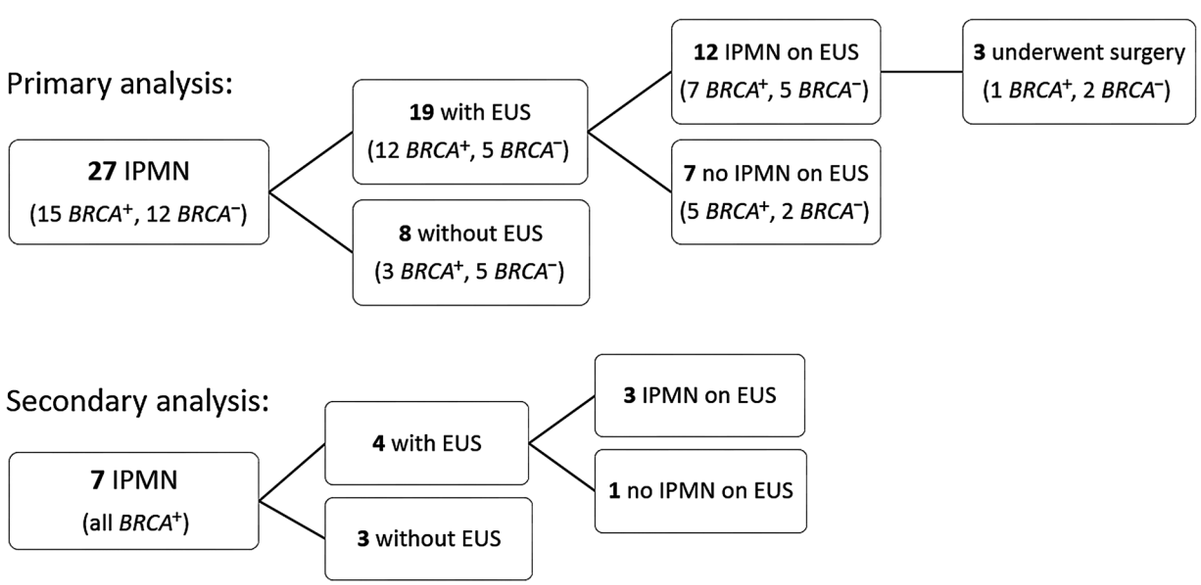

Figure 2.
Endoscopic ultrasound among HRIs with IPMN from primary and secondary analyses.

Surgery was later recommended due to increasing size of the cystic lesions and dilatation of the main pancreatic duct. Pathology revealed multifocal IPMN of borderline malignant potential. The patient was followed closely after surgery, with MRCP showing no evidence of suspicious lesion in the pancreatic remnant, until expiring from uterine cancer about 6 years later.

Patient 3, also *BRCA1/2* negative, had surgery after MRCP noted a cystic lesion in the tail of the pancreas. Endoscopic ultrasound with FNA (fine needle aspiration) identified mucinous cells consistent with a mucinous neoplasm. The decision to move forward with surgery was primarily patient driven; despite a lack of worrisome features such as increased cyst size and ductal dilatation, the patient opted for surgery given her family history of PDAC. Pathology showed PanIN-2, focal fibrosis, and chronic inflammation. The patient is in good health 9 years after surgery, with follow-up MRCPs showing no new or suspicious lesions in the residual portion of the pancreas.

MRCP identified few cystic lesions in the pancreatic body and uncinate process of patient 4, a *BRCA1* mutation carrier. Endoscopic ultrasound confirmed these lesions and the patient was referred to surgery to discuss these findings given her strong family history and *BRCA1* mutation; given the options to undergo surgery as a prophylactic measure overall or continue watchful surveillance of her cysts, the patient chose the latter. She continues to be under surveillance 10 years later with no significant change in the identified lesions.

One HRI, patient 6, was scheduled for a repeat endoscopic ultrasound for follow-up on a screen-identified oval mass at the time of writing; subsequent scans for all remaining HRIs with pancreatic abnormalities in this analysis did not indicate significant changes in the identified lesions.

In the secondary analysis of HRIs known to have *BRCA1/2* mutations, we identified 7 cases with screen-identified lesions (Fig. 2). Endoscopic ultrasound confirmed the pancreatic lesions in 3 of these cases; all were recommended to continue surveillance to monitor their presumed IPMN (see Supplementary Table S2).

Other factors related to presence of IPMNs in surveillance participants

We investigated characteristics of HRIs that might have influenced the presence of IPMNs. Table 3 shows characteristics of those with ($n = 27$) and those without IPMNs ($n = 56$); none of these differences reached statistical significance in χ^2 tests. Logistic regression models, with presence of IPMN as the outcome, found no significant associations either. ORs were close to 1 for presence of *BRCA*1/2 mutations and borderline significant for increasing age (Table 4).

Table 3. Selected characteristics of HRIs with and without IPMN

	IPMN (27; *n*, %)	No IPMN (56; *n*, %)	*P*
Age at first surveillance			
45–49	6 (22)	18 (32)	0.15
50–59	11 (41)	28 (50)	
60–69	10 (37)	10 (18)	
Sex			
Male	7 (26)	14 (25)	0.93
Female	20 (74)	42 (75)	
Ancestry			
≥2 Ashkenazi Jewish grandparents	18 (67)	27 (48)	0.11
No Ashkenazi Jewish grandparents[a]	9 (33)	29 (52)	
Smoking			
Ever	12 (44)	17 (30)	0.21
Never	15 (56)	39 (70)	
BMI			
Underweight or normal (<25)	17 (63)	40 (71)	0.44
Overweight or obese (≥25)	10 (37)	16 (29)	
Personal history of cancer			
None	15 (56)	29 (52)	0.75
≥1 diagnosis	12 (44)	27 (48)	
Family history of PDAC			
≥2 FDR	6 (22)	11 (20)	0.42
1 FDR and ≥1 SDR	12 (44)	18 (32)	
1 FDR only	9 (33)	27 (48)	

[a]No HRIs had only 1 Ashkenazi Jewish grandparent.

Discussion

Our Registry population and close coordination with the Clinical Genetics Service provide an opportunity to evaluate our hypothesis that surveillance in individuals with pathogenic mutations in *BRCA1/2* might be beneficial to them by identifying pancreatic lesions that could be characterized as premalignant. Our comparison group is unique: those known not to have mutations in either of these genes. We found no difference in pancreatic abnormalities between those with and without mutations. Results were similar in those with mutations in *BRCA1* and *BRCA2*. In an additional subset of 18 HRIs who were *BRCA1/2* positive but had weaker family history, the proportion of abnormalities found on MRCP was also similar. On the basis of our study, HRIs with mutations in *BRCA1/2* do not appear to be more likely to have pancreatic abnormalities on surveillance. Because this report is based on a small number of HRIs, research should be continued on outcomes of surveillance programs among the *BRCA*-positive population as well as the general

Table 4. Multivariate analysis of factors related to presence of IPMN

	OR (95% CI)
Age at first surveillance (per year)	1.07 (1.0–1.2)
≥2 Ashkenazi Jewish grandparents	2.7 (0.86–8.2)
Ever smoked	2.1 (0.69–6.5)
Family history of PDAC	
1 FDR only	1 (reference)
1 FDR and ≥1 SDR	1.7 (0.45–6.2)
≥2 FDR	1.4 (0.31–6.6)
BRCA1/2 mutation status	0.89 (0.26–3.0)

Abbreviation: CI, confidence interval.

high risk population. We do not recommend changes in clinical practice at this time.

A recent study (5), which focused on neoplastic progression in HRIs undergoing surveillance, included 41 HRIs with known mutations in *BRCA1/2* or *PALB2*; 2 of the 41 HRIs showed neoplastic progression, a similar proportion to that among all HRIs ($n = 354$) in that study. Bartsch and colleagues (30) studied a group of individuals at risk for pancreatic cancer based on their family history and *BRCA1/2/PALB2* mutation status in three European centers. Their study included 17 individuals with known mutations. In contrast to our study, they observed a higher proportion with potentially significant lesions compared with all others, 18% versus 6%.

The overall proportion of HRIs in our study with positive findings on MRCP was 35%; this was higher than the 17% reported in our previous study of a more broadly defined group of at-risk relatives (31) but consistent in other studies, where prevalence of lesions has ranged from 32% to 53% (30, 32, 33).

It is not clear why in this high risk cohort of patients with pathogenic *BRCA1/2* mutations, our imaging findings are no different from those individuals with *BRCA*-negative results. It may be that *BRCA1/2* mutations are more strongly associated with Pan-INs, which cannot be detected with the imaging modalities used in our study. Although most of the lesions found in this study were prevalent (found at initial surveillance), it is possible that more incident lesions or changes in existing lesions would be found with longer follow-up (34, 35).

This study has several limitations. Because the study was conducted at a tertiary referral hospital, the HRIs included here do not come from a well-defined population and results may not be generalizable to the overall population. As in other studies (5, 18, 36, 37), our population is not diverse in terms of race; in contrast to other studies, our population includes a relatively large proportion of Ashkenazi Jews. These characteristics reflect both our local population and the self-selection of HRIs for this program. We do not have information on reasons for undergoing testing for mutations in *BRCA1/2* and our data do not allow us to disentangle the roles of family history, personal history, and Ashkenazi Jewish background in their decisions. HRIs included in this analysis were not tested for all possible PDAC susceptibility genes. Some of the HRIs had testing only for the three Ashkenazi Jewish founder mutations. However, among the 13 HRIs of Ashkenazi background who tested negative for *BRCA1/2*, 10 provided documentation that they had more thorough testing with sequencing and/or large rearrangement analyses for mutations, making it unlikely that misclassification influenced the results. Another limitation is that our eligibility criteria changed over the study period. Although inclusion guidelines for the Registry have been consistent with past consensus and present recommendations for who should be screened (38), criteria changes have resulted in differences between those with and without *BRCA1/2* mutations in family history and length of follow-up. However, because family history was not related to presence of IPMNs, and most lesions were found on the initial scan and did not change in subsequent scans, these factors are unlikely to have influenced results.

This study includes only a subset of HRIs included in our Registry, and a larger analysis of findings in all surveillance participants is underway. The contribution of this analysis is the direct comparison of those with mutations in *BRCA1/2* to those known not to have mutations, with no differences noted on the basis of surveillance with dedicated MRCP/CT and endoscopic ultrasound. What is needed is a biomarker for PDAC that can reproducibly stratify PDAC risk and aide in identifying individuals who are in the early stage of developing a pancreatic neoplasm from those who are not. Work in the identification of such biomarkers is currently ongoing, and it is hoped that this will make an impact on the early identification of individuals at high risk for this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E. Salo-Mullen, P.J. Allen, K. Offit, R.C. Kurtz
Development of methodology: A. Saldia, P.J. Allen, R.C. Kurtz
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Saldia, P. Nunes, M.L. Samson, E. Salo-Mullen, V. Marcell, Z.K. Stadler, P.J. Allen, K. Offit
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Saldia, X. Liang, E. Salo-Mullen, V. Marcell, Z.K. Stadler, K. Offit, R.C. Kurtz
Writing, review, and/or revision of the manuscript: A. Saldia, P. Nunes, E. Salo-Mullen, V. Marcell, Z.K. Stadler, P.J. Allen, R.C. Kurtz
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Saldia, M.L. Samson, K. Offit, R.C. Kurtz
Study supervision: A. Saldia, R.C. Kurtz

Acknowledgments

This research was supported in part by the NIH/NCI Cancer Center Support Grant P30 CA008748. The following authors were directly supported by the grant: A. Saldia, S.H. Olson, P. Nunes, X. Liang, M.L. Samson, E. Salo-Mullen, V. Marcell, Z.K. Stadler, P.J. Allen, K. Offit, and R.C. Kurtz.

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Received July 20, 2018; revised January 22, 2019; accepted July 17, 2019; published first July 23, 2019.

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