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Identification of Germline Genetic Mutations in Pancreatic Cancer Patients

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Abstract

Background—Pancreatic adenocarcinoma (PAC) is part of several cancer predisposition syndromes; however, indications for genetic counseling/testing are not well-defined. We sought to determine mutation prevalence and characteristics that predict for inherited predisposition to PAC.

Methods—We identified 175 consecutive PAC patients who underwent clinical genetics assessment at Memorial Sloan Kettering between 2011–2014. Clinical data, family history, and germline results were evaluated.

Results—Among 159 PAC patients who pursued genetic testing, 24 pathogenic mutations were identified (15.1%; 95%CI, 9.5%–20.7%), including *BRCA2*(n=13), *BRCA1*(n=4), *p16*(n=2), *PALB2*(n=1), and Lynch syndrome(n=4). *BRCA1*/*BRCA2* prevalence was 13.7% in Ashkenazi Jewish(AJ) (n=95) and 7.1% in non-AJ(n=56) patients. In AJ patients with strong, weak, or absent family history of *BRCA*-associated cancers, mutation prevalence was 16.7%, 15.8%, and 7.4%, respectively. Mean age at diagnosis in all mutation carriers was 58.5y(range 45–75y) compared to 64y(range 27–87y) in non-mutation carriers(P=0.02). Although *BRCA2* was the most common mutation identified, no patients with early-onset PAC(≤50y) harbored a *BRCA2* mutation and the mean age at diagnosis in *BRCA2* carriers was equivalent to non-mutation carriers(P=0.34). Mutation prevalence in early-onset patients(n=21) was 28.6%, including *BRCA1*(n=2), *p16*(n=2), *MSH2*(n=1) and *MLH1*(n=1).

Conclusion—Mutations in *BRCA2* account for over 50% of PAC patients with an identified susceptibility syndrome. AJ patients had high *BRCA1*/*BRCA2* prevalence regardless of personal/family history, suggesting that ancestry alone indicates a need for genetic evaluation. With the exception of *BRCA2*-associated PAC, inherited predisposition to PAC is associated with earlier

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age at PAC diagnosis suggesting that this subset of patients may also represent a population warranting further evaluation.

Keywords

Pancreatic cancer; Germline; Genetics; Mutations; Hereditary; Ashkenazi Jewish; *BRCA*; Lynch; *p16*; *PALB2*

Introduction

Although the majority of pancreatic adenocarcinoma (PAC) cases appear to be sporadic, about 5–10% occur in the presence of a family history of the disease [1, 2]. Pancreatic cancer has been linked to inherited cancer susceptibility syndromes including Hereditary Breast and Ovarian Cancer syndrome (*BRCA1*, *BRCA2*), Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome (*p16*), Peutz-Jeghers syndrome (*STK11*), Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, PMS2, *EPCAM*), Hereditary Pancreatitis (*PRSS1*, *CFTR*, *CTRC*, *SPINK1*), and *PALB2*-associated PAC [3–16].

In the last two decades, significant strides have been made in the ability to diagnose and appropriately manage individuals with germline mutations, particularly in the *BRCA1* and *BRCA2* genes. The Breast Cancer Linkage Consortium observed a 3.51-fold relative risk for pancreatic cancer in families with *BRCA2* mutations; and *BRCA2* mutations were identified in 17% of kindreds in whom ≥3 members were affected with pancreatic cancer [6, 8]. The relative risk of pancreatic cancer in *BRCA1* mutation carriers is estimated to be 2-fold higher than the general population [4]. Recognizing the association of PAC with *BRCA1*/*BRCA2* mutations, the National Comprehensive Cancer Network (NCCN) incorporates a personal or family history of pancreatic cancer in their risk assessment and testing guidelines for Hereditary Breast and Ovarian Cancer syndrome [17].

Not surprisingly, given the presence of founder mutations (*BRCA1**185delAG, *BRCA1**5382insC; *BRCA2**6174delT), the Ashkenazi Jewish (AJ) PAC patient population has previously been shown to have a high prevalence of *BRCA1*/*BRCA2* genes mutations. For example, 5.5% of patients with Ashkenazi ancestry (unselected for family history of cancer) with resected PAC harbored one of the three common AJ founder mutations; while in AJ breast-and-pancreas cancer families, 14.2% were found to carry a *BRCA1*/*BRCA2* mutation with nearly equal distribution amongst the two genes [18, 19].

With the emergence of poly-ADP ribose polymerase (PARP)-inhibitors and the recognition of platinum-sensitivity for the treatment of *BRCA*-associated malignancies, the potential benefit of identifying *BRCA1*/*BRCA2* mutations in patients with pancreatic cancer is becoming evident [20–24]. Moreover, the identification of an inherited cancer predisposition syndrome in a patient with pancreatic cancer may have important implications for the individual's family members with respect to cancer risk and cancer surveillance and risk-reduction recommendations.

Given cost and overall low yield, genetic testing cannot be extended to all pancreas cancer patients, and therefore, the optimal selection of PAC patients for *BRCA1*/*BRCA2* or other

genetic testing remains a significant clinical challenge. In an effort to develop better selection criteria for genetic testing, we determined the prevalence of germline mutations in a consecutive series of pancreas cancer patients seen in the Clinical Genetics Service, assessed personal and familial characteristics predictive of genetic mutations, and determined concordance of current genetic testing guidelines, such as those of the NCCN, with the identification of germline genetic mutations in our patient cohort.

Methods

A review of the Memorial Sloan-Kettering Cancer Center (MSKCC) Clinical Genetics Service (CGS) clinical database identified all patients with a personal diagnosis of pancreatic cancer who underwent clinical genetic counseling consultation between 1/1/2011 to 12/31/2014. Clinical data (including age at diagnosis, cancer pathology, previous cancer history, genetic tests offered and completed, and genetic test results) were gathered. Information regarding family history of cancer and ancestry was obtained by a genetic counselor with construction of a three-generation pedigree. This retrospective study was approved by the MSKCC Institutional Review Board.

Genetic testing based upon the patient's personal and family histories was offered to patients in the clinical setting during genetic counseling consultations. Informed consent was obtained for all testing. *BRCA1*/*BRCA2* mutation analysis included targeted mutation analysis for the three common AJ founder mutations (*BRCA1**185delAG, *BRCA1**5382insC; *BRCA2**6174delT), full gene sequencing analysis, and/or large rearrangement analysis. Tumor tissue analyses for Lynch syndrome evaluation included immunohistochemical (IHC) staining analysis for the DNA mismatch repair proteins, microsatellite instability (MSI) analysis, and/or MLH1 promoter hypermethylation. Germline evaluation for Lynch syndrome, FAMMM, *PALB2*, and multi-gene panels were also performed either at our in-house laboratory or a New York State approved commercial laboratory. Statistical analysis was performed using Chi-square test.

Results

Patient Characteristics

One hundred and seventy-five (175) patients (89 females, 98 of AJ ancestry) with 176 pancreatic cancers (one patient had a metachronous primary pancreatic cancer) were seen in the MSKCC CGS between 1/1/2011 and 12/31/2014. The median and mean ages at PAC diagnosis were 64 and 63 years, respectively, with a range of 27 to 87 years. A description of patient characteristics is included in Table 1. In 73.7% of patients, pancreatic cancer was the only cancer diagnosis. In the 46 patients with more then one primary malignancy, the most common cancers to have occurred were breast cancer among women (18%, 16/89) and prostate cancer among men (16.3%, 14/86). Another 9 patients had melanoma and 4 had a urinary tract cancer (bladder and renal). Other primary cancers seen included colorectal cancer, lymphoma, GIST, cervical, thyroid, uterine, a carcinoid tumor in the duodenum, a neuroendocrine tumor of unknown primary, and as mentioned before, one patient had two metachronous primary PAC diagnoses.

Family histories were reviewed for the number of first- and second-degree relatives with breast, ovarian, pancreatic, and/or colorectal cancer diagnoses (Table 1). The side of the family with the most significant cancer history (based upon number and/or type of cancers present) was selected for inclusion. Breast cancer was the most common cancer seen in close family members, followed by pancreatic, colorectal, and ovarian, respectively. Forty patients (22.9%) met criteria for Familial Pancreatic Cancer, with pancreatic cancer seen in at least one of their first-degree relatives in addition to their own diagnosis.

Based upon personal and family histories of cancer, patients were referred to the CGS for evaluation of multiple inherited cancer predisposition syndromes. Out of the 175 total patients seen, evaluation for Hereditary Breast and Ovarian Cancer syndrome was considered for 166 patients with 151 patients pursuing testing (Table 2). Based upon a personal or family history of other Lynch syndrome-associated cancers and the availability of cancer tissue for tumor analyses, evaluation for Lynch syndrome was performed in 36 patients. *PALB2* germline genetic evaluation was considered in light of a personal and/or family history of pancreatic and breast cancer, with testing completed in 48 patients; and *p16* genetic testing was performed in 17 patients.

Genetic Test Results

Of the 159 PAC patients who pursued any genetic testing, a pathogenic germline mutation was identified in 24 patients (15.1%; 95% CI, 9.5% to 20.7%) (Table 2) and included mutations in *BRCA2* (n=13), *BRCA1* (n=4), *p16* (n=2), *PALB2* (n=1) and the DNA mismatch repair genes (n=4), consistent with Lynch syndrome. The mean age at PAC diagnosis in all germline mutation carriers was 58.5 years (range 45–75y) as compared to a mean age of 64 years (range 27–87y) in non-mutation carriers (*p* value, 0.024). Although *BRCA2* was the most common gene to be mutated in the overall cohort, no patients with early-onset PAC (diagnosed at ≤ age 50y) harbored a *BRCA2* mutation (Table 3); and the mean age at PAC diagnosis in *BRCA2* mutation carriers was 61 years, which was not different from the mean age of onset in non-mutation carriers (*p* value, 0.34). The prevalence of mutations in patients with early-onset PC was 28.6% and included *BRCA1* (n=2), *p16* (n=2), one *MSH2*, and one *MLH1* mutation (Table 3). In contrast, in patients with late-onset PAC (diagnosed at ≥ age 70y), the mutation prevalence was only 6.5% (*p* value, 0.01). Of the 34 patients with familial PAC (first-degree relative also with PAC) who underwent genetic testing, one *BRCA1* mutation (non-AJ patient) and one *BRCA2* mutation (AJ patient) was identified.

Hereditary Breast and Ovarian Cancer (HBOC) syndrome—A total of 151 PAC patients underwent genetic testing for HBOC (79 full *BRCA1*/*BRCA2* sequencing including 65 with large rearrangement analysis; 72 AJ *BRCA* founder mutation testing only). A *BRCA1/BRCA2* mutation was identified in 17 (11.3%) patients, with the majority being *BRCA2* mutations (Table 2). The prevalence of a *BRCA1/BRCA2* mutation was 13.7% and 7.1% in AJ (n=95) and non-AJ patients (n=56), respectively (Table 4). The mean age at PAC diagnosis for all *BRCA1*/*BRCA2* mutation carriers was 60.5 years (range 45–75 years). Despite the later age at which PAC occurred in the *BRCA* mutation carriers, a personal history of a prior *BRCA*-associated tumor was present only in 2 women, both with a prior

diagnosis of breast cancer. The two mutation carriers with early-onset PAC were of non-AJ ancestry and harbored *BRCA1* mutations.

Within the 56 patients with a very strong family history with ≥2 close relatives (first- or second-degree) with a *BRCA*-associated cancer (breast, ovarian, pancreas), mutation prevalence was 16.7% among the AJs (n=30) and 7.7% among the non-AJ (n=26) patients (Table 4). In the AJ patients with a weak family history (1 close relative with a *BRCA*-associated cancer) or isolated PAC only, mutation prevalence was 15.8% and 7.4%, respectively. In the non-AJ PAC patients, mutation prevalence was 11.1% in patients with a weak family history, albeit this dataset was limited by a small sample size. No mutations were identified in isolated non-AJ PAC patients.

Other inherited predisposition syndromes—Thirty-six patients underwent evaluation for Lynch syndrome with four pathogenic germline mutations (1 *MLH1*, 2 *MSH2*, 1 *MSH6*) identified. The families of all of the Lynch syndrome patients met Revised Bethesda guidelines, with two families also meeting the Amsterdam II Criteria. One of the *MSH2* gene mutation carriers had a PAC with a mixed pathology with neuroendocrine and acinar features. Notably, in three of the Lynch syndrome patients, the PAC was the sentinel cancer diagnosis and two of the patients were diagnosed under the age of 50 years. Immunohistochemical (IHC) staining analysis in two additional PAC patients demonstrated DNA mismatch repair deficiency, with subsequent germline testing being unrevealing (i.e. germline testing negative).

One of 48 individuals who underwent *PALB2* gene analysis was identified to have a pathogenic mutation. This patient had adenocarcinoma with squamous differentiation, no personal history of other cancers, and family history was positive only for a second-degree relative with late-onset breast cancer. Genetic testing of the *p16* gene was performed in 17 patients and identified two suspected pathogenic mutations. Both patients had early-onset pancreatic adenocarcinomas as well as personal histories of melanoma. Seven patients underwent multi-gene panel testing, including two specifically for hereditary pancreatitis. Upon these multi-gene panel tests, a single pathogenic *BRCA2* mutation was found, and a single variant of undetermined clinical significance in each of the following genes was found: *BRCA2*, *PALB2*, *APC*, and *CFTR*.

Discussion

In one of the largest consecutive series of PAC patients who presented for clinical cancer genetics evaluation from 2011–2014, we identified a pathogenic germline mutation in 15.1%, spanning seven different pancreatic cancer susceptibility genes, including *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *p16*, and *PALB2*. The most common gene found to be altered was the *BRCA2* gene, accounting for 54% of all identified pathogenic mutations. The overall mutation prevalence in our cohort is similar to the mutation prevalence in other selected PAC cohorts with a family history of cancer. In PAC patients with a personal or family history of breast or colorectal cancer, Grant et al. reported a mutation prevalence of 10.7% and 11.1%, respectively [25]. In our study, 85.5% of patients had either a personal

history of a second malignancy or at least one FDR/SDR with a history of breast, ovarian, pancreatic or colorectal cancer.

Distinct from prior studies, our population represents one of the largest cohorts of Ashkenazi Jewish PAC patients undergoing clinical genetic testing [25, 26]. Among 96 AJ PAC patients who underwent genetic evaluation, mutation prevalence was 15.6% with all identified mutations representing known AJ founder mutations (one *BRCA1**185delAG; one *BRCA1**5382insC; eleven *BRCA2**6174delT, one *MSH2**A636P, one *MSH6**3987ins4). Prior studies of AJ PAC populations assessing for just *BRCA1*/*BRCA2* found similar rates of mutations, again with the founder *BRCA2**6174delT mutation being the most common [19, 26]. Within AJ PAC patients that specifically underwent *BRCA1*/*BRCA2* testing, 13.7% were mutation positive, with prevalence rates of 16.7%, 15.8%, and 7.4% in patients with strong, weak, or absent family history of a *BRCA*-associated cancer, respectively. The National Comprehensive Cancer Network (NCCN) has acknowledged the association of pancreatic cancer with *BRCA1*/*BRCA2* mutations and, over the last few years, has started to incorporate a personal or family history of pancreatic cancer in their risk assessment and testing guidelines for HBOC [17]. Of the PAC patients tested for *BRCA1*/*BRCA2* mutations, 51% met the 2013, 73.5% the 2014 and 93.4% the recently published 2015 NCCN guidelines. The 2014 provision includes the recommendations of *BRCA1*/*BRCA2* testing in AJ PAC patients who have at least one other family member with a *BRCA*-associated malignancy, while the 2015 provision expands testing criteria to all AJ PAC patients. These important provisions resulted in an increase from 52.9% to 100% of our *BRCA1*/*BRCA2* mutation carriers meeting current NCCN guidelines, including 5 AJ PAC patients who only had one other family member with a *BRCA*-associated malignancy and 2 AJ patients with isolated PAC (i.e. no family history of *BRCA*-associated malignancies). Herein, we provide evidence for the appropriateness of the recently revised NCCN criteria that recognize the relatively high prevalence of founder mutations within PAC patients of Ashkenazi descent. Moreover, these recommendations reflect the *BRCA1/BRCA2* genetic testing criteria currently in use for AJ patients with breast, ovarian or male breast cancer where no additional family history is required to meet testing criteria. Notably, as the mean age at PAC diagnosis in the *BRCA1/BRCA2* positive patients was 60.5, with a range of 45–75 years of age, it is important that coverage for HBOC genetic testing for PAC patients be incorporated as part of Medicare coverage going forward.

Interestingly, while in the overall cohort, mutation carrier status was associated with an earlier age at pancreatic cancer diagnosis (58.5 years versus 64 years; *p* value 0.024), this result was driven by mutations in genes other than *BRCA2*. In fact, similar to other prior studies [8], the mean age at PC diagnosis in the *BRCA2* mutation carriers was not different from the mean age at diagnosis in the overall cohort. In many cancer predisposition syndromes, including HBOC and Lynch syndrome, early-age at diagnosis of a component tumor is a red flag for prompting referral for genetic risk assessment. In prior studies of PAC, age at onset of disease was not significantly associated with mutation carrier status [8, 18, 25]. However, such results may be limited given the rarity and small sample size of early-onset PACs in prior studies and may be biased due to a preponderance of older *BRCA2* mutation carriers. In this cohort, nearly 15% of patients had disease diagnosed at ≤ age 50 years, with a mutation identified in 28.6% of such patients who underwent testing. In

contrast, mutation prevalence among the PAC patients who were diagnosed at ≥ age 70 was only 6.5%. At the present time, genetic risk assessment for PAC is largely driven by family history, and, as such, all 6 of the early-onset PAC mutation carriers described here also had a previous personal or family cancer history. However, the high prevalence and the heterogeneity of the cancer susceptibility genes implicated in the early-onset PAC patients suggests that this unique subset of patients may derive benefit from genetic risk assessment. On the other hand, although *PALB2* germline mutations have been linked to pancreatic cancer susceptibility, our results are in line with prior research demonstrating low *PALB2* mutation prevalence in PAC patients and PAC families [26, 27].

Our study limitations include a selection bias in that our PAC cohort reflects patients who were referred and accepted clinical genetic counseling. The majority (90.8%) of those counseled accepted genetic testing. There may be PAC patients who were referred but either declined clinical genetics consultation or who were unable to proceed with genetic counseling given the severity of their disease. Despite the bias and limitation, this study population reflects one of the largest consecutive series of PAC patients to have undergone genetic risk assessment providing a real-world depiction of clinical genetics assessment and testing in the setting of PAC, including the largest AJ PAC ascertainment. As early-onset PAC is not by itself an existing criteria for referral for genetic risk assessment, the majority of our early-onset PAC patients had a previous personal or family history of cancer prompting referral to our service. Nonetheless, the identification of a nearly 30% mutation prevalence among early-onset PAC patients is striking and suggests a low threshold for referral for genetic testing in such patients, especially if personal or family history reveals component tumors of a hereditary cancer syndrome.

With the development of novel therapeutic agents such as PARP-inhibitors for *BRCA*-associated tumors and the recent remarkable results achieved with immunotherapy with PD-1 blockade in Lynch-like (mismatch-repair deficient) tumors, the identification of a germline genetic susceptibility syndrome in PAC patients is becoming increasingly relevant for treatment considerations[23, 28]. Our findings of a high *BRCA*-mutation prevalence in AJ PAC patients, including those with a weak or no family history of a *BRCA*-associated malignancy, support that every AJ PAC patient, regardless of age of onset, be extended genetic testing for the AJ *BRCA* founder mutations. With the exception of *BRCA2*-associated PAC, our results also suggest that an inherited predisposition to PAC appears to be associated with an earlier age at PAC diagnosis with an especially high mutation prevalence observed in early-onset PAC patients. While this unique subset of patients clearly warrants further study, as with many other early-onset cancers, genetic cancer risk assessment is reasonable to consider in patients with early-onset PAC. In the future, as genetic testing criteria for PAC expand and become more standardized, identification of at-risk family members will further allow for focused efforts on cancer prevention with initiation of surveillance and risk-reducing measures for associated malignancies, thereby potentially improving outcomes in entire families. Importantly, given the evidence provided here and in prior studies, we urge third-party payers, including Medicare, to recognize and incorporate coverage of genetic counseling and testing for selected PAC patients into their benefits.

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Table 1

Patient Baseline Characteristics.

Patient Characteristic (n=175 patients; 176 diagnoses)	Number of patients (%)
Age at diagnosis (mean, range)	63 years, 27–87 years
Gender	
Male	86 (49.1%)
Female	89 (50.9%)
Ashkenazi Jewish (AJ) ancestry	98 (56.0%)
Pathology	
Adenocarcinoma NOS	171 (97.7%)
Acinar	2 (1.1%)
Mixed (neuroendocrine, acinar, and ductal/adenocarcinoma features)	3 (1.7%)
Personal Cancer History	
>1 Primary cancer	46 (26.3%)
Breast	16 (9.1%)
Prostate	14 (8.0%)
Melanoma	9 (5.1%)
Urinary tract (bladder, renal)	4 (2.3%)
Metachronous pancreas cancer	1 (0.6%)
Other	10 (5.7%)
Family History	
FDR and/or SDR with breast cancer:	
0	89 (50.9%)
1	57 (32.6)
2	22 (12.6%)
≥3	7 (4.0%)
FDR and/or SDR with ovarian cancer:	
0	150 (85.7%)
1	24 (13.7%)
2	1 (0.6%)
≥3	0 (0.0%)
FDR and/or SDR with colorectal cancer:	
0	127 (72.6%)
1	38 (21.7%)
2	3 (1.7%)
≥3	7 (4.0%)
FDR and/or SDR with pancreatic cancer:	
0	114 (65.1%)
1	50 (28.6%)

Patient Characteristic (n=175 patients; 176 diagnoses)	**Number of patients (%)**
2	11 (6.3%)
≥3	0 (0.0%)
Familial Pancreatic cancer (PC in ≥2 FDRs including proband):	40 (22.9%)

FDR = first degree relative; SDR = second degree relative; PC = pancreatic cancer

Table 2

Evaluation and Identification of Cancer Predisposition Syndromes in Pancreatic Cancer Patients.

Syndrome	# of patients who completed evaluation	Mutation prevalence
Overall	159	24 (15.1%)
HBOC (BRCA1, BRCA2)	151	17 (11.3%) *4 BRCA1 mutations; 13 BRCA2 mutations*
Lynch syndrome (*MLH1, MSH2, MSH6, PMS2*)	36	4 (11.1%) *1 MLH1 mutation; 2 MSH2 mutations; 1 MSH6 mutation*
PALB2	48	1 (2.1%)
FAMMM *(p16)*	17	2 (11.8%)

HBOC = Hereditary Breast and Ovarian Cancer syndrome;

FAMMM = Familial Atypical Multiple Mole Melanoma syndrome

Table 3

Germline Mutation Prevalence in Pancreatic Cancer Patient Cohorts.

Patient population	N	Number of patients tested	Pathogenic mutation identified	*BRCA1* mutation	*BRCA2* mutation	Other Gene
Ashkenazi Jewish	98	96	15 (15.6%)	2	11	2
Non-Ashkenazi Jewish	77	63	9 (14.3%)	2	2	5
Early-onset (age ≤50)	26	21	6 (28.6%)	2	0	4
Late-onset (age ≥70)	51	46	3 (6.5%)	2	1	0
Familial Pancreatic	40	34	2 (5.9%)	1	1	0

Table 4

Prevalence of *BRCA1/BRCA2* Mutation by Ethnicity and Family Cancer History.

Patient & Family History	**Number of Patients who underwent *BRCA* testing**	***BRCA1/BRCA2* Mutation Prevalence**	**Gene/Mutation**
Ashkenazi Jewish ancestry	95	13 (13.7%)	1 *BRCA1**185delAG 1 *BRCA1**5382insC 11 *BRCA2**6174delT
≥2 FDR or SDR with *BRCA*-associated cancer*	30	5 (16.7%)	5 *BRCA2**6174delT
1 FDR or SDR with a *BRCA*-associated cancer*	38	6 (15.8%)	1 *BRCA1**185delAG 1 *BRCA1**5382insC 4 *BRCA2**6174delT
No family history	27	2 (7.4%)	2 *BRCA2**6174delT
Non-Ashkenazi ancestry	56	4 (7.1%)	2 *BRCA1* 2 *BRCA2*
≥2 FDR or SDR with *BRCA*-associated cancer*	26	2 (7.7%)	1 *BRCA1* 1 *BRCA2*
1 FDR or SDR with a BRCA-associated cancer*	18	2 (11.1%)	1 *BRCA1* 1 *BRCA2*
No family history	12	0	N/A

FDR = first degree relative; SDR = second degree relative

**BRCA*-associated cancer includes breast, ovarian, pancreas