Original Article

Cancers Associated With *BRCA1* and *BRCA2* Mutations Other Than Breast and Ovarian

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BACKGROUND: Previous studies have reported additional cancers associated with *BRCA* mutations; however, the type, magnitude of risk, and sex differences remain to be clarified. The purpose of this study was to evaluate the incidence of cancers other than breast and ovarian cancer in known mutation carriers. **METHODS:** An institutional review board–approved study identified 1072 patients who had genetic counseling at the authors' institution and tested positive for a deleterious *BRCA* mutation. The expected number of cancer cases was calculated from the number of individuals in the study sample multiplied by the cancer incidence rates for the general population. The expected and observed numbers of cases were calculated in 5-year intervals to accommodate different age-related incidence rates. Standardized incidence ratios (SIRs) for each cancer type were calculated. **RESULTS:** Among the 1072 mutation carriers, 1177 cancers of 30 different cancer types were identified. Individuals with a *BRCA1* mutation did not have a significant increase in cancers other than breast and ovarian cancer; however, a trend in melanoma was observed. Individuals with a *BRCA2* mutation had significantly higher numbers of observed cases versus expected cases for pancreatic cancer in both men and women (SIR, 21.7; 95% confidence interval [CI], 13.1-34.0; $P < .001$) and for prostate cancer in men (SIR, 4.9; 95% CI, 2.0-10.1; $P = .002$). **CONCLUSIONS:** The results of this study uphold the current recommendations for hereditary breast and ovarian cancer screening of cancers other than breast and ovarian cancer by the National Comprehensive Cancer Network. Larger cohorts and collaborations are needed to further verify these findings. ***Cancer*** **2015;121:269-75.** © *2014 American Cancer Society.*

KEYWORDS: *BRCA* mutation, genetics, hereditary breast and ovarian cancer syndrome, pancreatic cancer, prostate cancer.

INTRODUCTION

The *BRCA1* and *BRCA2* tumor suppressor genes repair DNA damage to prevent tumor development. Mutations in these genes predispose an individual to malignancy. The cancers associated with mutations in *BRCA1* and *BRCA2* have been studied continuously since their discovery in 1994 and 1995, respectively.[1,2] *BRCA1* and *BRCA2* mutation carriers have a significantly increased lifetime risk for developing breast and ovarian cancer (as high as 84% and 39%, respectively).[3-6]

Although the association of *BRCA1* and *BRCA2* mutations with breast and ovarian cancer risks is well defined, the potential association of these mutations with other cancers is inconsistent. Prior studies either have included families at high risk for a *BRCA* mutation or have combined *BRCA1* and *BRCA2* mutation carriers for analysis because of the small number of individuals with *BRCA* mutations.[7,8] These studies reported an increased incidence of cancers other than breast and ovarian cancer in mutation carriers; however, many reports did not differentiate between *BRCA1* and *BRCA2* mutation carriers.

In studies that have been able to focus on *BRCA1* or *BRCA2* mutation carriers separately, the number of participants has varied, with few studies containing more than 1000 mutation carriers. Ford et al[9] found an increased risk for both sexes,[9] whereas Thompson and Easton[10] found an increased risk only for women, and Moran et al[11] reported that *BRCA1* mutations are not associated with an increased risk for other cancers. Other studies have described a significantly increased risk of pancreatic, prostate, and colorectal cancers in mutation carriers.[9,10,12-14] *BRCA1* mutations have also been linked to increases in cervical, esophageal, liver, stomach, and uterine cancers; however, the increased risks have been inconsistent and have ranged from 1- to 4-fold.[9-12] Known environmental risk factors associated with these cancers have not typically been reported in these studies.

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The Breast Cancer Linkage Consortium[15] reported that *BRCA2* mutations are associated with an increased cancer risk in both sexes, whereas van Asperen et al[16] found a significantly increased risk for men only. The most commonly reported cancers with *BRCA2* mutations include pancreatic cancer, prostate cancer, and melanoma.[11,15-18] Additional cancers reported in the *BRCA2* spectrum include bone cancer, cancer of the buccal cavity and pharynx, esophageal cancer, gallbladder and bile duct cancer, laryngeal cancer, ocular cancer, male breast cancer, and stomach cancer, although this has been inconsistent across multiple studies.[11,15-17] Environmental risk factors for these cancers have not been regularly reported in these studies.

The purpose of this study was to determine whether cancers other than breast and ovarian cancers were detected more often in *BRCA* mutation carriers versus the general population. The limited number of studies and variable results indicate a need for further research into the occurrence of nonbreast or nonovarian cancers that are associated with *BRCA1* and *BRCA2* mutations. Ultimately, a consensus on additional cancer risk may aid in the better recognition of at-risk families for which genetic testing may be warranted and in more effective screening guidelines for the types of cancers that these families are at risk of developing.

MATERIALS AND METHODS

Study Population

This study was approved by the institutional review board of the University of Texas MD Anderson Cancer Center and by the committee for the protection of human subjects of the University of Texas Health Science Center at Houston. Individuals who had received genetic counseling at the Clinical Cancer Genetics clinics at the MD Anderson Cancer Center between 1997 and 2013 and who had a confirmed *BRCA1* or *BRCA2* deleterious mutation were eligible for this study. Individuals with variants suspected to be deleterious in *BRCA1* or *BRCA2* were included in this analysis because they were advised to follow the same high risk management guidelines as individuals with deleterious mutations in the clinical setting. The medical record number, date of birth, gene, mutation designation, number of cancers, type of cancer, and age at diagnosis were obtained from a secure Progeny database with data obtained during the genetic counseling session or from the patient's medical record. Additional information on the vital status, date of last contact with the institution, ethnicity, and selected risk factors were also obtained from the individual's medical record. Selected risk factors included tobacco use, alcohol use, radiation exposure, body mass index, and history of mastectomy and/or bilateral salpingo-oophorectomy. Information on a patient's personal cancer history was compared with information from both the medical record and the Progeny database to obtain the most current information.

Individuals with 2 *BRCA* mutations (either deleterious or suspected to be deleterious) in the same gene were included in the analysis. Individuals with mutations in both the *BRCA1* and *BRCA2* genes or with both a *BRCA* mutation and another known cancer-predisposing mutation or genetic condition were excluded from the analysis.

Statistical Methods

Cancer cases were counted for the total sample and for *BRCA1* and *BRCA2* mutation carriers separately. The earliest age at diagnosis was used in the analysis for individuals who developed the same cancer more than once in their lifetime. Most cancers were analyzed independently. Similar or related cancers were grouped together for analysis. For example, glioma, astrocytoma, and neuroblastoma were grouped together as brain/central nervous system cancers. Ovarian cancer was also defined to include primary peritoneal and fallopian tube cancers. Within each cancer or group of cancers, the data were stratified by sex and ethnicity.

We compared the cancer incidence in our sample with *United States Cancer Statistics: 1999-2010 Incidence and Mortality Web-Based Report* from the Centers for Disease Control and Prevention (CDC).[19] Data from the US Cancer Statistics (USCS) report combine the CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results program on cancer incidence in the US population. The USCS report includes incidence data for 20 of the 30 cancer types observed in our study population, including breast cancer, ovarian cancer, bladder cancer, brain and central nervous system cancer, cervical cancer, colorectal cancer, esophageal cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, kidney cancer, leukemia, lung cancer, melanoma, myeloma, oral cavity cancer, pancreatic cancer, prostate cancer, stomach cancer, thyroid cancer, and uterine cancer. Cancers without general population incidence rates in the USCS database were excluded from the analysis. The excluded cancer types were male breast cancer, eye/orbit cancer, lower gastrointestinal tract cancer, lymphoma, osteosarcoma, sarcoma, skin/nonmelanoma, cancer of an unknown primary site, upper gastrointestinal cancer, and vulvar cancer. The

defined reference time frame for age-specific incidence rates in the USCS report was 2006-2010. Standardized incidence ratios (SIRs) were calculated to compare the number of cases of cancer in the sample population with general population data. The expected number of cancer cases was calculated from the number of individuals in the study sample multiplied by the cancer incidence rates for the general population. The expected and observed numbers of cases were calculated in 5-year intervals to accommodate different age-related incidence rates. SIRs for each cancer type and associated confidence intervals (CIs) were calculated for the entire sample and for *BRCA1* mutation carriers and *BRCA2* mutation carriers separately. Data were also stratified by sex within the 3 groups. To account for multiple tests, we divided the standard *P* value of .05 for statistical significance by the number of cancer types; thus, with 20 tests, a P value $< .0025$ was considered statistically significant.

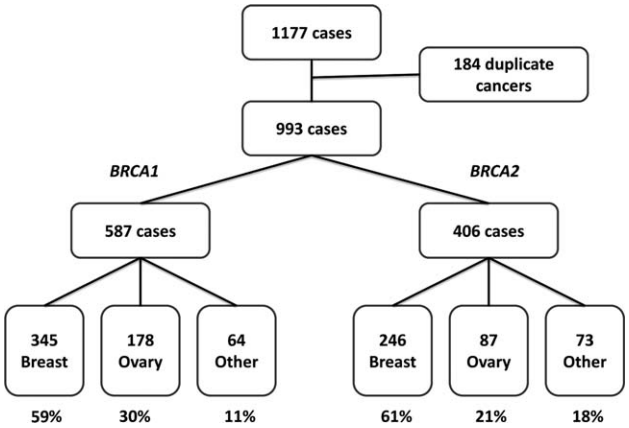

Figure 1. Distribution of mutations in *BRCA* genes in the study population.

RESULTS

We identified 1081 individuals with a deleterious mutation or variant suspected to be deleterious in *BRCA1* or *BRCA2* (Fig. 1). We excluded 3 individuals who had both *BRCA1* and *BRCA2* mutations and 6 who had another genetic mutation or genetic condition in addition to a *BRCA* mutation, including neurofibromatosis (2 individuals), Lynch syndrome, Turner syndrome, hereditary retinoblastoma, and 18p minus syndrome. The clinical characteristics of the eligible individuals are reported in Figure 1. Demographic characteristics, including sex and ethnicity, are reported in Table 1. The mean age at the date of last contact with the MD Anderson Cancer Center was 49.3 ± 12.76 years (range, 17-90 years). Most of the 1072 individuals included in our sample were alive at the date of last contact (912 or 85%).

We identified 1177 cancers of 30 different cancer types in the 1072 mutation carriers. After the exclusion of duplicate cancers in the same individual, the total number of cancer cases used in the analysis was reduced to 993 (Fig. 2).

A comparison of the observed and expected cases identified 4 types of cancers with an increased SIR (Table 2). As expected, breast and ovarian cancers were observed at significantly increased rates in *BRCA1* and *BRCA2* mutation carriers. Individuals with a *BRCA2* mutation had a higher incidence of pancreatic cancer than that expected in the general population (SIR, 21.745; 95% CI, 13.086-33.96; $P < .001$). When males and females with *BRCA2* mutations were analyzed separately, the number of pancreatic cancers was significantly higher than expected in both sexes (males: SIR, 82.559; 95% CI, 39.524-151.84; $P < .001$; females: SIR, 13.809; 95% CI, 6.301-26.216; $P < .001$). Prostate cancer was identified in significantly more men with a *BRCA2* mutation than

TABLE 1. Frequency of *BRCA1* and *BRCA2* Mutations by Sex and Ethnicity in the Study Population

All Subjects		*BRCA1*, n (%)	*BRCA2*, n (%)	Total, n
Sex ($P = .088$)[a]	Male	29 (46.77)	33 (53.23)	62
	Female	584 (57.82)	426 (42.18)	1010
	Total	613 (57.18)	459 (42.82)	1072
Ethnicity ($P = .002$)[b]	American Indian/Native American	1 (33.33)	2 (66.67)	3
	Asian/Pacific Islander	22 (53.66)	19 (46.34)	41
	Black	43 (56.58)	33 (43.42)	76
	Hispanic	103 (72.03)	40 (27.97)	143
	White	440 (54.79)	363 (45.21)	803
	Total[c]	609 (57.13)	457 (42.87)	1066

[a] *P* value from chi-square test.
[b] *P* value from Fisher's exact test.
[c] Six were missing.

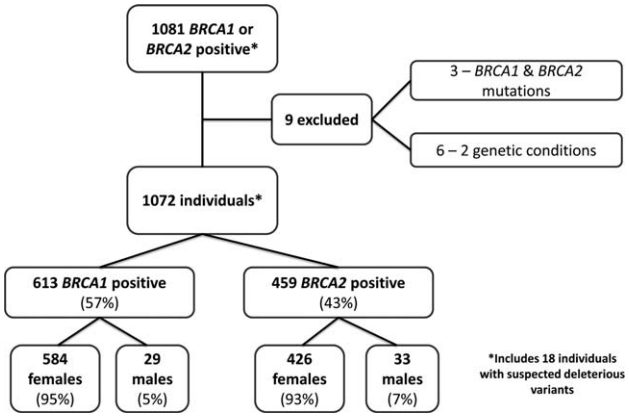

Figure 2. Demographics of cancers identified in the study population.

expected in the general population (SIR, 4.890; 95% CI, 1.959-10.075; $P = .002$).

We observed a trend of an increasing incidence of melanoma in *BRCA1* mutation carriers (SIR, 3.312; 95% CI, 1.511-6.288; $P = .004$) and an increasing incidence of cervical cancer in *BRCA2* mutation carriers (SIR, 4.410; 95% CI, 1.61-9.599; $P = .006$) in comparison with general population data. The *P* values for melanoma and cervical cancer were approaching significance, although they did not reach the conservative cutoff. The 95% CI did not include 1.0, and this indicated that the general population and the study sample were likely different populations. The increased incidence for these cancers was unlikely to occur by chance.

Ten additional cancer types representing 64 total cases were identified in the study population but were not available in the CDC USCS database for statistical analysis (Table 3). Individuals with *BRCA1* mutations made up 45.3% (29 cases) of this subset of cancers. Individuals with *BRCA2* mutations made up 54.7% (35 cases) of this subset of cancer types. Notably, all 7 cases of male breast cancer occurred in men with *BRCA2* mutations. Nonmelanoma skin cancer was the most common of these 10 types of cancer in *BRCA1* and *BRCA2* mutation carriers (18 and 19 cases, respectively).

DISCUSSION

This is one of the largest single-institution studies of the cancer spectrum associated with *BRCA1* and *BRCA2* mutations. This study found an increased incidence in 2 cancers (other than breast and ovarian) in individuals with a *BRCA* mutation when they were stratified by gene and sex. The number of observed cases of pancreatic and prostate cancer was higher than that expected in the general population for individuals with *BRCA2* mutations. Our findings support the rationale for pancreatic and prostate cancer screening in individuals with a *BRCA2* mutation. Furthermore, recent associations with additional cancers, including uterine and colorectal cancer, were not evident in our study population.

In our analysis, the occurrence of pancreatic cancer in males and females with a *BRCA2* mutation was nearly 22 times greater than that expected in the study population. Separately, males had an 82.5 times higher occurrence, and females had an approximately 14 times higher occurrence. Other studies have reported increased risks of a lesser magnitude for pancreatic cancer in men and women with *BRCA2* mutations, including relative risk estimates ranging from 3.51 to 5.9.[11,15,16] The increased number of observed cases in this study in comparison with previous relative risks could be attributed to personal factors or a referral bias. Nearly half of the individuals with pancreatic cancer (8/19) had a history of smoking, which is a well-documented risk factor for pancreatic cancer.[20] Other evaluated cancers also showed increases or trends of increases in risk. Prostate cancer occurred approximately 5 times more frequently in males with *BRCA2* mutations than expected in the general population. The increased risk for prostate cancer in our study population is consistent with previous studies, which have reported relative risk estimates ranging from 2.5 to 6.3.[11,15-17] Our data confirm prior evidence that men with *BRCA2* mutations are at increased risk for prostate cancer.

The incidence of melanoma in *BRCA1* mutation carriers approached significance in this study ($P = .004$). We established a conservative level of statistical significance for this study because the study sample included individuals in multiple cancer groups rather than mutually exclusive group comparisons. The 95% CI suggests that the increased incidence of melanoma in *BRCA1* mutation carriers differentiates it from the general population. Melanoma has been associated with *BRCA2* mutations in previous studies, although the risk with *BRCA1* mutations is unclear.[15] Therefore, this study suggests that screening for melanoma in *BRCA1* mutation carriers may be prudent.

The incidence of cervical cancer in *BRCA2* mutation carriers also approached statistical significance in this study ($P = .006$). The most common risk factor for cervical cancer is human papillomavirus (HPV) infection.[21] We were unable to determine whether the cause of cervical cancer was viral or was possibly associated with *BRCA2* mutations. The HPV status was available for 3 of the 6

TABLE 2. Observed and Expected Cancers for 1072 Individuals (Males and Females) With *BRCA* Mutations

Cancer	Gene	Observed Cases	Expected Cases	SIR	95% CI	*P*
Bladder	*BRCA1*	0	1.282	0	0-2.862	.554
	BRCA2	1	1.373	0.728	0.010-4.053	.791
Brain and CNS	*BRCA1*	3	1.268	2.367	0.849-8.078	.269
	BRCA2	1	1.077	0.929	0.012-5.168	.578
Breast, female	*BRCA1*	345	9.349	36.902	33.110-41.009	<.001[a]
	BRCA2	246	8.885	27.688	24.336-31.373	<.001[a]
Cervical	*BRCA1*	2	1.701	1.176	0.132-4.245	.990
	BRCA2	6	1.361	4.410	1.61-9.599	.006
Colorectal	*BRCA1*	6	3.800	1.579	0.577-3.437	.367
	BRCA2	2	3.783	0.529	0.059-1.909	.542
Esophagus	*BRCA1*	1	0.405	2.471	0.032-13.75	.654
	BRCA2	0	0.422	0	0-8.694	.677
Hodgkin lymphoma	*BRCA1*	3	0.792	3.788	0.761-11.067	.095
	BRCA2	0	0.634	0	0-5.787	.929
Non-Hodgkin lymphoma	*BRCA1*	0	2.114	0	0-1.735	.237
	BRCA2	1	1.980	0.505	0.007-2.81	.825
Kidney	*BRCA1*	2	1.806	1.107	0.124-3.998	.925
	BRCA2	3	1.735	1.729	0.348-5.052	.500
Leukemia	*BRCA1*	5	1.694	2.951	0.951-6.887	.060
	BRCA2	3	1.493	2.010	0.404-5.872	.376
Lung	*BRCA1*	2	4.547	0.440	0.049-1.588	.335
	BRCA2	5	4.867	1.027	0.331-2.398	.929
Myeloma	*BRCA1*	1	0.462	2.164	0.037-12.04	.728
	BRCA2	0	0.477	0	0-7.683	.747
Oral cavity	*BRCA1*	2	1.362	1.468	0.165-5.30	.784
	BRCA2	1	1.298	0.770	0.01-4.286	.739
Ovarian	*BRCA1*	178	1.280	139.115	119.427-161.122	<.001[a]
	BRCA2	87	1.1614	74.926	60.011-92.422	<.001[a]
Pancreas	*BRCA1*	4	0.846	4.730	1.273-12.11	.024
	BRCA2	19	0.874	21.745	13.086-33.96	<.001[a]
Prostate	*BRCA1*	3	1.788	3.809	0.766-11.13	.094
	BRCA2	7	1.432	4.890	1.959-10.075	.002[a]
Skin, melanoma	*BRCA1*	9	2.717	3.312	1.511-6.288	.004
	BRCA2	2	2.456	0.814	0.091-2.94	.887
Stomach	*BRCA1*	1	0.576	1.736	0.023-9.661	.864
	BRCA2	1	0.570	1.755	0.023-9.763	.858
Thyroid	*BRCA1*	5	2.736	1.828	0.589-4.265	.283
	BRCA2	2	2.319	0.862	0.097-3.114	.814
Uterus	*BRCA1*	4	2.872	1.393	0.375-3.566	.645
	BRCA2	3	2.636	1.138	0.229-3.326	.978

Abbreviations: CI, confidence interval; CNS, central nervous system; SIR, standardized incidence ratio.
[a] Statistically significant difference between the study population and the general population ($P < .0025$).

observed cervical cancer cases in women with a *BRCA2* mutation. All 3 tested negative for HPV; however, the test was performed 3 to 7 years after the cancer diagnosis. Thus, the tests may not have accurately identified HPV because the majority of HPV infections clear or become undetectable within 2 years of infection.[22] The HPV status was not reported in the medical record for the remaining 3 individuals. It will be important to monitor the cancers with a trend of increasing incidence over time to determine whether an association exists and what the magnitude of risk is for mutation carriers.

BRCA mutations have been associated with a risk for uterine cancer (specifically, more aggressive types).[23] In this recent analysis by Shu et al,[23] 4 cases of high-risk uterine cancer were diagnosed among 525 *BRCA* mutation carriers, and this rate was significantly increased in comparison with the general population (SIR, 14.48; $P < .001$). In our overall analysis, 7 cases of uterine cancer were observed, whereas 5.507 cases were expected. Three of our 7 observed cases were classified as high-risk (serous, clear cell, or sarcoma), 3 cases were low-risk, and 1 case did not have pathology available for review. Thus, uterine cancer was not more prevalent in our study population than expected, although the specific occurrence of high-risk uterine cancer was not statistically analyzed.

Our study has multiple limitations. Although our overall sample size of individuals with *BRCA* mutations is large in comparison with other published studies, the sample size remains a limitation for discovering small differences. The MD Anderson Cancer Center is also a tertiary

TABLE 3. Description of Additional Cancers in Remaining 64 Cases That Were Not Compared With the General Population

Cancer	*BRCA1*, n (%)	*BRCA2*, n (%)	Total, n (%)
Total	29 (100)	35 (100)	64 (100)
Breast, male	0 (0)	7 (20)	7 (10.9)
Eye and orbit	1 (3.4)[a]	1 (2.9)[b]	2 (3.1)
Lower GI	2 (6.9)[c]	0	2 (3.1)
Lymphoma	1 (3.4)	2 (5.7)	3 (4.7)
Osteosarcoma	0 (0)	1 (2.9)	1 (1.7)
Sarcoma	2 (6.9)	1 (2.9)	3 (4.7)
Skin, nonmelanoma	18 (62.1)	19 (54.3)	37 (57.8)
Unknown primary site	2 (6.9)	2 (5.7)	4 (6.3)
Upper GI	1 (3.4)[d]	1 (2.9)[e]	2 (3.1)
Vulvar	2 (6.9)	1 (2.9)	3 (4.7)

Abbreviation: GI, gastrointestinal.
[a] Uveal melanoma.
[b] Ocular melanoma.
[c] Anal canal and appendix.
[d] Small intestine.
[e] Cholangiocarcinoma.

care center, and individuals with complex cancer histories, a poor prognosis, or multiple cancer diagnoses are often referred for treatment. Another limitation is the use of general population incidence rates. The largest date range (2006-2010) in the USCS data set was used; however, individuals in our sample developed cancer outside this date range, and this required us to infer statistical associations. The SIR used in this study is not a relative risk. The SIR is an approximation of the relative risk; however, discrepancies can arise because the general population is composed of individuals with and without *BRCA* mutations. Also, cancers diagnosed at centers other than ours did not require pathological confirmation; thus, there may have been inaccurate reporting for some cancers. Because our study population was predominantly white (75%), the information learned from this study may not be generalizable across all ethnicities.

Our study observed more than the expected number of cases of pancreatic and prostate cancer in *BRCA2* mutation carriers. A trend toward statistical significance in the incidence of melanoma with *BRCA1* mutations was observed. The presence of male breast cancer, which was exclusively seen in the *BRCA2* mutation carriers in our cohort, is consistent with previous studies. Our findings do not rule out an increase of these cancers in both *BRCA* genes because of the limitations of our cohort. In addition, why some cancers may be more prevalent in one *BRCA* gene versus another is not yet well understood. These findings do, however, support the current National Comprehensive Cancer Network clinical practice guidelines in oncology for hereditary breast and ovarian cancer syndrome management.[24] Recommendations or considerations for prostate cancer, male breast cancer, and melanoma screening have been included for individuals with *BRCA1* or *BRCA2* mutations. These suggestions currently include digital rectal examination and prostate-specific antigen serum testing beginning at the age of 40 years, clinical male breast examinations beginning at the age of 35 years followed by baseline mammography at the age of 40 years, and full-body skin examinations for men and women. Although the risk for pancreatic cancer has been acknowledged by the National Comprehensive Cancer Network, specific screening guidelines do not exist. A lack of effective procedures for early pancreatic cancer detection prevents the development of screening guidelines. Investigational protocols into pancreatic screening include endoscopic ultrasound and/or magnetic resonance imaging cholangiopancreatography rather than computed tomography scans; however, there is inconsistency in follow-up intervals, and when fine-needle aspirations are needed continues to be debated.[25-27]

The high rate of pancreatic cancer in men and women with *BRCA2* mutations in this study further emphasizes the need for effective screening and recommendations for this high-risk population.

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CONFLICT OF INTEREST DISCLOSURES

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