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Pathological characteristics of *BRCA*-associated breast cancers in Hispanics

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Abstract

The immunophenotype of *BRCA*-associated breast cancer has been studied in predominantly non-Hispanic whites (NHW). We evaluated the pathological characteristics of *BRCA*-associated invasive breast cancer in Hispanics.

Methods—A case-control study was conducted on breast cancers from Hispanic and NHW women who enrolled in an IRB-approved registry and underwent *BRCA* gene analysis. *BRCA* negative controls (41 Hispanic, 39 NHW) were matched on age and ethnicity to *BRCA* positive cases (39 Hispanic, 35 NHW). A tissue array was constructed to characterize the expression of estrogen receptor (ER), progesterone receptor (PR), HER2, Ki-67 and p53 by immunohistochemistry.

Results—Mean age at diagnosis was 37.1 years (range 24-59) for Hispanics (80% with Mexican ancestry) and 40.1 years (range 21-63) for NHW (P=0.03). Hispanic *BRCA1* cases were more likely than *BRCA* negative controls to have tumors that were ER-negative (P<0.001) and PR-negative (P=0.001), had higher levels of Ki-67 (P=0.001) and p53 expression, and lower levels of HER2 overexpression. When stratified by genes, there were no significant differences in expression of ER, Ki-67, HER2 and p53 by ethnicity among mutation carriers. However, a significantly higher proportion of *BRCA*-positive Hispanics had PR-negative tumors compared to *BRCA*-positive NHW (80% vs. 57%, OR=2.9, 95% CI 1.0-8.1, P=0.04).

Conclusion—Hispanic *BRCA*-associated breast cancers were found to have the unique immunophenotype associated with *BRCA* mutations; however, there was a trend towards a difference in PR expression among Hispanic *BRCA1* and *BRCA2* cases. Additional research on the molecular mechanisms involved in the loss of PR in this population is warranted as it could have important implications for the treatment and prevention of breast cancer in Hispanics.

Keywords

Hispanic; breast cancer; *BRCA*; progesterone receptor; estrogen receptor

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INTRODUCTION

Breast cancer is the leading cause of cancer-related death and the most commonly diagnosed cancer among Hispanic women living in the United States. Hispanic women are more likely to be diagnosed at a younger age and at a later, less curable stage than non-Hispanic white (NHW) women [1-4]. In addition, breast cancers in Hispanic women are reported to have multiple adverse prognostic indicators, including steroid receptor negativity and high cellular proliferation [5,3,6,2,7-9]; however, somatic p53 mutations are less frequently identified in this population [10].

Sporadic breast cancers in Hispanic women have a phenotype similar to that seen in *BRCA1*-associated breast cancer. Invasive breast tumors from *BRCA1* carriers are often high grade [11-12], steroid receptor negative [13-18], frequently of ductal histology with typical or atypical medullary features [12,19], have higher proliferation levels [20], express low levels of HER2 [13,19,21] and have a higher frequency of somatic p53 mutations [13,19,22]. In addition, it has been reported that *BRCA1*-associated breast cancers are more likely to express a basal epithelial phenotype and overexpress cytokeratin 5 and/or 6 [13]. *BRCA2*-associated breast cancers have been reported to more likely be high grade, of ductal histology, ER positive, and express a luminal phenotype [23-24].

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; however, to date the majority of *BRCA*-associated breast cancer research has been conducted in NHW populations, with few studies focusing on other races and ethnicities. Even less is known about hereditary breast cancer in Hispanics, though we previously documented that *BRCA* gene mutations accounted for a large proportion of young Hispanic women with breast cancer who were attending a high-risk clinic [25]. A Spanish study of *BRCA*-associated breast cancers found that breast cancers in *BRCA1* carriers had low rates of estrogen receptor (ER), progesterone receptor (PR) and HER2 expression, and higher rates of basal cell markers and p53 expression [26]. *BRCA2* carriers were reported to have higher levels of steroid receptor expression and higher expression of several other proteins including BCL2, cyclin D1, D3, p27, p16, p21, CDK4, CDK2 and CDK1. As the larger immigrant Hispanic population in the United States has more diverse origins, these findings may not be relevant to Hispanics residing in this country.

To date there are no published studies on the pathology of breast cancer in a high-risk largely immigrant Hispanic population living in the United States with known *BRCA* gene mutation status. The purpose of this study was to evaluate the pathological characteristics of invasive breast cancers diagnosed in Hispanic women with germline deleterious *BRCA* mutations and compare these characteristics to Hispanic non-carriers and NHW *BRCA* carriers and non-carriers.

METHODS

Study population

The sample population studied included self-identified Hispanic and NHW women who underwent genetic cancer risk assessment and *BRCA* testing at a high-risk referral clinic, the City of Hope *Cancer Screening and Prevention Program*, between 1997 and 2005. These women provided informed consent to participate in an IRB-approved hereditary cancer registry. All research was conducted in accordance with ethical guidelines as described in the IRB-approved protocol #96144.

All patients had a diagnosis of invasive breast cancer. Those diagnosed with ductal or lobular carcinoma in-situ without an invasive component were excluded. Only women with either a deleterious *BRCA* mutation or without mutations in the *BRCA* genes were included; women with unclassified *BRCA* variants were excluded. Additional eligibility criteria included the absence of known germ-line mutations in other genes associated with hereditary breast cancer, such as *TP53* or *PTEN*.

This study was designed as a case-control study. *BRCA* negative cases served as controls and were matched by age at breast cancer diagnosis and ethnicity.

Data collection

Data on age at diagnosis, tumor size, histology, and grade were abstracted from pathology reports for all participants. Tissue samples were not available for 20 Hispanics; data on ER, PR, HER2, p53 and Ki-67 expression were obtained from pathology reports for these cases. Tumor size was based on largest diameter. For tumors that were multifocal (n=5) the largest tumor size was used. Data on BMI were abstracted from a clinic questionnaire or medical records.

Pathology reports with a description of well, moderately or poorly differentiated histology were assigned to grades 1, 2 and 3 respectively. Cancers of mixed grade were assigned to the higher category. A 10% threshold was used for categorization of ER, PR, Ki-67 and p53 expression; and 0, 1+ or 2+ immunostaining was scored as low expression with 3+ scored as overexpression for HER2 based on reported immunohistochemical assay results from pathology reports.

Sources of tissue

Tumor specimens were submitted to the Department of Clinical Cancer Genetics at City of Hope National Medical Center. Tumor tissues were obtained from paraffin blocks from primary breast tumors stored at the time of diagnosis.

Tissue array construction

A checkerboard tissue block was constructed based on the technique summarized by Battifora and Mehta [27]. Sections ranging from 4-5 microns in thickness were cut from the block. Those cases in which the tumor size was less than 1cm, cases with microinvasion, cases in which the tumor was spread out within the tissue, or cases from core biopsy specimens were sectioned individually at 4 or 5 microns and mounted on poly-l-lysine coated or plus slides.

Immunohistochemistry

Immunohistochemical staining was performed using standard techniques as described elsewhere in detail [28-32]. Antigen retrieval was used for tissue sections immunostained for ER and Ki-67 by heating slides in 0.1M citrate buffer (pH 6.0) for 1 hour. Immunohistochemical localization was performed using the following primary monoclonal antibodies: anti-ER IgG (1D5 Dako) at a concentration of 10μg/mL, anti-PR IgG (PGR636) at a concentration of 5.8μg/mL [29], MIB1 for Ki-67 detection at a concentration of 2.8μg/mL, 10H8 for HER2 detection at a concentration of 4μg/mL [30,28,31], and anti-p53 antibody (DO-7) at a concentration of 3.35 μg/mL for p53 detection[33]. Appropriate breast cancer cell lines with known high or normal expression of each of the proteins were used as positive and negative controls, respectively.

Immunohistochemical evaluation

Staining of the 134 tissue samples available for assay evaluation was scored by one pathologist (M. Press) who was blinded to *BRCA* carrier status and ethnicity. Quantification of percentage of stained nuclei for ER and PR was performed by scoring the amount of staining on an intensity scale of 0 (none), 1+ (weak), 2+ (moderate) and 3+ (strong) with the percentage of tumor cells recorded at each immunostaining level. The overall percentage of tumor cells immunostained was recorded. Tumor specimens that showed 10% or greater nuclear staining were scored as positive while specimens with 1 to 9% staining were assessed as ER or PR borderline, and those with no staining were ER-negative or PR-negative as described previously [29].

Only HER2 membrane immunostaining was considered specific. HER2 membrane immunostaining was scored as follows: 0 when no staining was observed or when staining was observed in less than 10% of tumor cells; 1+ when weak/barely perceptible membrane staining was detected in more than 10% of the tumor cells; 2+ when weak to moderate circumferential membrane staining was observed in more than 10% of the tumor cells; and 3+ when strong membrane staining was observed for more than 10% of the tumor cells as summarized previously [28,31].

The proliferative activity was evaluated by staining for Ki-67 and was evaluated by assessing the percentage of tumor cells with immunostained nuclei on a scale of 0 to 100%. Tumor specimens with less than 10% staining were scored as low, staining between 10% to 20% as intermediate and greater than 20% staining was scored as high.

P53 immunostaining was characterized by scoring the percentage of tumor cells with immunostained nuclei on a scale from 0 to 100%. Tumors with less than 10% p53 immunostaining were scored as low expression while staining of 10% or more cells was scored as high expression. Immunostaining in more than 10% of tumor nuclei is highly correlated with the presence of missense TP53 mutations as described elsewhere [33,32,34].

Data analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software package (SPSS, Inc., Chicago, IL, USA). Missing data was excluded from data analysis. Probability values less than 0.05 were used to represent statistical significance.

ER and PR were coded as either positive or negative. ER or PR borderline cases (3 ER cases and 8 PR cases) were scored as positive. A HER2 score of 0, 1+, or 2+ was coded as low expression while a score of 3+ was coded as overexpressed. Ki-67 intermediate and high staining was combined for analyses.

Descriptive statistics including means, SDs and frequencies were generated for each variable. Data were analyzed using chi square, Fisher's exact test, T test or ANOVA as appropriate. Logistic regression analysis was conducted to evaluate associations between ethnicity, *BRCA* status and marker expression.

RESULTS

Data was available for 80 Hispanic and 74 NHW women. Among Hispanics, 31 were identified to have a *BRCA1* mutation, 8 had a *BRCA2* mutation and no *BRCA* mutation was identified in 41 women. Of the 74 NHW women, 20 women tested positive for a *BRCA1* mutation, 15 had a *BRCA2* mutation and 39 were *BRCA* negative.

Demographics

The majority (80%) of Hispanics were of Mexican ancestry (data not shown). Additional regions of origin included Central America (11.3%), South America (1.2%), and Spain (1.2%). Five Hispanic women reported mixed Hispanic and non-Hispanic ancestry (6.3%).

Expression of ER, PR, HER2, Ki-67 and p53

BRCA1-positive Hispanics were more likely than *BRCA*-negative Hispanics to have tumors that were ER-negative (81% vs. 39%, $P<0.001$) and PR-negative (87% vs. 49%, $P=0.001$) (Table 1). They were also more likely to have intermediate/high expression of Ki-67 (79% vs. 40%, $P=0.001$) and p53 (61% vs. 45%) and low HER2 expression (94% vs. 80%) compared to Hispanic non-carriers (Table 1). Similar to Hispanic non-carriers, *BRCA2*-positive Hispanic tumors had higher rates of ER-positive (75% vs. 61%) tumors (Table 1). Half of the Hispanic *BRCA2* tumors expressed PR. All of the Hispanic *BRCA2*-associated breast cancers had low HER2 expression, while the majority (83%) had low p53 expression and intermediate/high Ki-67 expression (57%).

Hispanic *BRCA* carriers were more likely to have PR-negative tumors compared to *BRCA*-positive NHW women (80% vs. 57%, OR=2.9, 95% CI 1.0-8.1, $P=0.04$). The trend was apparent for both *BRCA1* and *BRCA2* when considered separately, though the association was not statistically significant. Overall, Hispanics were twice as likely to have PR-negative tumors compared to NHW women (OR=2.7, 95% CI 1.1-3.9, $P=0.03$). There were no significant differences by ethnicity in expression of ER, Ki-67, HER2 and p53 among *BRCA1* and *BRCA2* carriers, when examined together or separately by gene (Table 1).

Triple-negative breast cancer

A slightly higher proportion of Hispanic breast cancers were ER-, PR- and HER2-negative [44% (35/80)] compared to NHW breast cancers [35% (26/74)] (data not shown). Among *BRCA1* cases, 74% (23/31) of Hispanic breast cancers had a triple-negative immunophenotype compared to 70% (14/20) of NHW breast cancers.

Age at first breast cancer diagnosis

Mean age at first breast cancer diagnosis was 37.1 years (range 24-57) for Hispanics and 40.1 years (range 21-63) for NHW women ($P=0.03$) (Table 1). Among *BRCA1* carriers, mean age at first breast cancer diagnosis for Hispanics and NHW women was similar at 36.9 years (range 27-54 years) and 37.8 years (range 21-59 years) respectively. NHW *BRCA2* carriers were older than Hispanic *BRCA2* carriers at the time of their first breast cancer diagnosis (43.3 vs. 36.9 years).

Tumor size

The average tumor size was 3.1cm (SD±2.2cm) for Hispanic carriers and 2.3cm (SD ±1.5cm) for NHW carriers (Table 1). Though average tumor size was largest among Hispanic *BRCA2* carriers, no significant difference was detected when all groups were compared.

Tumor grade

A higher proportion (97% vs. 89%) of Hispanic women were diagnosed with moderately to poorly differentiated tumors compared to NHW; however, poorly differentiated tumors were more common among NHW *BRCA* carriers than Hispanic *BRCA* carriers (Table 1). Hispanic *BRCA* carriers (83% *BRCA1*, 75% *BRCA2*) had higher rates of poorly differentiated tumors compared to Hispanic non-carriers (59%).

Tumor histology

Ductal histology was the most common tumor histology across the entire sample (82%). Irrespective of *BRCA* status, medullary histology was identified more often among Hispanics compared to NHW (7 cases vs. 2 cases) (Table 1). Five women were diagnosed with tumors of other histological types including mucinous (n=3), inflammatory (n=1) and metaplastic (n=1) carcinoma. There were no significant differences in the distribution of tumor histology.

Bilateral breast cancer

Thirty women were diagnosed with bilateral breast cancer (20 Hispanic and 10 NHW women) (data not shown). Twenty-three were *BRCA* carriers (13 Hispanic and 10 NHW women). Of the Hispanic women diagnosed with bilateral breast cancer, 4 were diagnosed with synchronous breast cancer and 16 with metachronous breast cancer. All of the NHW women diagnosed with bilateral breast cancer were diagnosed with metachronous breast cancer. For those with data available on both tumors, the pathological characteristics of the second breast cancer were similar to those of the first breast cancer.

Body Mass Index (BMI)

BMI data was available for 73% (112/154) of study participants; 51 Hispanic women and 61 NHW women. Hispanic women had a slightly higher mean BMI compared to the NHW women (27.2 kg/m^2 vs. 26.1 kg/m^2) (data not shown). Hispanic women with PR-negative breast cancers also had a slightly higher mean BMI (27.0 kg/m^2, n=31) than NHW women (26.3 kg/m^2, n=27). BMI was also found to be higher in the subset of Hispanic women with PR-negative *BRCA1*-associated breast cancers as compared to NHW women with PR-negative *BRCA1*-associated breast cancers (Hispanic 27.1 kg/m^2 vs. NHW 26.4 kg/m^2).

DISCUSSION

This study was conducted to evaluate the pathological characteristics of *BRCA*-associated invasive breast cancer in Hispanic women. The findings of this study are consistent with previous knowledge of the tumor characteristics of *BRCA* carriers. In particular, Hispanic *BRCA1* carriers exhibited many of the same pathological characteristics that have been described in predominantly NHW *BRCA1* carrier populations such as higher rates of steroid receptor negativity, low HER2 expression and high cellular proliferation as compared to Hispanic non-carriers. Likewise, as previously reported, the majority of Hispanic *BRCA2*-associated breast cancers in this study were high grade ductal carinomas and ER positive.

Hispanic *BRCA*-associated breast cancers had significantly lower levels of PR expression than NHW *BRCA*-associated breast cancers, irrespective of mutation status. Additional research on the possible clinical implications and molecular mechanisms involved in the loss of PR in this population is warranted as it could have important implications for the treatment and prevention of breast cancer in Hispanic women, particularly since PR has been found to be an independent predictor of endocrine therapy response [35-37]. Studies have found that patients with ER-positive/PR-negative tumors who received adjuvant endocrine therapy have higher rates of recurrence and poorer survival compared to patients with ER-positive/PR-positive tumors.

The molecular mechanisms that have been hypothesized to explain the loss of PR in breast tumors include a nonfunctional ER, low circulating levels of estrogen, hypermethylation of the PR promoter, loss of heterozygosity at the PR gene locus, selective ER modulator or growth factor-induced membrane-initiated steroid signaling activity of ER, and altered ER coregulator levels or activity [38]. In addition, recent data suggests that increased BMI

($\geq 30 kg/m^2$) is associated with reduced ER and PR expression among younger women (under age 50) with breast cancer [39]. The Hispanic women in this study had a slightly higher BMI compared to the NHW women. BMI was also slightly higher among the Hispanic women with PR-negative breast cancers. Additional studies with a larger sample are necessary to determine if there is a significant difference in BMI that may be contributing to the difference in PR expression identified in this study.

HER2 overexpression occurs in only 20-30% of sporadic breast cancers. Low levels of HER2 expression have been documented in studies of breast cancer in women of Hispanic descent [40-42]. In this study, Hispanic and NHW breast cancers had similar HER2 expression within each of the three groups–*BRCA1* carriers, *BRCA2* carriers and non-carriers. Breast cancers from non-carriers had HER2 expression levels comparable to levels previously reported for sporadic breast cancers. Hispanic *BRCA1*-associated breast cancers had low levels of HER2 expression, consistent with previous descriptions of the breast cancer immunophenotype in *BRCA1* carriers [13,19,21]. Although all of the Hispanic *BRCA2* carriers also had low levels of HER2 expression, additional studies with a larger sample of Hispanic *BRCA2* carriers are necessary to confirm this finding.

BRCA1 mutations are prevalent among women with triple-negative breast cancers (i.e., ER- and PR-negative and HER2 non-amplified) compared to women with non-triple-negative breast cancer. In addition, triple-negative breast cancers have been found to occur more frequently in non-Hispanic black and Hispanic women and are related to poorer overall survival [43-44]. A higher proportion of Hispanic breast cancers in this study had a triple-negative immunophenotype compared to NHW breast cancers. The majority of the triple-negative breast cancers were identified among *BRCA1* carriers of both ethnicities.

TP53 mutations usually result in p53 protein accumulation and prolonged half-life of the protein making immunohistochemistry a surrogate for mutational analysis. It has been hypothesized that loss of p53 function may be critical in the development of *BRCA1*-related tumors and therefore higher rates of p53 overexpression are observed among carriers. We observed p53 overexpression in a higher proportion of breast cancers in each group, except Hispanic *BRCA2* carriers. This observation is consistent with findings from other studies in the literature for most of these groups, except for NHW women with breast cancer where p53 overexpression is approximately 20%. It is not clear if this discrepancy is due to the potentially non-representative nature of this small cohort, therefore a follow-up study is needed to further explore this issue.

The breast cancer tumors from Hispanic women in this study exhibited histological characteristics that have been previously reported in this ethnic population, including lower levels of lobular carcinoma (n=1) and higher levels of medullary carcinoma (n=7) [45]. Although medullary histology is also known to be common among *BRCA1* carriers, three of the seven with tumors of medullary histology were non-carriers.

Limitations

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. In addition, due to administrative barriers at the respective hospital, tumor samples were not available for repeat testing for 20 Hispanic women. As a result, data from pathology reports was used to complete the data for analysis. As none of the pathology reports contained information on p53 expression, the lack of statistically significant results for p53 expression may have been due to missing data.

There was the potential for the introduction of bias related to year of diagnosis during the selection process due to matching for age at diagnosis. During the selection process, if a potential control tumor was not available for analysis, this individual was not selected for participation in the study. As a result, the majority of the tumors included in the study were those diagnosed within the last ten years as it is the practice of many hospital pathology laboratories to archive tumor tissue for less than ten years.

Likewise, for the metachronous bilateral breast cancer cases, the tumor more frequently available for study was the tumor most recently diagnosed. However this may not significantly affect the results of the study as no significant differences were detected when the tumors were compared. In addition, a study of bilateral breast cancer in *BRCA* carriers revealed a high rate of concordance between independent primary tumors in these women [46]. The majority of the bilateral breast cancer cases in this study were *BRCA* carriers (23/30, 77%).

Differing fixation practices across institutions may have affected the immunohistochemical analysis of some tumor samples. Prolonged fixation may reduce the immunohistochemical reactivity of many paraffin section antibodies and as a consequence false negative immunohistochemical results may occur [47].

Conclusion

This is the first report of a comparative study of the immunophenotype for a large set of *BRCA*-associated breast cancers in Hispanics and NHW. Our study suggests that Hispanic *BRCA*-associated breast cancer phenotypes are not substantially different from that of NHW *BRCA*-associated breast cancers; however there was a trend toward a difference in PR expression among *BRCA1* and *BRCA2* cases that could become significant in larger cohorts. This difference could impact the prevention, treatment, or outcome of breast cancer in Hispanic women and may reflect the effects of population-specific environmental or reproductive influences. Understanding the factors that impact PR expression and the influence of *BRCA* mutation status may provide insight into a potentially different mechanism of breast cancer development in Hispanic *BRCA* carriers.

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Table 1

Breast Cancer Characteristics by Ethnicity and *BRCA* Status

	Hispanic N=80			NHW N=74		
Characteristic	***BRCA1* carriers n=31**	***BRCA2* carriers n=8**	**Non-carriers n=41**	***BRCA1* carriers n=20**	***BRCA2* carriers n=15**	**Non-carriers n=39**
Mean age at 1st breast cancer diagnosis[1] (range)	36.9 ± 6.9 (27-54)	36.9 ± 6.9 (27-54)	36.8 ± 6.8 (24-57)	37.8 ± 10.6 (21-59)	43.3 ± 10.0 (27-63)	40.1 ± 9.2 (24-60)
Average tumor size ± SD (range)	2.8cm ± 1.9 (0.6-10.0)	4.2cm ± 3.3 (1.3-9.8)	2.3cm ± 1.5 (0.3-6.0)	2.4cm ± 1.9 (0.4-8.5)	2.2cm ± 0.7 (1.1-3.3)	2.3cm ± 1.5 (0.2-6.0)
Histology n (%)						
ductal	27 (87.1)	7 (87.5)	33 (82.9)	19 (95.0)	10 (66.7)	30 (76.9)
lobular	0	0	1 (2.4)	1 (5.0)	0	4 (10.3)
ductal & lobular	0	1 (12.5)	2 (4.9)	0	3 (20.0)	2 (5.1)
medullary	4 (12.9)	0	3 (7.3)	0	2 (13.3)	0
other[2]	0	0	2 (4.8)	0	0	3 (7.7)
Grade n (%)						
1	0	0	2 (5.1)	0	0	8 (20.5)
2	5 (16.7)	2 (25.0)	14 (35.9)	1 (5.0)	2 (13.3)	14 (35.9)
3	25 (83.3)	6 (75.0)	23 (59.0)	19 (95.0)	13 (86.7)	17 (43.6)
missing	1	0	2	0	0	0
ER n (%)						
negative	25 (80.6)	2 (25.0)	16 (39.0)	16 (80.0)	6 (40.0)	10 (25.6)
positive	6 (19.4)	6 (75.0)	25 (61.0)	4 (20.0)	9 (60.0)	29 (74.4)
PR n (%)						
negative	27 (87.1)	4 (50.0)	20 (48.8)	15 (75.0)	5 (33.3)	14 (35.9)
positive	4 (12. 9)	4 (50.0)	21 (51.2)	5 (25.0)	10 (66.7)	25 (64.1)
HER2 n (%)						
low expression	29 (93.5)	7 (100.0)	32 (80.0)	19 (95.0)	14 (93.3)	33 (84.6)
over expression	2 (6.5)	0	8 (20.0)	1 (5.0)	1 (6.7)	6 (15.4)
missing	0	1	1	0	0	0

Characteristic	Hispanic N=80			NHW N=74		
	***BRCA1* carriers n=31**	***BRCA2* carriers n=8**	**Non-carriers n=41**	***BRCA1* carriers n=20**	***BRCA2* carriers n=15**	**Non-carriers n=39**
Ki-67 n (%)						
low	6 (20.7)	3 (42.9)	23 (60.5)	6 (30.0)	4 (26.7)	22 (56.4)
intermediate/high	23 (79.3)	4 (57.1)	15 (39.5)	14 (70.0)	11 (73.3.)	17 (43.6)
unknown	2	1	3	0	0	0
P53 n (%)						
low expression	9 (39.1)	5 (83.3)	17 (54.8)	10 (50.0)	5 (33.3)	20 (51.3)
high expression	14 (60.9)	1 (16.7)	14 (45.2)	10 (50.0)	10 (66.7)	19 (48.7)
unknown	8	2	10	0	0	0

[1] Includes only one breast cancer diagnosis for those with synchronous bilateral breast cancer (n=4)

[2] Other-mucinous, inflammatory or metaplastic carcinoma

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