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Cancers Associated with BRCA1 and BRCA2 Mutations Other Than Breast and Ovarian

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CANCERS ASSOCIATED WITH *BRCA1* AND *BRCA2* MUTATIONS

OTHER THAN BREAST AND OVARIAN

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Mutations in *BRCA1* and *BRCA2* cause tumor development in Hereditary Breast and Ovarian Cancer syndrome (HBOC) through accumulation of unrepaired DNA damage. Extensive research of *BRCA1* and *BRCA2* mutations has led to well-defined breast and ovarian cancer risks in individuals with HBOC. Previous studies have reported additional cancers associated with *BRCA* mutations; however, the type of cancer, magnitude of risk, and differences between sexes remains to be clarified. Ultimately, a consensus of additional cancer risks can aid in better recommendations for genetic testing and more effective screening and prevention guidelines.

A retrospective chart review of MD Anderson Cancer Center patients identified 1081 individuals with a *BRCA* mutation. A detailed cancer history for each person was collected and compared to the general population incidence rates reported by the CDC using standardized incidence ratios (SIR). Individuals with a *BRCA2* mutation had significantly higher number of observed cases compared to expected cases for pancreatic cancer (SIR 21.7, 95% CI 13.1-34.0, p value <0.001) in both men and women and prostate cancer in men (SIR 4.9, 95% CI 2.0-10.1, p value = 0.002). Individuals with a *BRCA1* mutation did not have a significant increase in cancers other than breast and ovarian; however, a trend in melanoma was observed in men and women. The results of this study uphold the current recommendations for HBOC screening of cancers other than breast and ovarian by the National Comprehensive Cancer Network.

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Introduction

BRCA1 and *BRCA2* tumor suppressor genes repair DNA damage to prevent tumor development. Mutations in these genes predispose an individual to malignancy. The types of cancers associated with mutations in *BRCA1* and *BRCA2* have been studied continuously since their discovery in 1994 and 1995 respectively (Miki et al., 1994 & Wooster et al., 1995). Individuals with *BRCA1* and *BRCA2* mutations have a significantly increased lifetime risk for developing breast and ovarian cancer, as high as 84% and 39% respectively (Antoniou et al., 2003; Chen et al., 2006; Easton et al., 1995; Ford et al., 1998).

While 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 have included families either at high risk for a *BRCA* mutation or combined *BRCA1* and *BRCA2* mutations carriers for analysis due to small numbers of individuals with *BRCA* mutations (Bermejo & Hemminki, 2004; Noh et al., 2012). These studies reported an increased incidence of cancers, other than breast and ovarian, in mutation carriers; however, these reports did not differentiate between *BRCA1* and *BRCA2* mutation carriers.

Studies have been able to focus on *BRCA1* or *BRCA2* mutation carriers separately; however, the number of participants varies, with few studies containing more than 1000 mutation carriers. Ford et al (1994) found an increased risk for both sexes, while Thompson and Easton (2000) found an increased risk only in women and Moran et al (2012) reported *BRCA1* mutations are not associated with an increased risk for other cancers. *BRCA1* mutation carriers have a significantly increased risk of pancreatic, prostate, and colorectal cancer as reported in multiple studies (Brose et al, 2002; Ford et al, 1994; Iqbal et al., 2012; Phelan et al., 2014; Thompson et al., 2002). *BRCA1* mutations have been linked to increases in cervical, esophagus, liver, stomach, and uterine cancers; however, the increased risks were inconsistent and ranged from one to four fold (Brose et al, 2002; Ford et al, 1994; Moran et al, 2012;

Thompson et al., 2002). Known environmental risk factors associated with these cancers were not typically reported in these studies.

The Breast Cancer Linkage Consortium (BCLC) reported *BRCA2* mutations were associated with an increased cancer risk in both sexes (1999), while van Asperen found a significantly increased risk for men only (2005). The most commonly reported cancers with *BRCA2* mutations include pancreas, prostate, and melanoma (BCLC, 1999; Easton et al., 1997; Moran et al., 2012; Tai et al., 2007; van Asperen et al., 2005). Additional cancers reported in the *BRCA2* spectrum include bone, buccal cavity and pharynx, esophagus, gallbladder and bile duct, laryngeal, ocular, male breast cancer, and stomach, although inconsistently across multiple studies. (BCLC, 1999; Easton et al., 1997; Moran et al., 2012; Tai et al., 2007; van Asperen et al., 2005). Environmental risk factors for these cancers were not regularly reported in these studies.

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

Methods

Study Population

This study was approved by the MD Anderson Cancer Center Institutional Review Board and by The University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects. Individuals who had received genetic counseling in the Clinical

Cancer Genetics clinics at the UT MD Anderson Cancer Center (MDACC) 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 are advised to follow the same high risk management guidelines as individuals with deleterious mutations in the clinical setting. 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 comprised of data obtained during the genetic counseling session or from the patient's medical record. Additional information on 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 (BSO). Information on personal cancer history was compared using information from both the medical record and the Progeny database to obtain the most current information.

Individuals with two *BRCA* mutations, either deleterious or suspected 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 this analysis.

Statistical Methods

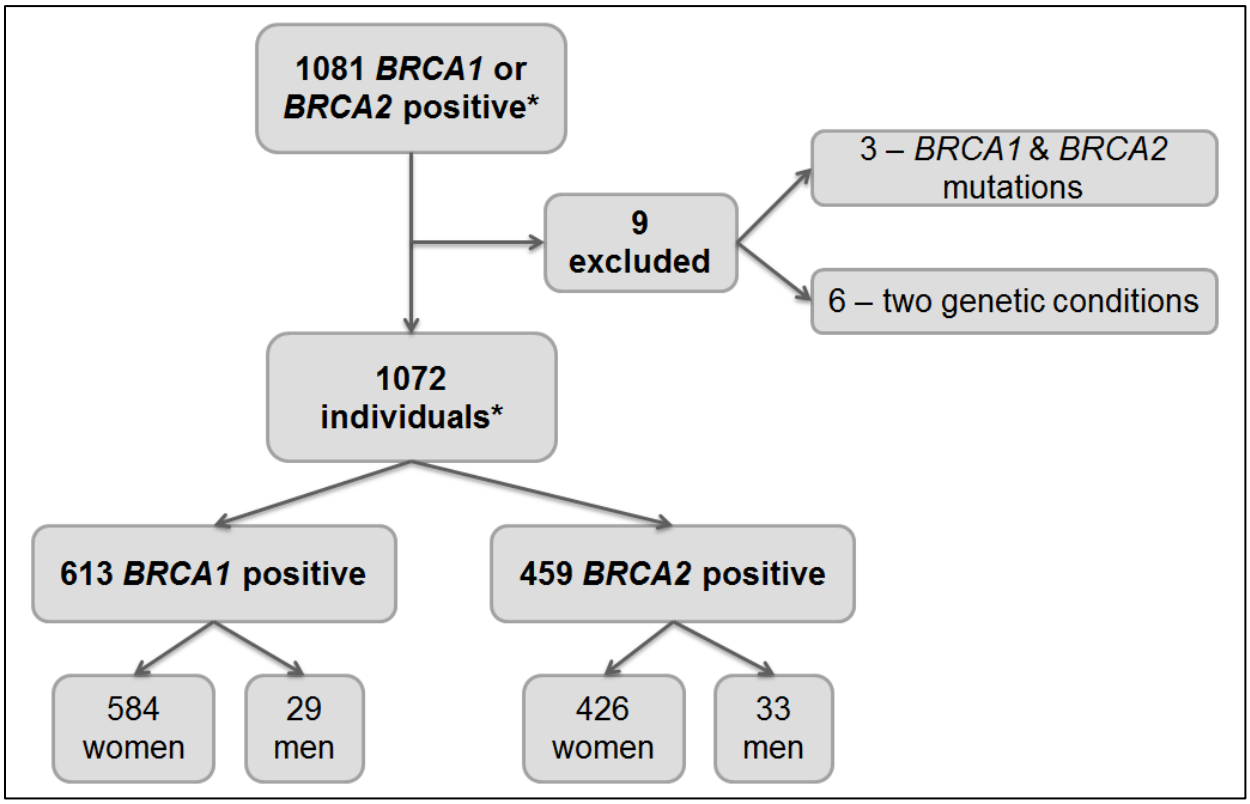
Cancer cases were counted for the total sample as well as for *BRCA1* and *BRCA2* mutation carriers separately. The earliest age at diagnosis was used in the analysis for individuals that developed the same cancer more than once in their lifetime. Most cancers were analyzed independently. Similar or related cancers were grouped together for analysis. For example glioma, astrocytoma, and neuroblastoma were grouped into 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 cancer incidence in our sample with the United States Cancer Statistics: 1999-2010 Incidence and Morality Web-based Report (USCS) from the Centers of Disease Control and Prevention (CDC). Data from the USCS report combines the CDC's National Program of Cancer Registries and National Cancer Institute's Surveillance, Epidemiology, and End Results Program on cancer incidence in the United States population. The USCS report includes incidence data for 20 out of the 30 cancer types observed in our study population, including breast, ovarian, bladder, brain & CNS, cervical, colorectal, esophagus, Hodgkin lymphoma, non-Hodgkin lymphoma, kidney, leukemia, lung, melanoma, myeloma, oral cavity, ovarian, pancreas, prostate, stomach, thyroid, and uterine (USCS Working Group, 2013). Cancers without general population incidence rates in the USCS database were excluded from analysis. The excluded cancer types were male breast cancer, eye/orbit, lower GI, lymphoma, osteosarcoma, sarcoma, skin/nonmelanoma, unknown primary site, upper GI, and vulvar. The defined reference time frame for age-specific incidence rates in USCS was 2006-2010. Standardized incidence ratios (SIR) were calculated to compare 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 general population cancer incidence rates. 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 three groups. To account for multiple tests, we divided the standard *p* value of 0.05 for statistical significance by the number of cancer types; thus with 20 tests a *p* value of <0.0025 was considered statistically significant.

Results

We identified 1081 individuals with a deleterious mutation or variant suspected to be deleterious in *BRCA1* or *BRCA2* (Fig. 1). We excluded 3 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 (two individuals), Lynch syndrome, Turner syndrome, hereditary retinoblastoma, and 18p minus syndrome. Clinical characteristics of eligible individuals are reported in Figure 1. Demographic characteristics including sex and ethnicity are reported in Table 1. The mean age at date of last contact with MDACC was 49.3 years (± 12.76, range 17-90). Of the 1072 individuals included in our sample, most were alive at the date of last contact (912, 85%).

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



***** Includes 18 individuals with suspected deleterious variants

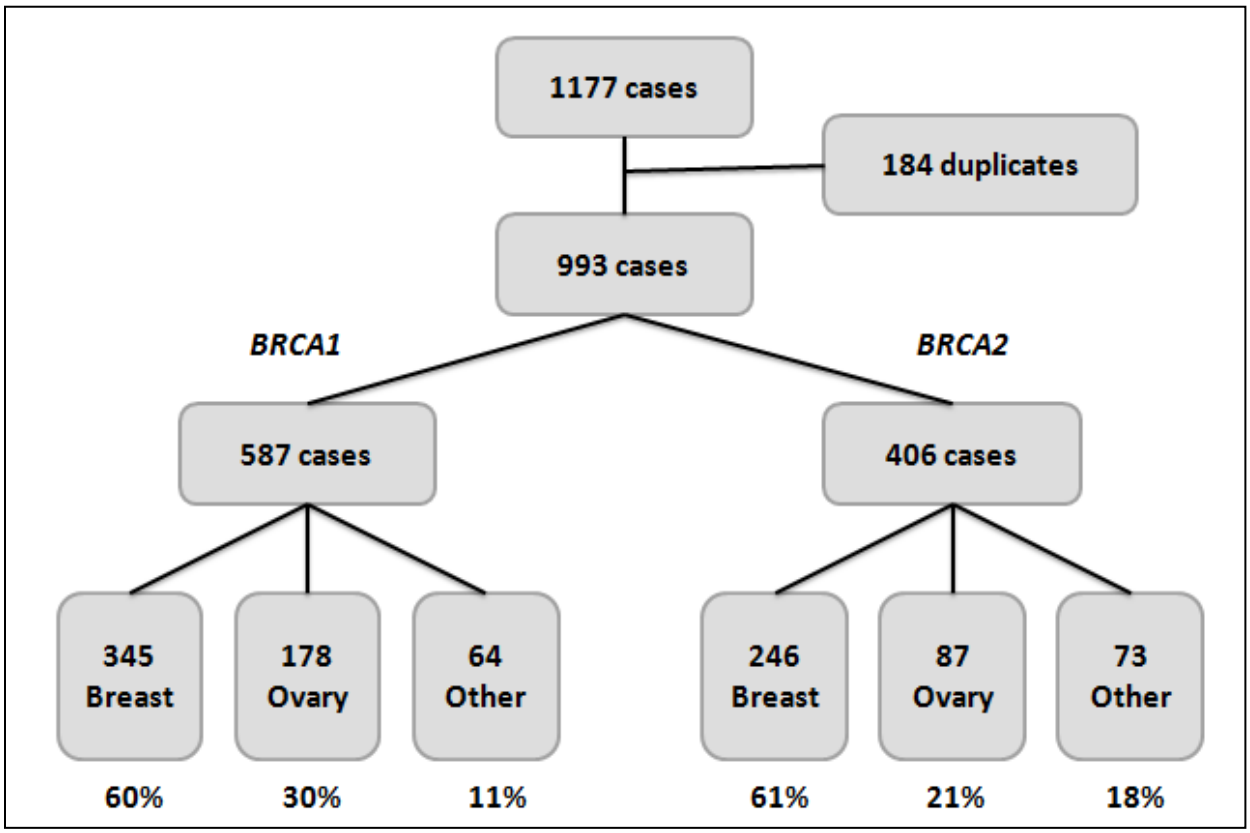
Table 1. Frequency of *BRCA1* and *BRCA2* mutations by sex and ethnicity in study population.

All Subjects		***BRCA1*** **n (%)**	***BRCA2*** **n (%)**	**Total n**
Sex (p value=0.088[*])	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 value=0.002[†])	Am Indian/Native Amer	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 (missing=6)	**609 (57.13)**	**457 (42.87)**	**1066**

[*] p value from Chi-Square test; [†] p value from Fisher's exact test

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

Figure 2. Demographics of cancers identified in study population.



Comparison of the observed and expected cases identified four types of cancer 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 expected in the general population (SIR 21.745, 95% CI 13.086-33.96, $p<0.001$). 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, $p<0.001$; females: SIR 13.809, 95% CI 6.301-26.216, $p<0.001$). Prostate cancer was identified in significantly more men with a *BRCA2* mutation than expected in the general population (SIR 4.890, 95% CI 1.959-10.075, $p=0.002$).

Table 2. Observed and expected cancers for 1072 individuals (males and females) with *BRCA* mutations.

Cancer	Gene	Obs	Exp	SIR	95% CI	*p* value
Bladder	*BRCA1*	0	1.282	0	0-2.862	0.554
	BRCA2	1	1.373	0.728	0.010-4.053	0.791
Brain & CNS	*BRCA1*	3	1.268	2.367	0.849-8.078	0.269
	BRCA2	1	1.077	0.929	0.012-5.168	0.578
Breast – female	*BRCA1*	345	9.349	36.902	33.110-41.009	<0.001*
	BRCA2	246	8.885	27.688	24.336-31.373	<0.001*
Cervical	*BRCA1*	2	1.701	1.176	0.132-4.245	0.990
	BRCA2	6	1.361	4.410	1.61-9.599	0.006
Colorectal	*BRCA1*	6	3.800	1.579	0.577-3.437	0.367
	BRCA2	2	3.783	0.529	0.059-1.909	0.542
Esophagus	*BRCA1*	1	0.405	2.471	0.032-13.75	0.654
	BRCA2	0	0.422	0	0-8.694	0.677
Hodgkin Lymphoma	*BRCA1*	3	0.792	3.788	0.761-11.067	0.095
	BRCA2	0	0.634	0	0-5.787	0.929
Non-Hodgkin Lymphoma	*BRCA1*	0	2.114	0	0-1.735	0.237
	BRCA2	1	1.980	0.505	0.007-2.81	0.825
Kidney	*BRCA1*	2	1.806	1.107	0.124-3.998	0.925
	BRCA2	3	1.735	1.729	0.348-5.052	0.500
Leukemia	*BRCA1*	5	1.694	2.951	0.951-6.887	0.060
	BRCA2	3	1.493	2.010	0.404-5.872	0.376
Lung	*BRCA1*	2	4.547	0.440	0.049-1.588	0.335
	BRCA2	5	4.867	1.027	0.331-2.398	0.929
Myeloma	*BRCA1*	1	0.462	2.164	0.037-12.04	0.728
	BRCA2	0	0.477	0	0-7.683	0.747
Oral Cavity	*BRCA1*	2	1.362	1.468	0.165-5.30	0.784
	BRCA2	1	1.298	0.770	0.01-4.286	0.739
Ovarian	*BRCA1*	178	1.280	139.115	119.427-161.122	<0.001*
	BRCA2	87	1.1614	74.926	60.011-92.422	<0.001*
Pancreas	*BRCA1*	4	0.846	4.730	1.273-12.11	0.024
	BRCA2	19	0.874	21.745	13.086-33.96	<0.001*
Prostate	*BRCA1*	3	1.788	3.809	0.766-11.13	0.094
	BRCA2	7	1.432	4.890	1.959-10.075	0.002*
Skin – Melanoma	*BRCA1*	9	2.717	3.312	1.511-6.288	0.004
	BRCA2	2	2.456	0.814	0.091-2.94	0.887
Stomach	*BRCA1*	1	0.576	1.736	0.023-9.661	0.864
	BRCA2	1	0.570	1.755	0.023-9.763	0.858
Thyroid	*BRCA1*	5	2.736	1.828	0.589-4.265	0.283
	BRCA2	2	2.319	0.862	0.097-3.114	0.814
Uterus	*BRCA1*	4	2.872	1.393	0.375-3.566	0.645
	BRCA2	3	2.636	1.138	0.229-3.326	0.978

* statistically significant difference between study population and general population (p<0.0025)
Obs – observed cases; Exp – expected cases; SIR – standardized incidence ratio; CI – confidence interval

We observed a trend of increasing incidence of melanoma in *BRCA1* mutation carriers (SIR 3.312, 95% CI 1.511-6.288, p=0.004) and of cervical cancer in *BRCA2* mutation carriers (SIR 4.410, 95% CI 1.61-9.599, p=0.006), compared to general population data. The p values for melanoma and cervical cancer are approaching significance although they did not reach the conservative cutoff. The 95% confidence interval does not include 1.0 indicating that the general population and study sample are 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) in this subset of cancers. Individuals with *BRCA2* mutations comprised 54.7% (35 cases) in this subset of cancer types. Of note, all seven cases of male breast cancer occurred in men with *BRCA2* mutations. Non-melanoma skin cancer was the most common of these 10 types of cancer in *BRCA1* and *BRCA2* mutation carriers (18 and 19 cases, respectively).

Table 3. Description of additional cancers in remaining 64 cases of cancer that were not compared to the general population.

Cancer	*BRCA1* n (%)	*BRCA2* n (%)	Total n (%)
Total	**29 (100)**	**35 (100)**	**64 (100)**
Breast – Males	0 (0)	7 (20)	7 (10.9)
Eye and Orbit	1 (3.4) Uveal Melanoma	1 (2.9) Ocular Melanoma	2 (3.1)
Lower GI	2 (6.9) Anal Canal & Appendix	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) Small Intestine	1 (2.9) Cholangiocarcinoma	2 (3.1)
Vulvar	2 (6.9)	1 (2.9)	1 (1.7)

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 two cancers, other than breast and ovarian, in individuals with a *BRCA* mutation when stratified by gene and sex. The number of observed cases of pancreatic and prostate cancer was higher than expected in the general population for individuals with *BRCA2* mutations. Individuals with a *BRCA1* mutation did not have an increased incidence of any specific type of cancer. 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, 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 expected in the study population. 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 3.51-5.9 (BCLC, 1999; Moran et al., 2012; van Asperen et al., 2005). The increased number of observed cases in this study above previous relative risks could be attributed to personal factors or a referral bias. Nearly half (8 of 19) individuals with pancreatic cancer had a history of smoking, which is a well documented risk factor for pancreatic cancer (Lowenfels & Maisonneuve, 2006). MDACC is a tertiary care center and individuals with complex cancer histories, poor prognosis, or multiple cancer diagnoses are often referred for treatment. Of note, the SIR used in this study is not 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. Therefore, it is difficult to truly compare these statistical analyses.

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 that have reported relative risk estimates ranging from 2.5-6.3 (BCLC, 1999; Easton et al., 1997; Moran et al., 2012; van Asperen et al., 2005). Our data confirms prior evidence that men with *BRCA2* mutations are at an increased risk of prostate cancer.

The incidence of melanoma in *BRCA1* mutation carriers approached significance in this study ($p = 0.004$). We established a conservative level of statistical significance for this study because the study sample included individuals in multiple cancer groups rather than being mutually exclusive group comparisons. The 95% confidence interval suggests 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 (BCLC, 1999). Therefore this study suggests 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=0.006). The most common risk factor for cervical cancer is human papillomavirus infection (Schiffman et al., 2007). We were unable to determine whether the cause of cervical cancer was viral or possibly associated with *BRCA2* mutations. HPV status was available for three out of the six observed cervical cancer cases in women with a *BRCA2* mutation. All three tested negative for HPV; however, the test was performed 3 to 7 years after cancer diagnosis. Thus the tests may not have accurately identified HPV because the majority of HPV infections clear or become undetectable within two years of infection (Moscicki et al., 1998). HPV status was not reported in the medical record for the remaining three individuals. It will be important to monitor the cancers with a trend of increasing incidence over time to determine if an association exists and what the magnitude of risk is for mutation carriers.

BRCA mutations have been associated with uterine cancer risk, specifically more aggressive types (Shu et al., 2014). Women in the study had a *BRCA1* or *BRCA2* mutation and underwent a BSO, and their uterus remained intact. Four cases of high-risk uterine cancer were diagnosed out of 525 women during the study, which was significantly increased over the general population (SIR 14.48, p<0.001). In our overall sample, 7 cases of uterine cancer were observed compared to 5.507 expected. Three of the observed cases were classified as high risk (serous, clear cell, or sarcoma), three cases were low risk, and one case did not have pathology available for review. Thus, uterine cancer was not more prevalent in our study population than expected, although the occurrence of high risk uterine cancer was not specifically assessed.

Male breast cancer was not able to be analyzed in this study because of insufficient general population data for comparison. Of note, all seven cases were observed in men with *BRCA2* mutations which represent 21% of the men with a mutation in this gene. Our results appear to be consistent with prior studies that have found a stronger association with *BRCA2* mutations and male breast cancer compared to BRCA1 mutations (Tai et al., 2007).

Although our overall sample size of individuals with *BRCA* mutations is large in comparison to other published studies, the sample size remains a limitation for discovering small differences. Therefore a larger sample size is needed to assess the statistical significance of rare cancer in association with *BRCA* mutations. This might be accomplished by analyzing family histories for additional cancer or by collaborating with another large center. Another limitation is the use of general population incidence rates. The largest date range (2006-2010) in the USCS dataset was used; however, individuals in our sample developed cancer outside of this date range which required us to infer statistical associations. Also, cancers diagnosed at centers other than ours did not require pathological confirmation; thus there may be 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 exclusively with *BRCA2* mutation carriers is consistent with previous studies. These findings support the current National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Hereditary Breast and Ovarian Cancer syndrome management (NCCN, 2014). Recommendations or considerations for prostate cancer, male breast cancer, and melanoma screening have been included for individuals with *BRCA1* or *BRCA2* mutations. While the risk for pancreatic cancer has been acknowledged by NCCN, specific screening guidelines do not exist. Lack of effective procedures for early pancreatic cancer detection prevents the development of screening guidelines. The high rate of pancreatic cancer in men and women with *BRCA2* mutations in this study further emphasizes the need for effective screening guidelines in this high-risk population.

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