Ethnic Disparities in Breast Tumor Phenotypic Subtypes in Hispanic and Non-Hispanic White Women

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Abstract

Aims: Hispanic women are at a lower risk of getting breast cancer than non-Hispanic white (NHW) women, yet they experience a higher risk of mortality after diagnosis. There is some evidence to suggest differences in tumor pathology; however, very limited research has been published on Hispanic women. This represents one of the first studies to evaluate the prevalence of tumor markers and phenotypic subtypes that are associated with poorer prognosis (human epidermal growth factor receptor 2 [HER2], triple negative and basal-like tumors) among Hispanic women.

Methods: We reviewed pathology reports, obtained paraffin blocks of breast cancer tissue, and established tissue microarrays from NHW ($n=119$) and Hispanic women ($n=69$) who were Colorado participants in the 4-Corners Breast Cancer Study. We evaluated ethnic differences in the prevalence of tumor markers and phenotypic subtypes and assessed the contribution of risk factors in explaining the observed differences.

Results: Consistent with other studies, Hispanic women had a higher prevalence of estrogen receptor-negative tumors compared with NHWs (36.2% vs. 22.7%, $p=0.05$). Hispanics also had an unexpectedly higher proportion of HER2-positive tumors compared with NHWs (31.9% vs. 14.3%, $p<0.01$). Independent of other prognostic factors, Hispanics were 2.8 times more likely to have a HER2-positive tumor (95% confidence interval [CI] 0.98-7.86). Hispanics were less likely to have the more favorable luminal A subtype, but no significant differences were observed for the less favorable basal-like or triple negative subtypes. However, there were suggestive differences when considering menopausal status.

Conclusions: These findings provide evidence that breast cancers among Hispanic women comprise a distinct spectrum of tumor subtypes when compared with NHW women.

Introduction

THERE IS A GROWING BODY of literature to support the contributing role of biologic factors in ethnic disparities in breast cancer outcomes. Several studies have observed a higher proportion of tumor subtypes associated with worse prognosis (e.g., basal-like and triple negative breast cancers) among African American (AA) women, who have a higher breast cancer mortality rate than non-Hispanic white (NHW) women in the United States.¹⁻⁸ Hispanic women have a lower risk for incident breast cancer compared with NHW women, yet they experience a higher risk of mortality after a breast cancer diagnosis.⁹⁻¹⁴ Relatively little research has been done

on this ethnic population. To date, there have been consistent reports of a higher proportion of estrogen receptor (ER)-negative and progesterone receptor (PR)-negative breast tumors among Hispanic women,¹⁵⁻²⁰ and a few recent studies based on data from the California Cancer Registry (CCR) indicate a higher proportion of triple negative tumors.^{2,3,6}

As the majority of United States cancer registries have not routinely collected data on human epidermal growth factor receptor 2 (HER2) status, tumor subtypes, or breast cancer risk factors (e.g., reproductive factors, obesity), there is limited research on breast cancer among Hispanic women. A recent study provided one of the first observations that Hispanic women were less likely to be tested for HER2 status compared

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with both NHWs and AAs, yet they were more likely to have a HER2-positive tumor among those who were tested.⁸ Although the sample size of Hispanic women was small, the study provides a strong rationale for additional research on the role of HER2 in breast cancer among Hispanic women. Furthermore, to our knowledge, no studies have reported the relative frequency of “the basal-like tumor subtype” among Hispanic women compared with other patient populations.

The goal of this research is to provide additional insight into the etiology of breast cancer among Hispanic women by evaluating putative differences in the prevalence of tumor markers and phenotypic subtypes that are known to be associated with poorer prognosis but have not been well-studied among Hispanic women (HER2 status, triple negative and basal-like tumors). To investigate this, we created a tissue microarray collection from a subset of Hispanic and NHW breast cancer patients who participated in the 4-Corners Breast Cancer Study, a population-based case-control study. In addition, we provide preliminary exploration of the contribution of breast cancer risk factors in explaining the observed ethnic differences.

Materials and Methods

Study population

For this study, we reviewed pathology reports, obtained paraffin blocks of breast cancer tissue, and established tissue microarrays from NHW and Hispanic breast cancer patients from a subset of Colorado participants in the 4-Corners Breast Cancer Study ($n=285$). The 4-Corners Breast Cancer Study is a population-based case-control study designed to investigate diet, lifestyle, and genetic factors that contribute to disparities in breast cancer rates observed between NHW and Hispanic women. Methods for selection, recruitment, and interview of 4-Corners participants have been previously described in detail.²¹ In brief, women (age range 25–79 years) diagnosed with an incident primary breast cancer between December 1999 and September 2004 were identified through statewide cancer registries in Arizona, Colorado, New Mexico, and Utah and recruited for participation in this study. Subjects completed an interviewer-administered in-person computer-assisted questionnaire, which included questions about diet, physical activity, family history, reproductive history, menopausal status, and other breast cancer risk factors. Questions referred to exposures that occurred the year before diagnosis. Women were considered premenopausal/perimenopausal if they were ≤ 57 years old and reported one of the following: still having regular periods, pregnant or breastfeeding, having periods or possibly going through menopause, or having periods while taking hormone replacement therapy (HRT). Postmenopausal status was assigned to women who reported that their periods stopped either naturally or artificially.

Data describing tumor characteristics, such as tumor stage, grade, histology, and ER and PR status, were obtained through the National Cancer Institute’s (NCI) Surveillance, Epidemiology, and End Results (SEER) cancer registry or the state tumor registry database. Patients diagnosed before 2001 were coded according to the second edition of the *International Classification of Diseases for Oncology* (ICD-O-2), and those diagnosed from 2001 and on were coded according to the ICD-O-3. The histologic types were grouped accordingly: ductal carcinoma (8230, 8500, 8521, 8523), lobular carcinoma (8520,

8524), ductal/lobular (8522), all others, and unknown. Tumor stage classifications were based on SEER summary stage codes according to the 1977 definitions for cases diagnosed before 2001 or the 2000 definitions for cases diagnosed from 2001 on. ER and PR status was recorded as positive, negative, or unknown (test not done, borderline, or results not entered in chart) based on laboratory results from medical records at the time of data collection by the state tumor registry. All aspects of this study were conducted in accordance with human subjects’ research protocols approved at each institution.

Tissue microarrays and immunohistochemical staining

Requests for consent from patients to obtain their tissue blocks were made of the Colorado women when they enrolled in the 4-Corners Breast Cancer Study. In total, we obtained paraffin blocks from the breast cancers of 285 of the total 504 Colorado patients. For each case, optimal areas for inclusion as cores in the tissue microarrays (TMAs) were marked on the hematoxylin and eosin (H&E) slides. Cores were obtained from the corresponding paraffin blocks. Duplicate, 1-mm diameter cores were obtained from each of the following entities when feasible: invasive carcinoma, ductal carcinoma *in situ* (DCIS), and normal breast tissue from each case. The TMA collection was used to evaluate ER, PR, HER2, HER1, and cytokeratin 5/6 (CK 5/6) status by immunohistochemical (IHC) staining. For this study, scoring was based on cores from invasive carcinoma tissue only.

ER, PR, CK 5/6, HER1, and HER2 expression were determined using standard IHC staining methods. For ER and PR, sections were subjected to heat-induced epitope antigen retrieval. The primary antibodies (ER, RM-9101-S, Lab Vision; PR, RM-9102-S, Thermo Fisher Scientific) were applied at 1:200 dilution for 1 hour. For HER1, HER2, and CK 5/6, antigen retrieval was performed in a decloaking steam chamber. The primary antibodies (HER2, BioGenex AM134-5M ready to use; CK 5/6, DAKO M 7237 at 1:50 dilution; HER1, Zymed Laboratories 28-0005 at 1:10 dilution) were applied for 1 hour. Following a 30-minute incubation with the appropriate secondary antibody, substrate-chromogen solution was added.

The arrays were graded on a 0–3+ intensity scale for all the biomarkers. Each sample was scored as follows: 0 = absence of staining or membrane staining in $<10\%$ of tumor cells; 1+ = faint membrane staining in $>10\%$ of the cells and cells with only part of the cell membrane staining; 2+ = moderate complete membrane staining in $>10\%$ of the cells; 3+ = strong complete membrane staining in $>10\%$ of cells. For HER2, the Herceptest™ scoring criterion (preceding the 2008 American Society of Clinical Oncology/College of American Pathologists guideline recommendations [ASCO/CAP]²²) was in use at the time of the original evaluation of the cases, so the same criterion was used for this study. Tumors with 2+ or 3+ scores were interpreted as positive for protein overexpression, and tumors with 0 and 1+ scores were interpreted as negative. For ER and PR, tumors with $>10\%$ positively stained nuclei were considered positive, which is consistent with established cutoffs for positivity. HER1 and CK 5/6 was considered positive if any membrane or cytoplasmic staining was observed in tumor cells.

Among cases with ambiguous results (e.g., core was not interpretable, poor quality staining) or 2+ scores for HER2 from TMA evaluation, HER2 status was reevaluated using conventional whole slides ($n=89$). Among these women, 79

had a score of 0 or 1+, 8 had a score of 3+, and 2 had a score of 2+. Because the inclusion/exclusion of these two NHW 2+ cases would have minimal impact on the overall findings, additional fluorescence in situ hybridization (FISH) analysis was not conducted.

Data for ER and PR status was also obtained from the tumor registry and cross-checked with pathology reports. It is worth noting that these cases were diagnosed before the current ASCO/CAP guidelines for ER/PR went into effect.²³ For ER and PR status only, data were available from the tumor registry for approximately 85% of the subjects included in this analysis. When data were unavailable for these markers from the tumor registry, we used data obtained from the TMA staining. Based on a preliminary assessment, TMA results were consistent with the tumor registry for approximately 92% of subjects for ER status and 86% for PR status.

For this analysis, we included only subjects diagnosed with invasive carcinoma who had data available for ER, PR, and HER2 ($n=119$ NHW and 69 Hispanic). Consistent with the literature,^{1, 24} the following basal/luminal phenotypic subtype definitions were used: basal-like (ER-, PR-, HER2-, CK 5/6+, and/or HER1+), HER2+/ER- subtype (HER2+, ER-, PR-), luminal A (ER+ and/or PR+, HER2-), luminal B (ER+ and/or PR+, HER2+), and unclassified (ER-, PR-, HER2-, CK 5/6-, and HER1-). Triple negative was classified as ER-, PR-, and HER2-, which includes both the basal-like and unclassified subtypes.

Statistical analysis

Statistical analyses were conducted using SAS, version 9.1. To compare risk factors and prognostic characteristics between Hispanic and NHW breast cancer patients, univariate methods, such as chi-square tests and t tests, were initially used. Logistic regression models were used to compute the odds ratios (ORs) and 95% confidence intervals (CIs) when assessing the relationship between ethnicity (Hispanic, NHW) and HER2 status (positive, negative). The following prognostic variables were adjusted for in the multivariable models: age at diagnosis (<46, 46–69, 70+ years), menopausal status at diagnosis (premenopausal/perimenopausal, postmenopausal), stage (local, not local), grade (1, 2, 3–4, unknown), histology (ductal only, other), tumor size (<2 cm, >2 cm, unknown), ER status (positive, negative), PR status (positive, negative), first primary breast tumor (yes, no), mammogram screening before diagnosis (never had one, had at least one), family history of breast cancer (yes, no), interaction between number of full-term pregnancies and age at first birth (never, 1–2 children and <25 years old, 1–2 children and ≥25 years, 3 or more children and <25 years old, 3 or more children and ≥25 years), total duration of breastfeeding (<1 month, >1 month), alcohol consumption (nondrinker, drinker), oral contraceptive use (never used, have used), height (<1.56 meters, >1.56 meters), body mass index (BMI) (<25 kg/m², 25–30 kg/m², >30 kg/m²), and age at menarche (<13 years, >13 years). Because of the limited sample size of this study, certain categories for the specified covariates (e.g., grade, histology) were collapsed.

Results

Overall, the subset of cases included in this study was reflective of the 4-Corners Study population as a whole

with respect to the observed ethnic differences among known breast cancer risk factors (Table 1).^{25–27} Among this subset of women, age at diagnosis was slightly younger for Hispanic compared with NHW women (51.3 vs. 54.3 years, $p=0.08$), yet there was no significant difference in menopausal status (56.5% vs. 58.0% postmenopausal, respectively). When compared with Hispanic patients, NHW patients were more likely to have the majority of breast cancer risk factors, including having fewer children ($p=0.05$), a later age at first birth ($p<0.01$), heavier alcohol consumption ($p<0.01$), and increased use of oral contraceptives ($p=0.02$). In contrast, Hispanic women were more likely to be shorter in height ($p<0.01$). Hispanic women were also more likely to be overweight, have an earlier age at menarche, less likely to breastfeed, and more likely to not have had a mammogram before diagnosis; however, these differences did not reach statistical significance in this subset of women.

With respect to breast tumor characteristics, this subset of cases and the observed ethnic differences reflect the 4-Corners Study population as a whole.²⁵ Hispanic women had more characteristics associated with worse prognosis compared with NHW women; however, many of the observed differences did not reach statistical significance (Table 2). Specifically, Hispanics were more likely to have larger tumors ($p=0.22$), advanced tumor stage ($p=0.29$), and higher tumor grade ($p<0.01$). Tumor histologic type distribution was similar between the two groups, with ductal carcinoma comprising the majority of tumors.

Table 3 reflects the distribution of tumor subtypes among the participating Colorado 4-Corners Hispanic and NHW cases. Because these were prevalent breast cancer cases, the distribution of tumor subtypes were presented with the distribution observed among California women diagnosed from 1999 to 2005 (CCR) obtained from Parise et al.²⁸ No data were available for the basal-like phenotypic subtype among the California women. In comparison to the California incident cases, there was a larger representation of women in the younger age categories in Colorado, which was consistent with age restriction (<80) for recruitment into the 4-Corners Study. Among Colorado cases, there was a significantly smaller proportion of ER-positive (63.8% vs. 77.3%, $p=0.05$) and a nonsignificantly smaller proportion of PR-positive (58.0% vs. 64.7%, $p=0.36$) tumors among Hispanic women compared with NHW women. The ER and PR proportions were similar between Colorado and California cases. In addition, Hispanics had a strikingly higher proportion of HER2-positive tumors (31.9% vs. 14.3%, $p<0.01$). The observed ethnic difference was also apparent among California patients, although the difference was not as large. With respect to the distribution of luminal/basal phenotypic subtypes, Hispanics were less likely to have the more favorable and most prevalent luminal A phenotype, which was consistent between both Colorado and California cases. However, no notable difference was observed for the less favorable basal-like phenotype among Colorado cases (data not available for California cases). A higher proportion of triple negative (i.e., ER, PR, and HER2 negative) tumors was reported previously for Hispanics among California cases. In this study, Hispanics had a slightly higher proportion of triple negative tumors compared with NHWs; however, this difference was not statistically significant.

TABLE 1. BREAST CANCER RISK FACTORS AMONG INVASIVE BREAST CANCER CASES IN SUBSET OF HISPANIC AND NON-HISPANIC WHITE WOMEN FROM COLORADO

Characteristics	Non-Hispanic white women (n=119)	Hispanic women (n=69)	p value
Age at diagnosis, years (mean±SD)	54.3±10.7	51.3±12.7	0.08
Menopausal status, n (%)			0.85
Premenopausal	50 (42.0)	30 (43.5)	
Postmenopausal	69 (58.0)	39 (56.5)	
Family history of breast cancer, ^a n (%)			0.94
Yes	18 (15.1)	10 (14.5)	
No	101 (84.9)	58 (84.1)	
Mammography before diagnosis, n (%)			0.32
Never	16 (13.5)	13 (18.8)	
At least one	103 (86.5)	56 (81.2)	
Number of live births (mean±SD)	1.93±1.2	2.35±1.8	0.05
Age at first birth, years ^b (mean±SD)	24.6±5.1	22.5±4.9	<0.01
Body mass index, kg/m ² (mean±SD)	27.0±6.1	28.2±5.4	0.16
Age at menarche, ^a years (mean±SD)	12.7±1.6	12.2±2.9	0.20
Alcohol consumption, ^a n (%)			<0.01
None	38 (31.9)	36 (52.9)	
>0 g/day	81 (68.1)	32 (47.1)	
Breastfeeding, ^b n (%)			0.15
<1 month	58 (48.7)	41 (59.4)	
≥1 month	61 (51.3)	28 (40.6)	
Height, n (%)			<0.01
<1.56 meters	15 (12.6)	34 (49.3)	
≥1.56 meters	104 (87.4)	35 (50.7)	
OC use, n (%)			0.02
Never used	35 (29.4)	32 (46.4)	
Have used	84 (70.6)	37 (53.6)	

^aMissing data: n=1 Hispanic for family history, alcohol consumption, and age at menarche.

^bAmong parous women only, n=102 NHW and 64 Hispanic women.

OC, oral contraceptive; SD, standard deviation.

TABLE 2. BREAST CANCER TUMOR CHARACTERISTICS AMONG INVASIVE BREAST CANCER CASES IN SUBSET OF HISPANIC AND NON-HISPANIC WHITE WOMEN FROM COLORADO

Characteristics	Non-Hispanic white women (n=119)	Hispanic women (n=69)	p value
Age at diagnosis, years (mean±SD)	54.3±10.7	51.3±12.7	0.08
First primary breast tumor, n (%)			0.46
Yes	112 (94.1)	63 (91.3)	
No	7 (5.9)	6 (8.7)	
Tumor size, ^a n (%)			0.22
<2 cm	83 (72.8)	43 (64.2)	
>2 cm	31 (27.2)	24 (35.8)	
SEER summary stage, n (%)			0.29
Local	77 (64.7)	38 (55.1)	
Regional	41 (34.5)	31 (44.9)	
Distant	1 (0.8)	0 (0.0)	
Tumor grade, ^a n (%)			<0.01
Well differentiated, grade I	33 (29.0)	5 (7.7)	
Moderately differentiated, grade II	41 (36.0)	36 (55.4)	
Poorly differentiated, grade III	37 (32.5)	22 (33.9)	
Undifferentiated, grade IV	3 (2.6)	2 (3.1)	
Histology, n (%)			0.24
Ductal	86 (72.3)	50 (72.5)	
Lobular	10 (8.4)	7 (10.1)	
Ductal/lobular	14 (11.8)	3 (4.4)	
Other	9 (7.6)	9 (13.0)	

^aMissing data: n=5 non-Hispanic white (NHW) and 2 Hispanic for tumor size; n=5 NHW and 4 Hispanic for tumor grade.

SEER, Surveillance, Epidemiology, and End Results.

TABLE 3. DISTRIBUTION OF TUMOR PHENOTYPIC SUBTYPES OBSERVED IN SUBSET OF BREAST CANCER CASES FROM COLORADO COMPARED WITH DATA PUBLISHED FROM CALIFORNIA CANCER REGISTRY (1999–2005)

	NHW women		Hispanic women		p-value ^a
	4-Corners	CCR	4-Corners	CCR	
	(n = 119) n (%)	(n = 48,863) %	(n = 69) n (%)	(n = 9,588) %	
Age at diagnosis					0.60
<46	27 (22.7)	13.4	20 (29.0)	27.4	
46–69	79 (66.4)	57.0	43 (62.3)	55.9	
70+	13 (10.9)	29.5	6 (8.7)	16.7	
Single marker ^b					
ER+	92 (77.3)	80.7	44 (63.8)	70.8	0.05
PR+	77 (64.7)	68.9	40 (58.0)	60.8	0.36
HER2+	17 (14.3)	21.1	22 (31.9)	25.8	<0.01
Phenotypic subtype					0.13
ER+/PR+/HER2+ Luminal B	8 (6.7)	10.9	9 (13.0)	11.9	
ER+/PR+/HER2– Luminal A	67 (56.3)	56.6	28 (40.6)	47.0	
ER+/PR–/HER2+ Luminal B	2 (1.7)	3.5	2 (2.9)	3.7	
ER+/PR–/HER2– Luminal A	15 (12.6)	9.8	5 (7.2)	8.6	
ER–/PR+/HER2+ Luminal B	0 (0.0)	0.5	1 (1.4)	0.9	
ER–/PR+/HER2– Luminal A	2 (1.7)	0.9	2 (2.9)	1.3	
ER–/PR–/HER2+ HER2+/ER–	7 (5.9)	6.2	10 (14.5)	9.7	
ER–/PR–/HER2– Triple negative (TN)	18 (15.1)	11.7	12 (17.4)	17.5	
Basal-like TN with HER1+ and/or CK 5/6+	7/118 (5.9)	NA ^c	3/66 (4.5)	NA ^c	0.69

Data adapted from Parise et al.²⁸^ap value obtained from comparing 4-Corners Hispanic and NHW women.^bPercentages for single marker frequencies were calculated for California Cancer Registry (CCR) using data presented in Parise et al.²⁸^cData not available.

CK, cytokeratin; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

The distribution of luminal/basal phenotypic subtypes differed according to both menopausal status and ethnicity (Table 4). Among premenopausal women, Hispanics had a higher proportion of the less favorable basal-like and HER2+/ER– subtypes and a lower proportion of the luminal A subtype compared with NHW women, although the dif-

ference in distribution was not statistically significant. Among postmenopausal women, Hispanic women were more likely to have the luminal B subtype. Triple negative breast cancers were also more prevalent among Hispanics for premenopausal women (26.7% vs. 12.0%, $p=0.10$) but not for postmenopausal women (10.3% vs. 17.4%, $p=0.30$).

TABLE 4. DISTRIBUTION OF TUMOR PHENOTYPIC SUBTYPES ACCORDING TO MENOPAUSAL STATUS AMONG HISPANIC AND NON-HISPANIC WHITE WOMEN WITH BREAST CANCER FROM COLORADO

Characteristics	Non-Hispanic white women n (%)	Hispanic women n (%)	p value
Premenopausal women	n = 49	n = 29	
Basal/luminal phenotypic subtype			0.14
Luminal A (ER+ and/or PR+, HER2–)	37 (75.5)	14 (48.3)	
Luminal B (ER+ and/or PR+, HER2+)	4 (8.2)	3 (10.3)	
HER2+/ER– (ER–, PR–, HER2+)	3 (6.1)	5 (17.2)	
Basal-like (ER–, PR–, HER2– with HER1+ and/or CK 5/6+)	3 (6.1)	3 (10.3)	
Unclassified (ER–, PR–, HER2– with HER1– and CK 5/6–)	2 (4.1)	4 (13.8)	
Triple negative (ER–, PR–, HER2–) ^a	6/50 (12.0)	8/30 (26.7)	0.10
Postmenopausal women	n = 69	n = 37	
Basal/luminal phenotypic subtype			0.05
Luminal A (ER+ and/or PR+, HER2–)	47 (68.1)	21 (56.8)	
Luminal B (ER+ and/or PR+, HER2+)	6 (8.7)	9 (24.3)	
HER2+/ER– (ER–, PR–, HER2+)	4 (5.8)	5 (13.5)	
Basal-like (ER–, PR–, HER2– with HER1+ and/or CK 5/6+)	4 (5.8)	0 (0.0)	
Unclassified (ER–, PR–, HER2– with HER1– and CK 5/6–)	8 (11.6)	2 (5.4)	
Triple negative (ER–, PR–, HER2–) ^a	12/69 (17.4)	4/39 (10.3)	0.32

^aFour subjects who were missing data on CK 5/6 or HER1 were included for the evaluation of triple negative status. Proportions reflect the number of subjects who were positive divided by the total in the specified category. p values reflect the results from chi-square analysis when comparing the proportion of triple negatives among Hispanic and NHW women.

To determine if the observed ethnic differences in breast cancer risk factors and tumor characteristics (Tables 1 and 2) contributed to the higher proportion of HER2-positive tumors among Hispanic women, logistic regression modeling was conducted (Table 5). When unadjusted for any other factors, Hispanics were nearly three times more likely to have a HER2-positive tumor compared with NHWs (OR 2.81, 95% CI 1.37-5.78). This relationship did not appear to be affected by other factors. When adjusting for other tumor characteristics (e.g., grade, stage, ER status) and breast cancer risk factors (e.g., number of children, alcohol consumption), Hispanics were still three times more likely to have a HER2-positive tumor compared with NHWs (OR 2.77, 95% CI 0.98-7.68).

Discussion

Consistent with other studies, Hispanic women had a higher proportion of ER-negative and PR-negative tumors compared with NHWs among Colorado participants in the 4-Corners Breast Cancer Study. An unexpected finding was the higher proportion of HER2-positive tumors among Hispanics. Irrespective of other tumor characteristics and prognostic factors, Hispanics were more likely to have a HER2-positive tumor compared with NHW women. Hispanics were also less likely to have the more favorable luminal A tumor subtype; however, no notable differences were observed for the less favorable basal-like or triple negative subtypes. There were suggestive ethnic differences in these subtypes when considering menopausal status of the women; however, these findings need to be confirmed in larger studies. This study represents one of the first to evaluate HER2 and luminal/basal phenotypic subtypes among Hispanic women. The observed ethnic differences in breast tumor subtypes are likely to contribute to the poorer prognosis experienced among Hispanic women compared with NHW women.

The reasons for racial/ethnic frequency differences in breast tumor subtypes are not completely understood. It has been shown previously that Hispanic women were more likely to have unfavorable tumor characteristics compared to NHW women despite equal access to healthcare services and screening practices,²⁰ which provides support for the role of biologic factors in promoting ethnic disparities in breast cancer outcomes. Etiologic differences in breast cancer development may evolve from varying risk factors associated with breast tumor subtype(s). Several studies have shown that breast cancer risk factors differ according to ER/PR status

and luminal/basal phenotypic subtype.²⁹⁻³² This hypothesis is additionally supported by findings from our recent comparative analysis, which found that established breast cancer risk factors account for a substantially larger proportion of cases among NHW than among Hispanic women.²⁷

The majority of studies evaluating breast tumor subtypes among Hispanic women are based on data collected by U.S. tumor registries,^{2,3,6,15-19,33} which do not routinely collect information on HER2 status, luminal/basal-like phenotypic subtypes, or breast cancer risk factors (e.g., reproductive factors, obesity). Thus, there is limited research with respect to these markers, as well as the relationship between breast cancer risk factors and breast tumor subtypes. Lund et al.⁸ provided one of the first observations that Hispanics were less likely to be tested for HER2 status (20.7% not tested) compared with both NHWs (10.2%) and AAs (8.7%), yet more likely to be diagnosed with HER2-positive tumors among women (38% vs. 13.2% NHW and 16% AA among those tested). However, the sample size of Hispanic women was small in that study ($n=32$). Among the 4-Corners women in this study, we also observed a higher proportion of HER2-positive tumors among Hispanic women, and the percentage differences are similar to those in the prior study. In this study, the ethnic difference in HER2 status did not appear to be explained by the observed differences in other tumor characteristics or breast cancer risk factors evaluated. The multivariate results must be interpreted with caution, however, because of the modest sample size of this study.

Studies based on data collected by the CCR reported a higher representation of triple negative tumors among Hispanic women.^{2,3,6} In this smaller study among Colorado women, we did not observe a significant difference in the frequency of triple negative tumors among Hispanic women. In comparison to incident cases in California who were diagnosed around the same time period, we observed a similar but slightly lower proportion of ER-positive and PR-positive tumors among both NHWs and Hispanics. This could be partially attributed to the different age distribution of cases in Colorado, which had a relatively younger group of women because of the age restriction for recruitment into the original 4-Corners study. Ethnic distributions of luminal subtypes were also comparable between Colorado and California, which strengthens the validity of our findings. Among Colorado cases, Hispanics were slightly younger than NHW women; however, this difference alone cannot account for all the observed difference in frequency of tumor markers.

TABLE 5. ADJUSTED RISK OF HAVING A HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-POSITIVE TUMOR FOR HISPANIC COMPARED WITH NON-HISPANIC WHITE COLORADO WOMEN WITH BREAST CANCER

<i>Model</i>	<i>OR (95% CI) Hispanic vs. non-Hispanic white</i>
Unadjusted	2.81 (1.37-5.78)
Adjusted for age	2.78 (1.33-5.82)
Adjusted for age and tumor characteristics (Table 2) ^a	2.48 (1.10-5.58)
Adjusted for age, tumor characteristics and breast cancer risk factors (Tables 1 and 2) ^b	2.77 (0.98-7.86)

^aMultivariate model adjusted for all of the following: age at diagnosis, SEER summary stage, grade, histology, tumor size, ER status, PR status, and first primary breast tumor.

^bIn addition to the previously described factors, multivariate model adjusted for all of the following: menopausal status at diagnosis, mammogram screening before diagnosis, family history of breast cancer, number of children, age at first birth, total duration of breastfeeding, alcohol consumption, oral contraceptive use, height, body mass index, and age at menarche.

To our knowledge, this study is the first to report on the frequency of basal-like tumors among Hispanic women. We did not observe an ethnic difference in the frequency of basal-like tumors. The frequency of luminal/basal phenotypic subtypes observed in this study is within range of previous reports from population-based breast cancer subtype studies in other racial/ethnic populations. The frequency of basal-like tumors has been reported to be as low as 8% and as high as 39%.^{34–37} The frequency observed in this study is slightly lower, which could be attributed to survivor bias, as the 4-Corners cases represent cases recruited about a year after diagnosis. The wide range of estimates is likely to be attributed to both ethnic/racial differences and other factors, including menopausal status, age, and differences in criteria and methods for defining marker positivity.^{34–37} Clinical guidelines for HER2 testing have changed over the past decade,²² and to date, no standardized methods have been established for CK 5/6 and HER1 staining and reporting of IHC results.

Although the sample size of this study is modest, this study represents one of the few reports on tumor subtypes among Hispanic women. Additional strengths of this study include the representation of both Hispanic and NHW women and the ability to account for a number of risk factors and prognostic factors. There are also several limitations that suggest the use of caution in interpreting these findings. As previously mentioned, the use of prevalent cases vs. incident cases introduces the potential for survivor bias. Thus, it is questionable how well these cases reflect the population as a whole. In addition, the 4-Corner cases were diagnosed between 1999 and 2004, an era in which the current guidelines for HER2 testing and reporting had not yet been established. Although this factor may have an effect on the overall frequency estimates, it is not likely to account for the observed ethnic differences. Finally, the use of TMAs may introduce within-tumor sampling variation when comparing with studies where TMAs were not used for evaluating tumor markers; however, it has been shown previously that TMAs can be representative of whole slides for evaluating both ER and PR positivity.³⁸

Conclusions

This study represents one of the first studies to evaluate the prevalence of tumor markers and phenotypic subtypes that are associated with poorer prognosis (HER2, triple negative and basal-like tumors) among Hispanic women. The findings provide initial insight into factors that may contribute to ethnic disparities in breast cancer outcomes among Hispanic women. The higher prevalence of HER2-positive tumors (and HER2+ /ER– subtype) could contribute to the poorer prognosis observed among Hispanic women. Given the observed differences in tumor characteristics, it is highly plausible that breast cancers among Hispanic women comprise a different distribution of tumor subtypes compared with NHW women. Additional studies of breast cancer among Hispanic women are warranted.

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Disclosure Statement

The authors have no conflicts of interest to report.

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