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Genotype-Phenotype Correlations by Ethnicity and Mutation Location in *BRCA* Mutation Carriers

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Abstract

Background—The genotype-phenotype correlations of the specific *BRCA1* and *BRCA2* mutations in multi-ethnic populations in United States have not yet been fully investigated. This study is designed to evaluate the effects of ethnicity at specific mutation locations and breast/ovarian cancer phenotypes.

Methods—Our cohort included 445 women with different ethnic backgrounds who underwent *BRCA* genetic testing between 1997 and 2010. Known clinical and pathologic characteristics were compared with Chi-Square Analysis or Fisher's Exact test as appropriate.

Results—The 3 most common mutation locations in *BRCA1* (exons 2, 11, and 20) and *BRCA2* (exons 10, 11, and 25) genes were chosen. Prevalence of *BRCA1* exon 2 mutations were significantly higher in Ashkenazi Jewish (AJ) women compared to Caucasians (41% vs. 15%; $P=0.001$). Similarly, AJ women with breast cancer were more likely to have *BRCA1* exon 2 mutation (47% positivity in AJ women vs. 0%-12.5% positivity in other ethnicities; $P=0.004$). Women carrying the exon 20 *BRCA1* mutation had the highest probability of having combined breast and ovarian cancers compared to women carrying other exon mutations ($P=0.05$). The

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median age at initial cancer diagnosis, phenotypic features of breast cancer tumors, and overall survival did not vary significantly by ethnicity or mutation location.

Conclusion—Our data suggest that ethnicity does not affect age of onset, overall survival or confer different risks of breast and ovarian cancer development in *BRCA* carriers. These results also suggest that women carrying the exon 20 *BRCA1* mutation may warrant mutation-specific counseling and be more aggressively managed for risk reduction.

Keywords

ethnicity; BRCA1; BRCA2; breast cancer; ovarian cancer; mutation location

INTRODUCTION

Known mutations in the breast cancer susceptibility genes *BRCA1* or *BRCA2* account for more than 50% of hereditary breast cancers(1). Women who carry a germ line mutation in *BRCA1* or *BRCA2* have a 43% to 84% risk of developing breast cancer and a 23% to 54% risk of developing ovarian cancer by age 70 years (2-4). Mutations in the *BRCA* genes are more frequently present in individuals with multiple relatives having breast or ovarian cancer, early-onset breast cancer, or with Ashkenazi Jewish (AJ) ancestry(5, 6).

Several studies have reported the prevalence of *BRCA1* and *BRCA2* mutations in the United States (US) racial/ethnic minority populations. In a study by John et al(7), estimates of *BRCA1* prevalence were 3.5% (95% CI, 2.1%-5.8%) in Hispanic patients (n=393), 1.3% (95% CI, 0.6%-2.6%) in African American patients (n=341), and 0.5% (95% CI, 0.1%-2.0%) in Asian American patients (n=444), compared with 8.3% (95% CI, 3.1%-20.1%) in AJ patients (n=41) and 2.2% (95% CI, 0.7%-6.9%) in Caucasians (n=508). Prevalence was particularly high in young (<35 years) African American patients (5/30 patients [16.7%]; 95% CI, 7.1%-34.3%). In a recent study, the prevalence of *BRCA1* and *BRCA2* mutations among Hispanics in the Southwestern US (n=746) with a personal or family history of breast and/or ovarian cancer were found to be higher than in the previous reports; 16.6% and 8.7%, respectively (8).

Furthermore, studies have attempted to evaluate the effects of ethnicity on mutation type. The 3 founder mutations in *BRCA1* (187delAG and 5385insC) and *BRCA2* (6174delT) are thought to account for the 29% to 44% of *BRCA* mutations in AJ individuals(9-11). Other studies identified the 187delAG AJ founder mutation in *BRCA1* recurrently in Hispanics(7, 12, 13). Weitzel et al documented the first Mexican founder mutation (*BRCA1* ex9-12del), accounting for 10% to 12% of all *BRCA1* mutations in clinic- and population-based cohorts in the US(8).

More importantly, structural and functional changes of mutated proteins caused by different *BRCA1* mutations are not identical and can lead to various phenotypes of cancers (genotype-phenotype correlations)(14). Gayther et al(15) reported that the risk of ovarian cancer relative to the risk of breast cancer was higher in families with mutations located 5' to exon 13 of the *BRCA1* gene compared with families with mutations located 3' to exon 13. Mutations in exon 11 (nucleotides 2388-4185) of the *BRCA1* gene have been associated

with almost equal breast and ovarian cancer incidence among mutation carriers in comparison with mutations in other parts of the *BRCA1* gene. On the other hand, mutations located 3' of nucleotide 4185 were associated with a higher risk of breast cancer development and with a relatively lower ovarian cancer risk(16). Nevertheless, the genotype-phenotype correlations of the specific *BRCA1/2* mutations in multi-ethnic populations in the US have not yet been fully investigated. Therefore, this study was designed to evaluate differences in the demographic and clinical characteristics of women from multi-ethnicities in the US carrying the various *BRCA* gene mutations.

MATERIALS AND METHODS

Patient Population and Data Collection

The prospectively maintained Breast Cancer Management System database at the University of Texas MD Anderson Cancer Center (UTMDACC) identified 445 women with different ethnic backgrounds, per patient report, who underwent clinical genetic testing and were found to be positive for *BRCA1* and *BRCA2* germ-line mutations between 1997 and 2010. All women were referred to the Clinical Cancer Genetics Program Clinic at UTMDACC based on personal history of breast cancer or ovarian cancer, family history of breast and/or ovarian cancer. This study was approved by the UTMDACC Institutional Review Board.

Pathologic Assessment and Mutation Analysis

All pathologic specimens were reviewed by dedicated breast pathologists at MDACC. Initial clinical stage of all patients was reviewed and based on the seventh edition of the American Joint Committee on Cancer (AJCC) staging criteria(17).

Genetic testing was offered to women in the clinic-based cohort who met National Comprehensive Cancer Network (NCCN) criteria(18). *BRCA* genetic testing was performed at Myriad Genetic Laboratories (Salt Lake City, UT) and included full gene sequencing analysis of the coding regions and flanking intronic segments(19), five specific *BRCA1* rearrangements (exon 13 del 3.835 kb, exon 13 ins 6 kb, exon 22 del 510 bp, exon 8 to 9 del 7.1 kb, and exon 14-20 del 26 kb) for testing done after 2002, and multiplex quantitative differential polymerase chain reaction (PCR; *BRCAAnalysis* Rearrangement Testing [BART™]) done after 2006, for large rearrangement mutation testing for cases that met the laboratory's previously established criteria(20).

Statistical Analysis

Known clinical and pathologic characteristics were compared with Chi-Square Analysis or Fisher's Exact test as appropriate. Logistic regression was performed to evaluate the specific mutation among ethnicity groups. Overall survival (OS) for breast cancer patients was calculated from the time of initial diagnosis until the date of death from any cause or last follow-up. OS were estimated using the Kaplan-Meier product-limit method and was tested for differences between groups by log-rank test. P-values < 0.05 were considered statistically significant; all tests were two-sided. Statistical analysis was carried out using SAS 9.3 and TIBCO Spotfire S+ 8.2.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 445 patients were identified for this analysis, of whom 57% (n=252) were found to carry a *BRCA1* mutation, and 43% (n=193) had a *BRCA2* mutation. Eight ethnicities were represented in the study population (Figure 1). Among 445 clinic-based cohort, there were 251 (57%) with breast cancer, 62 (14%) with ovarian cancer, 37 (8%) with both breast and ovarian cancer, and 95 (21%) unaffected.

The 3 most common mutation locations among *BRCA1* carriers were in exon 2, exon 11, and exon 20; and the three most common mutation locations among *BRCA2* carriers were in exon 10, exon 11, and exon 25. The 3 AJ founder mutations, 187delAG, 5385insC, and 6174delT, represented 90%, 82%, and 18% of all mutations identified at exon 2 and exon 20 of *BRCA1* gene, and exon 11 of *BRCA2* gene, respectively. These 3 founder mutations accounted for 39% of mutations identified in AJ subjects, whereas 61% AJ patients and 84% of Caucasians harbored non-AJ founder mutations.

I. Genotype-Phenotype Correlations by Ethnicity—With the exception of Middle Eastern subjects (of only 20% were *BRCA1* carriers) and unspecified Jewish, *BRCA1* mutations were more common (52.4% to 63.2%) than *BRCA2* mutations (36.8% to 47.6%) across all ethnicities. Overall, mutations were most frequently located at exon 11 of *BRCA1* (103/445, 23.2%) and exon 11 of *BRCA2* (92/445, 20.7%). The frequencies of exon 11 mutation in different ethnic groups were as follow: 42.9% in African American, 42.6% in AJ, 53.3% in Asian, 40.9% in Caucasian, 55.6% in Hispanic, 40.0% in Middle Eastern, 42.1% in Native American, and 50% in unspecified Jewish subjects.

We analyzed the prevalence of *BRCA1* and *BRCA2* mutations at the 3 most common locations (each) in relation to ethnicity. While the frequency of *BRCA1* exon 2 mutations were significantly higher in AJ subjects compared to Caucasians (40.6% vs. 15.3%; $P=0.001$), the frequency of mutations in other exons among minority ethnic groups were not significantly different compared to Caucasians. When the frequencies of exon mutations were stratified by cancer type, AJ women with breast cancer still had the highest prevalence of *BRCA1* exon 2 mutations across all ethnicities (47.1% (8/17) positivity in AJ women vs. 0%-12.5% positivity in other ethnicities; $P=0.004$). Among ovarian cancer patients, only *BRCA1* exon 11 mutations were significantly different across ethnicities (0% in African American vs. 50% in AJ vs. 100% in Asian vs. 17.4% in Caucasian vs. 33.3% in Hispanic vs. 100% in Native American; $P=0.01$) (data not shown).

Median age at initial breast cancer diagnosis ($P=0.82$), or the side of the family (paternal or maternal) as a source of the genetic disorder, breast cancer tumor characteristics, or the cancer prevalence (breast cancer only, ovarian cancer only, or both) did not vary significantly by ethnicity in the overall study population. The OS analyses included 285 patients with a median follow-up time of 8.1 years. There were no significant differences in the OS of the overall study population with respect to different ethnicities ($P=0.3$).

II. Genotype-Phenotype Correlations by Mutation Type—The median age at initial breast cancer diagnosis in relation to the *BRCA1* (exon 2, 11, and 20) and *BRCA2* (exon 10, 11, and 25) mutation locations were similar [(42, 41 and 41 years; $P=0.66$), and (45, 42, and 38 years, $P=0.49$), correspondingly]. Women carrying the exon 20 *BRCA1* mutation were more likely to develop combined breast and ovarian cancers compared to women carrying other exon mutations ($P=0.05$, Table 1). Furthermore, the difference in the breast and ovarian cancer relative risks associated with the 3 common *BRCA1* exon mutations were calculated as follow: exon 2 vs.11 [odds ratio (OR)= 0.55 (95% CI = 0.19 to 1.58)]; exon 2 vs. 20: [OR = 1.36 (95% CI= 0.37 to 5.02)]; exon 11 vs. 20 [OR = 2.46 (95% CI = 0.78 to 7.75)]. None reached statistical significance, nor in the common *BRCA2* mutations. When pathological characteristics of breast cancer tumors expressed by different BRCA mutation types were examined, no significant differences were observed either. .

In addition, we investigated the ethnic-specific differences in clinical and pathologic characteristics of all exon mutations under three combined exon groups: exons 1-10, exons 11, and exons 12-24 (*BRCA1*) or 12-25 (*BRCA2*). The frequency of *BRCA1* mutations in exons 1-10 were significantly higher in AJ subjects compared to Caucasians (50.0% vs. 23.8%; $P=0.004$), the frequency of mutations in other exons among minority ethnic groups were not significantly different compared to Caucasians. Similarly, the median age at initial breast cancer diagnosis in relation to the *BRCA1* and *BRCA2* (exons 1-10, 11, and 12-24 or 12-25) mutation locations were similar [(40, 41 and 41 years; $P=0.78$), and (43, 42, and 40 years, $P=0.23$), correspondingly]. When all mutation locations are considered, we observed differences in the relative risks of breast and/or ovarian cancers by exon groups. Unlike the previous results herein, only women carrying mutations in exons 12-25 of *BRCA2* were more likely to develop combined breast and ovarian cancers compared to women carrying other combined exon group mutations ($P=0.02$, Table 2). We also detected significant differences in the breast and ovarian cancer relative risks between *BRCA2* exons 1-10 vs.11 [OR = 1.26 (95% CI = 1.06 to 1.48; $P=0.03$)] and *BRCA2* exons 1-10 vs. 12-25: [OR = 1.25 (95% CI= 1.03 to 1.52, $P=0.04$)]. There were no differences in the pathological characteristics of breast cancer tumors by *BRCA* exon group mutations (data not shown).

The 10-year OS estimates were 94% (95% CI= 84% to 100%) in the *BRCA1* exon 2 group in comparison with 83% in the *BRCA1* exon 11 group (95% CI= 73% to 94%), and 60% in the *BRCA1* exon 20 group (95% CI = 36% to 98%). The 10-year OS estimates for the *BRCA2* carriers were as follow: 92% (95% CI= 79% to 100%) in the exon 10 group in comparison with 97% in the exon 11 group (95% CI= 92% to 100%), and 67% in the exon 25 group (95% CI = 30% to 100%). No significant differences were noted in OS in regards to *BRCA* mutation locations 2, 11 and 20 among *BRCA1* carriers ($P=0.06$) and 10, 11 and 25 among *BRCA2* carriers ($P=0.55$). The Kaplan-Meier estimates of OS by mutation location for *BRCA1* and *BRCA2* carriers are shown in Figure 2A and 2B, respectively. When the OS was analyzed according to the three combined exon groups, the 10-year OS estimates were significantly better for *BRCA2* carriers with mutations in exon 11 97% (95% CI= 92% to 100%) and with mutations in exons 1-10 96% (95% CI= 89% to 100%), compared to mutations in exons 12-25 79% (95% CI= 63% to 92%; $P=0.02$). However the

OS was not significantly different among the three combined exon groups in *BRCA1* carriers ($P=0.31$) (Figure 3A and 3B).

DISCUSSION

While the *BRCA1* and *BRCA2* genes clearly play a key role in breast and ovarian cancer pathogenesis and in determining its phenotypic features in AJ and Caucasians, the prevalence and precise role of *BRCA* mutations at different locations of the genes in minority ethnic populations is largely unknown. Our study demonstrated that AJ women had the highest prevalence of mutations in exon 2 in *BRCA1* gene among the eight ethnic groups. Additionally, among ovarian cancer patients, the frequencies of *BRCA1* exon 11 mutations were significantly different across different ethnicities. Despite these differences, ethnicity does not seem to influence the age at initial breast cancer diagnosis, likelihood of having breast vs. ovarian cancers, or the OS in *BRCA* carriers. The current study also suggest that women carrying exon 20 *BRCA1* mutation are more likely to develop combined breast and ovarian cancers compared to women carrying other exon mutations. The 6 most common exon mutations did not confer any difference in the breast:ovarian cancer relative risk or OS among the carriers. However, when all the exon mutations were examined, significant differences were detected in the breast and ovarian cancer relative risks between mutations in *BRCA2* exons 1-10 vs.11 (OR = 1.26); and *BRCA2* exons 1-10 vs. 12-25 (OR = 1.25); and the 10-year OS estimates were significantly better for *BRCA2* carriers with mutations in exon 11. These results need to be confirmed with future prospective studies.

Previous studies have indicated that ancestral mutations (*BRCA1*: 187delAG in exon 2, and 5385insC in exon 20, *BRCA2*: 6174delT in exon 11) of the *BRCA1* and *BRCA2* tumor suppressor genes account for approximately 29%-44% of mutations detected in AJ (9-11, 21, 22). In our study, these 3 founder mutations accounted for the vast majority (39%) of mutations in this subpopulation, and also the frequency of AJ founder mutations detected in Caucasians (16%) who reported no known AJ heritage were higher than expected. Previous studies have documented that the *BRCA1* 187delAG mutation at exon 2 is a recurrently identified in Hispanics [9.5% and 24% of *BRCA* mutations(7, 8)], occurring on the Jewish haplotype(7, 12, 13, 23). Conversely, the *BRCA1* 187delAG mutation represented only 3.2% (2/63) of *BRCA* mutations identified in our Hispanic cohort, and was observed in 24.5% (13/53) of AJ patients and in 7% (19/259) of non-AJ Caucasians. These observations would be strengthened by future studies on the prevalence of ethnic specific *BRCA* mutations which could be used as a guide resource allocation for genetic testing and genetic counseling.

Phenotypic features specific to *BRCA1* vs. *BRCA2* carriers have been well recognized. For example, *BRCA1* carriers have a higher cumulative risk of ovarian cancer and a propensity toward the development of “triple-negative (TN)” breast cancers that lack ER/PR as well as HER2 overexpression(24, 25). Confirming the previous findings(26, 27), tumor histopathological features were different in *BRCA1* carriers compared to *BRCA2* carriers in our study. *BRCA1* carriers were more likely to have high nuclear grade, and TN tumors than *BRCA2* carriers regardless of ethnicity. In this study, breast cancer cases had similar ER/PR, HER2 expression, clinical stage at presentation when stratified by ethnicity or by each of the

three most common exon mutation groups in *BRCA1* and *BRCA2* carriers. However in a study by Lagos-Jaramillo et al(28), significantly higher proportion of *BRCA*-positive Hispanics had PR-negative tumors compared to *BRCA*-positive Caucasians (80% vs. 57%, OR=2.9, 95% CI= 1.0-8.1, P=0.04). To the best of our knowledge, to date there are no other published studies on the pathology of breast cancer in minority ethnic populations residing in US with known *BRCA* gene mutations.

Several studies have shown phenotypic variations associated with mutations, located in different parts of the *BRCA1* or *BRCA2* genes. In one study, major differences between the phenotype of AJ families carrying the 3 founder mutations were detected. The 5385insC emerged as an aggressive mutation type, carrying the highest cumulative incidence rates for breast cancer, and the highest proportion of families and family members with bilateral breast cancer and breast-ovarian cancer combination(29). In the same study, ovarian cancer, but not breast cancer, was detected at a significantly younger age among carriers of 187delAG (52.4 years) compared with carriers of the 5385insC (60.8 years) and 6174delT (60.7 years) mutations (P=0.005). Satagopan et al found that the estimated lifetime risk of ovarian cancer development in AJ women were two times as high for the 187delAG mutation (66%) than for the 5385insC mutation (29%)(30). The UK study found that *BRCA1* mutations were most frequently located in exons 2, 11, 13, 20. Mutations in exon 2, specifically 187delAG, had age dependent, lower incidence of cancer when compared to the exon 13 duplication(31). In a study conducted in Latvia, the prevalence of breast and ovarian cancer cases (breast: ovarian cancer ratio) differed significantly among the carriers of the 5385insC in exon 20 and 4153delA in exon 11 founder mutations (OR= 2.98, 95%CI=1.58 to 5.62, P<0.001). In addition, among the breast cancer cases, the 4153delA mutation was associated with a later age of onset and worse clinical outcomes in comparison with the 5385insC mutation.

Certain limitations of this study should be acknowledged. Sample size may have contributed to a lack of statistical significance when stratifying the analyses by genes and ethnicity. As such, some of the comparisons might have been underpowered to detect a difference between the groups. Moreover, women who underwent *BRCA* testing prior to 2006 did not receive BART™, as it was not clinically available before 2006. With inclusion of testing for large genomic rearrangements for all patients who undergo full gene sequencing, population-based studies may strengthen our understanding of the precise prevalence of rearrangements in minority ethnic populations. To this aim, the latter recommendation was included in the 2012 NCCN guidelines(18), wherein comprehensive genetic testing includes full sequencing of *BRCA1* and *BRCA2* and testing for large genomic rearrangements.

In conclusion, the findings from this study suggest that we should not only screen for founder mutations but rather do comprehensive genetic testing until prospective studies evaluate the sensitivity of ethnic-specific *BRCA* panels. Marked increased risk of combined breast and ovarian cancers in women carrying the exon 20 *BRCA1* mutation may warrant mutation-specific counseling to families seeking risk reduction advice. Once validated in other clinic- and population-based studies, it may be appropriate to consider adjusting the threshold for recommending prophylactic surgeries for prevention in these high-risk individuals.

This study offered an initial analysis of genotype-phenotype correlations in *BRCA* mutation carriers based on ethnicity. Future studies examining type of mutation instead of mutation location within the gene could offer further insight into this complex topic. In addition, studies exploring the genotype-phenotype correlations of specific *BRCA1* and *BRCA2* mutations in multi-ethnic populations are needed to clarify the role, if any, for *BRCA* modifiers in pathogenesis and outcome of breast or ovarian cancers.

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Figure 1.
Ethnicities represented in the study population

Figure 2. Kaplan–Meier estimates of overall survival (OS) by *BRCA* mutation location for *BRCA1* carriers (2A); for *BRCA2* carriers (2B).

Figure 3. Kaplan–Meier estimates of overall survival (OS) by three combined exon groups for *BRCA1* carriers (3A); for *BRCA2* carriers (3B).

Table 1

Cancer prevalences by *BRCA* mutation location in overall study population

Diagnosis	BRCA1			BRCA2		
	Mutation Location 2 * P=0.15	Mutation Location 11 * P=0.62	Mutation Location 20 * P=0.05	Mutation Location 10 * P=0.45	Mutation Location 11 * P=0.17	Mutation Location 25 * P=0.57
	Yes/Total (%)	Yes/Total (%)	Yes/Total (%)	Yes/Total (%)	Yes/Total (%)	Yes/Total (%)
Breast Cancer Only	19/150 (12.7%)	64/150 (42.7%)	12/150 (8.0%)	13/101 (12.9%)	43/101 (42.6%)	7/101 (6.9%)
Ovarian Cancer Only	7/40 (17.5%)	13/40 (32.5%)	6/40 (15.0%)	1/22 (4.5%)	13/22 (59.1%)	0/22
Both	4/22 (18.2%)	8/22 (36.4%)	6/22 (27.3%)	1/15 (6.7%)	5/15 (33.3%)	1/15 (6.7%)
Neither	11/40 (27.5%)	18/40 (45.0%)	4/40 (10.0%)	10/55 (18.2%)	31/55 (56.4%)	2/55 (3.6%)

* P values are comparisons of each mutation location among tumor types by Fisher's exact test

Table 2

Cancer prevalence by *BRCA* combined exon group in overall study population

Diagnosis	BRCA1				BRCA2			
	Mutation Location 1-10 * P=0.35	Mutation Location 11 * P=0.49	Mutation Location 12-24 * P=0.18	Mutation Location Yes/Total (%)	Mutation Location 1-10 * P=0.09	Mutation Location 11 * P=0.15	Mutation Location 12-25 * P=0.02	Mutation Location Yes/Total (%)
Breast Cancer Only	33/143 (23%)	64/143 (44.8%)	37/143 (25.9%)	Yes/Total (%)	27/98 (27.6%)	43/98 (43.9%)	27/98 (27.6%)	Yes/Total (%)
Ovarian Cancer Only	11/40 (27.5%)	13/40 (32.5%)	15/40 (37.5%)	Yes/Total (%)	1/22 (4.6%)	13/22 (59.1%)	8/22 (36.4%)	Yes/Total (%)
Both	4/22 (18.2%)	8/22 (36.4%)	8/22 (36.4%)	Yes/Total (%)	2/15 (13.4%)	5/15 (33.3%)	8/15 (53.3%)	Yes/Total (%)
Neither	14/39 (35.9%)	18/39 (46.2%)	7/39 (18.0%)	Yes/Total (%)	13/53 (24.5%)	31/53 (58.5%)	8/53 (15.1%)	Yes/Total (%)

* P values are comparisons of each mutation location among tumor types by Fisher's exact tes