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Original Article

Clinical and pathological characteristics of Hispanic BRCA-associated breast cancers in the American-Mexican border city of El Paso, TX

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Abstract: Hispanics in El Paso, TX, a large American-Mexican border city constitute 85% of the population. Limited cancer research has been conducted in this population. We sought to study the prevalence of *BRCA* mutations among Hispanic patients of Mexican origin, identify reported Mexican founder or recurrent mutations, and study the breast cancer characteristics in mutation carriers. Methods: Hispanic women of Mexican descent with a personal history of breast cancer, who presented consecutively for genetic cancer risk assessment, were enrolled in an Institutional Review Board-approved registry and underwent *BRCA* testing based on national guidelines. The characteristics of tumors and patients with positive *BRCA* mutation were analyzed. Results: 88 patients were screened; 18 patients (20%) were *BRCA* carriers. Among *BRCA* carriers, 72% were diagnosed with breast cancer at younger than 50 years, 61% had "Triple negative disease". *BRCA* carriers had a significantly higher Body Mass Index (BMI) than non-carriers. Thirteen patients had *BRCA*1 mutations and five had *BRCA*2 mutations. A total of 17 deleterious *BRCA* Mutations were observed. Seven have been previously reported as specific genes from Mexico as country of origin. Five new mutations in *BRCA* carriers of Mexican descent were identified. Conclusion: Hispanic breast cancer patients of Mexican origin present at a younger age, and have predominantly triple negative tumors and high BMI. We identified 5 new mutations not reported previously in Hispanic *BRCA* carriers of Mexican descent. Interestingly, 41% of *BRCA* mutations identified have been reported as recurrent mutations in Hispanic individuals from Mexico as the country of origin. A more cost-effective approach to initial screening of Hispanic individuals based on country of origin is desirable and would potentially decrease the number of cases requiring complete sequencing.

Keywords: BRCA1, BRCA2, hispanic, estrogen receptor, progesterone receptor, HER2

Introduction

Hispanics (Latinos) are the largest and fastest growing ethnic minority group in the United States [1]. Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death in Hispanic (Latina) women in the United States [2]. Although the incidence of breast cancer in Hispanics is less than in non-Hispanic whites, the prevalence of hereditary deleterious mutations in the breast cancer genes *BRCA*1 and *BRCA*2 (*BRCA*) is reported to be higher in Hispanics with breast cancer than in non-Ashkenazi Jewish populations [3, 4]. Hispanic women are also more likely to be diagnosed at a younger age and advanced stage and to have a higher mortality than non-Hispanic whites [2, 5, 6]. Breast cancers in Hispanic women are reported to have multiple adverse prognostic indicators that might account for this disparity, including high cellular proliferation and more triple negative breast cancers [7-12]. The identification of factors that contribute to ethnic variation in breast cancer incidence and outcome is essential to understanding the differences that exist among breast cancer patients of different ethnicities.

To date, the majority of *BRCA*-associated breast cancer research has been conducted in non-Hispanic white populations, with few studies focusing on other races and ethnicities [3, 5, 8, 9]. *BRCA*1-associated breast cancers are often high grade [13, 14], steroid receptor negative

Table 1. Clinical and pathological characteristics of the entire cohort

Variable	N	%
Age at diagnosis (years)		
≤ 50	66	75.00
> 50	22	25.00
BMI (Kg/m^2)		
≤ 30	54	61.36
> 30	34	38.64
Diagnosis		
Ductal	76	86.36
Lobular	12	13.64
Stage		
1 and 2	70	79.55
3	16	18.18
4	2	2.27
Chemotherapy		
No	16	18.60
Yes	70	81.40
Radiotherapy		
No	39	44.32
Yes	49	55.68
Surgery		
Lumpectomy	43	48.86
Mastectomy	45	51.14
Genetic mutation		
Negative	70	79.55
BRCA1	13	14.77
BRCA2	5	5.68
ER positive		
No	39	44.32
Yes	49	55.68
PR positive		
No	48	54.55
Yes	40	45.45
HER2 positive		
No	70	79.55
Yes	18	20.45
ER, PR, HER2 all negative		
No	57	64.77
Yes	31	35.23
ER, PR positive & HER2 negative		
No	49	55.68
Yes	39	44.32

[15-18], have higher proliferation levels [19, 20], and express low levels of the Human Epidermal Growth Factor Receptor 2 (HER2) [15, 20]. *BRCA*2-associated breast cancers have been reported to be more likely estrogen receptor (ER) or progesterone receptor (PR) positive [21, 22]. To date there are a few published studies on the pathology of breast cancer and the specific *BRCA* mutations found in Hispanics living in the United States [23-26]. Also, the Hispanic population in the Southwestern United States is primarily of Mexican ancestry, whereas individuals of Puerto Rican, Dominican, and Cuban ancestry predominate in the Eastern United States. Studies combining Hispanics from significantly different ancestral populations might not lead to specific risk assessment strategies generalizable to all Hispanics living in the U.S.

The purpose of this study is to evaluate the pathological and clinical characteristics of invasive breast cancers diagnosed in Hispanic women of Mexican origin with germline deleterious *BRCA* mutations and the type of the *BRCA* mutations. El Paso, TX is a large American-Mexican border city of population around 900,000; 85% are Hispanics of Mexican origin. Limited cancer research has been conducted in this population. The relative homogeneity of this Hispanic population offers the ideal setting to study the spectra of *BRCA* mutations among Hispanic patients of Mexican origin, possibly identify reported Mexican founder or recurrent mutations, and study the breast cancer characteristics in mutation carriers.

Materials and methods

Self-identified Hispanics of Mexican descent with breast cancer referred to the genetic counseling clinic at the Texas Tech University Breast Care Center were recruited consecutively between January 2012 and December 2013. Genetic testing was offered to women who met the National Comprehensive Cancer Network (NCCN) criteria [27]. *BRCA* testing was performed at Myriad Genetic Laboratories (Salt Lake City, UT) and included multiplex quantitative differential polymerase chain reaction (PCR) *BRCA* Analysis Rearrangement Testing (BART) for large rearrangement mutation testing for cases that met the vendor's automatic criteria (*BRCA* mutation probability ≥ 30%). BART was conducted electively when covered by private insurance or patient payment. Demographic and clinical data were obtained. A bilingual cancer risk counselor conducted genetic counselling sessions for Spanish-spea-

Table 2. Comparison of clinical characteristics between BRCA mutation carriers and non-carriers

Variable	Genetic Mutation		*P*-value
	No	Yes	
	N (%)	N (%)	
Age at diagnosis (years)			0.766
≤ 50	53 (75.7)	13 (72.2)	
> 50	17 (24.3)	5 (27.8)	
BMI (Kg/m^2)			0.002
≤ 30	49 (70.0)	5 (27.8)	
> 30	21 (30.0)	13 (72.2)	
Diagnosis			1.000
Ductal	60 (85.7)	16 (88.9)	
Lobular	10 (14.3)	2 (11.1)	
Stage			1.000
1 and 2	55 (78.6)	15 (83.3)	
3	13 (18.6)	3 (16.7)	
4	2 (2.9)	0 (0.0)	
Chemotherapy			0.019
No	16 (23.5)	0 (0.0)	
Yes	52 (76.5)	18 (100.0)	
Radiotherapy			0.038
No	27 (38.6)	12 (66.7)	
Yes	43 (61.4)	6 (33.3)	
Surgery			0.431
Lumpectomy	36 (51.4)	7 (38.9)	
Mastectomy	34 (48.6)	11 (61.1)	
ER positive			0.120
No	28 (40.0)	11 (61.1)	
Yes	42 (60.0)	7 (38.9)	
PR positive			0.296
No	36 (51.4)	12 (66.7)	
Yes	34 (48.6)	6 (33.3)	
HER2 positive			0.018
No	52 (74.3)	18 (100.0)	
Yes	18 (25.7)	0 (0.0)	
Triple negative			0.014
No	50 (71.4)	7 (38.9)	
Yes	20 (28.6)	11 (61.1)	
ER, PR positive & HER2 negative			0.791
No	38 (54.3)	11 (61.1)	
Yes	32 (45.7)	7 (38.9)	

P-values were obtained using Fisher's exact test.

king patients. Age at diagnosis and Body Mass Index (BMI) were dichotomized and all the variables were summarized using frequencies and proportions. The distribution of variables between *BRCA* mutation carriers and non-carriers were compared using Fisher's exact test. A logistic regression was used to determine adjusted associations of clinical and pathological characteristics with *BRCA* mutation carriers. A *p*-value less than or equal to 5% was considered as significant result. The results of logistic regression were summarized using odds ratio (OR) with 95% confidence interval (CI) and *p*-values. All the statistical analyses were carried out using SAS 9.3.

Results

A total of 88 patients met screening criteria and were included for data analysis. Eighteen patients with *BRCA*-associated breast cancer were identified, representing 20% of the total high-risk patients referred for genetic testing. Among those patients, 13 had *BRCA*1 mutations and 5 patients had *BRCA*2 mutations. **Table 1** shows the summary of clinical and pathological characteristics of all the patients. Two third (75%) of the patients were less than 50 years old. Around one third of the patients had a BMI higher than 30 Kg/m^2. Eighty six percent (86 %) of the patients were diagnosed with invasive ductal carcinoma while 14% had lobular carcinoma; 80% of the patients presented with stages I or II of breast cancer while 18% of the patients presented at stage III and 2% of the patients at stage IV. Fifty six percent (56%) of the patients had an ER receptor positive breast cancer, 45% PR receptor positive disease and 20% HER2 positive cancer; 35% of all the patients screened had ER, PR and HER2 negative (Triple negative) breast cancer. Eleven (85%) of the *BRCA*1 carriers had triple negative breast cancer compared to 20 (27%) of *BRCA*1 non-carriers (p-value < 0.001). None of the *BRCA*2 carriers had triple negative cancer compared to 31 (37%) of *BRCA*2 non-carriers. All *BRCA*2 carriers had ER or PR positive and HER2 negative cancers compared to 41% *BRCA*2 non-carriers (p-value = 0.015). **Table 2** shows the comparison of important variables between *BRCA* mutation carriers (including *BRCA*1 and *BRCA*2) and non-carriers. BMI, treatment with chemotherapy and radiotherapy, HER2 status, and

Table 3. Comparison of clinical characteristics between BRCA mutation carriers and non-carriers who have "triple negative" cancer

Variable	Genetic Mutation		*P*-value
	No	Yes	
	N (%)	N (%)	
Age at diagnosis (years)			0.638
≤ 50	17 (85.0)	8 (72.7)	
> 50	3 (15.0)	3 (27.3)	
BMI (Kg/m^2)			0.057
≤ 30	12 (60.0)	2 (18.2)	
> 30	8 (40.0)	9 (81.8)	
Diagnosis			0.118
Ductal	20 (100.0)	9 (81.8)	
Lobular	0 (0.0)	2 (18.2)	
Stage			0.631
1 and 2	16 (80.0)	10 (91.9)	
3	4 (20.0)	1 (9.09)	
Radiation therapy			0.056
No	5 (25.0)	7 (63.6)	
Yes	15 (75.0)	4 (36.4)	
Surgery			0.273
Lumpectomy	12 (60.0)	4 (36.4)	
Mastectomy	8 (40.0)	7 (63.6)	

P-values were obtained using Fisher's exact test.

triple negative status were found to be different in *BRCA* mutation carriers compared with *BRCA* non-carriers: 72% of *BRCA* mutation carriers were diagnosed with breast cancer at age younger or equal to 50; 72% of *BRCA* mutation carriers had a high BMI (> 30) compared to 30% of the non-carriers (*p*-value = 0.002). All the *BRCA* mutation carriers received chemotherapy compared to 76% for non-carriers (*p*-value = 0.009). Only one third of the *BRCA* carriers were treated with radiation treatment compared to 61% of non-carriers (*p*-value = 0.038). None of the *BRCA* carriers had HER2 positive breast cancer compared to 26% of non-carriers (*p*-value = 0.018). The majority (61%) of *BRCA* carriers had triple negative breast cancer compared to 29% of non-carriers (*p*-value = 0.014). In the adjusted analysis, we found BMI, radiotherapy, and triple negative statuses were significantly associated with *BRCA* mutation carriers. Patients with BMI > 30 had more than 4 times of odds of having *BRCA* carriers as compared with their counterparts after adjusting other significant factors (*p* = 0.02). Triple negative patients had 3.7 times more odds of being *BRCA* carriers. The specific characteristics of the patients with *BRCA* associated, triple negative breast cancer are shown in **Table 3** and are compared to non-carriers with triple negative breast cancer. The 2 groups (carriers and non-carriers) had overall similar clinical characteristics however 81.8% had a high BMI > 30 compared to 40% in non-carriers. Among the carriers, 72% are diagnosed at a younger age (less or equal 50). The majority (81%) had invasive ductal cancer and most patients (63.6%) underwent mastectomy. Regarding *BRCA* mutation profile in our patients population a total of 17 deleterious *BRCA* mutations were observed in 18 patients (2 patients had *BRCA*1 del exons 1-2) (**Table 4**).

Discussion

This study suggests that *BRCA*-associated breast cancers in Hispanics of Mexican origin have low rates of ER, PR and HER2 expression. They present at a young age at diagnosis, and have predominantly triple negative tumors, which is consistent with *BRCA*-associated breast cancer in non-Hispanics. As expected, many more breast cancer patients (61%) who are mutation carriers undergo mastectomy versus lumpectomy (39%). In this study, the *BRCA* carriers were predominantly overweight, when compared to non-carriers (72% vs. 30%), *p*-value = 0.002). This finding need to be further investigated to delineate possible correlations between BMI and risk of breast cancer in *BRCA* carriers. A total of 17 deleterious *BRCA* mutations were observed in 18 patients (2 patients had *BRCA*1 del exons 1-2). Remarkably 12 of 17 mutations (70%) have been recurrent mutations reported in Hispanic population [3, 24, 26, 28-31]: *BRCA*1 [2552delC; 3148delCT; 3878delTA; A1708E (5242C>A); C17875 (5478T>A), G1788D (5482G>A); R71G (330A>G); del exons 9-12) and *BRCA*2 (3492insT; E49X (373G>T); Q742X (2451c>T); W2586X (7986G>A)]. Also, seven out of 17 (41%) types of gene mutations have been previously reported as specific genes from Mexico as country of origin [3, 4, 26]: *BRCA* 1 (*BRCA*1 exon 9-12 del; C1787S & G1788D; R71 G; and A1708E) and *BRCA*2 (BRCA 2 3492insT; E49X and Q742X). Of note is that *BRCA*1 ex 9-12 del is the first Mexican founder mutation, and has also been reported

Table 4. *BRCA* mutations in Mexican Hispanics in El Paso, Texas

BRCA2 mutations
3492insT
E3002k (9Z32G>A)*
E49X (373G>T)
Q742X (2451c>T)
W2586X (7986G>A)
BRCA1 mutations
2552delC
3148delCT
3878delTA
A1708E (5242C>A)
C1225X (3794C>A)*
C1787S (5478T>A), G1788D (5482G>A)
C1787S (6475T>A), G1788D (5482G>A)
R1751X (5370C>T)*
R71G (330A>G)
del exons 1-2*
del exons 9-12
del exons 16-17*

*Not previously reported in Hispanic patients with *BRCA*-associated breast cancer of Mexican descent.

in 3.8% of *BRCA* sequence-negative high risk Hispanic families [4]. To our knowledge, the following *BRCA*1 mutations C1225X (3794C>A); R1751X (5370C>T); Del exons 1-2; Del exons 16-17 and BRCA2 E3002k (9Z32G>A) have not been reported previously in Hispanic BRCA carriers of Mexican descent.

In conclusion, we believe that Hispanic with BRCA-associated breast cancers have distinctive clinical and disease-specific characteristics. Also a more cost-effective approach to initial screening of Hispanic individuals based on country of origin might be possible and would potentially decrease the number of cases requiring complete sequencing. Increasing breast cancer awareness and encouraging genetic counseling among high-risk younger patients of Mexican descent is also needed. In addition, implementing risk reduction strategies including maintenance of a healthy weight and lifestyle should be encouraged.

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Disclosure of conflict of interest

None.

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