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EPIDEMIOLOGY

Heterogeneity of breast cancer subtypes and survival among Hispanic women with invasive breast cancer in California

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Abstract There are limited data regarding breast cancer subtypes among Hispanic women. The current study assessed the distribution and prognosis of molecular subtypes defined by joint expression of the hormone receptors (HR; estrogen and progesterone) and human epidermal growth factor receptor 2 (HER2). Using California Cancer Registry data, we identified Hispanic women diagnosed with invasive breast cancer from 2005 to 2010. Breast cancer subtypes were defined as HR+/HER2−, HR+/HER2+, HR−/HER2+, and HR−/HER2− (triple negative). We estimated breast cancer subtype frequencies and used polytomous logistic regression, Kaplan–Meier survival plots and Cox regression to examine differences in relation to demographic and clinical characteristics. Among 16,380 Hispanic women with breast cancer, HR+/HER− subtype was the most common (63 %), followed by triple negative (16 %), HR+/HER2+ (14 %), and HR−/HER2+ (8 %). Women in lower SES neighborhoods had greater risk of triple negative and HR−/HER2+ subtypes relative to HR+/HER2− ($p < 0.05$). Hispanic women with triple negative and HR−/HER2+ tumors experienced poorer survival than those with HR+/HER− tumors. Breast cancer-specific mortality increased with decreasing SES, relative to the highest SES quintile, from HR = 1.38 for quintile 4 to HR = 1.76 for quintile 1 (lowest SES level). Our findings indicate that Hispanic women residing in low SES neighborhoods had significantly increased risk of developing and dying from HR− than HR+ breast cancers. Similar patterns of subtype frequency and prognosis among California Hispanic women and studies of other racial/ethnic groups underscore the need to better understand the impact of SES on risk factor exposures that increase the risk of breast cancer subtypes with poor prognosis.

Keywords Breast cancer · Hispanic · Latina · Socioeconomic status · Triple negative

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Introduction

Hispanic women may be prone to developing breast cancer molecular subtypes [defined by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)] associated with poor prognosis, such as ER−/PR−, and triple negative (ER−/PR−/HER2−) breast cancers [1–3]. Studies among Hispanics point to a 20–40 % increased risk of developing triple negative and ER−/PR− breast cancers, compared with non-Hispanic white women [2, 3]. Women diagnosed with ER−/PR− or triple negative tumors have significantly greater risk of death than more favorable prognosis subtypes (i.e., ER+/PR+) [4, 5]. Thus, defining the population-based distribution of breast cancer subtypes among Hispanic women provides information of clinical, prognostic, and therapeutic value.

However, only two studies have examined the patterns of breast cancer subtypes among Hispanic women [6, 7]. Hines and colleagues assessed breast tumors of 69 Hispanic women [6], and found that the four most prevalent subtypes were ER+/PR+/HER2− (41 %), triple negative (17 %), ER−/PR−/HER2+ (15 %), and ER+/PR+/HER2+ (13 %). Ortiz et al. [7] showed a similar subtype distribution among 663 women with breast cancer in Puerto Rico, and reported a higher risk of death for triple negative and ER+/PR+/HER2+ tumors, compared with the ER+/PR+/HER2− subtype. To expand on this work, data from the California Cancer Registry (CCR) on 16,380 Hispanic women diagnosed with invasive breast cancer were used to characterize the molecular subtypes defined by joint hormone receptor (HR) and HER2 status. Our objective was to conduct a large, population-based assessment of the distribution and survival by breast cancer subtype and examine associations with demographic and clinical attributes.

Methods

Study population

We obtained data from the CCR on all Hispanic female California residents aged 25 years and older, diagnosed with a first primary invasive breast cancer between 2005 and 2010. Patient sociodemographic information included age at diagnosis, race/ethnicity, birthplace, insurance status, marital status, and residential address at diagnosis. Race/ethnicity and birthplace data are abstracted from medical records or death certificates [8]. The North American Association of Central Cancer Registries Hispanic Identification Algorithm (NHIA) was used to improve the classification of Hispanic ethnicity [9]. Patient clinical information included the American Joint Committee on Cancer (AJCC) stage, tumor grade, tumor size, lymph node involvement, tumor metastasis, and first course of treatment (surgery, chemotherapy, and radiation).

Nativity

Patient nativity was classified as previously described [10], based on (1) cancer registry-based data from medical records and/or death certificates and (2) imputation using the first five digits of the patient's social security number (SSN), for those with unknown birthplace (34.5 %). SSN digits are linked to the state and year of issuance, from which nativity was imputed as follows: women who received their SSN before age 21 years were considered as United States (US)-born, whereas those who received their SSN on or after age 21 years as foreign-born. The age threshold was determined and validated based on a prior cohort of Hispanic cancer patients [11].

Neighborhood socioeconomic status (SES) and Hispanic enclave

Each patient's residential address at diagnosis was geocoded to a census block group. Participants with incomplete residential address information (7.3 %) were assigned an SES value based on their county of residence. Neighborhood SES was determined based on an index that incorporates 2000 Census (for cases diagnosed in 2005) and 2006–2010 American Community Survey data (for cases diagnosed after 2005) on education, occupation, unemployment, household income, poverty, rent, and house values [22]. Hispanic enclave was based on 2000 Census variables (% linguistically isolated, % linguistically isolated who speak Spanish, % speaking limited English, % speaking limited English who spoke Spanish, % recent immigrants, % Hispanic, and % foreign-born), developed via principal components analysis. Participants were assigned to a neighborhood SES quintile and Hispanic enclave quintile based on the distribution of each variable across California block groups.

Breast cancer subtype definition

A detailed description of the methods used for classification of breast cancer subtypes has been published elsewhere [12]. Based on joint tumor expression of ER, PR, and HER2, as described in the pathology record, breast cancers were classified into four distinct subtype categories: HR+/HER2− was defined as ER+ or PR+ and HER2+; HR+/HER2+ as ER+ or PR+ and HER2+; HR−/HER2+ as ER− and PR− and HER2+; and triple negative as ER−, PR−, and HER2− [4, 13–17]. Participants missing the tumor marker information needed to assign to a subtype were excluded [$n = 3{,}253$ (16.6 %)].

Statistical analysis

Associations between breast cancer subtypes and patient attributes

Adjusted polytomous regression models were used to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) by sociodemographic and clinical attributes for triple negative, HR+/HER2+ and HR−/HER2+ versus HR+/HER2- subtypes. Tests for trend were considered statistically significant at $p \leq 0.05$.

Kaplan–Meier survival curves depicting time from diagnosis to death were calculated for triple negative, HR+/HER2+ and HR−/HER2+ versus HR+/HER2− subtypes. Surviving participants were censored at the time of last known follow-up. Wilcoxon rank order test was used to test homogeneity of survival by subtype (SAS Institute v 9.3, Cary, NC).

Table 1 Demographic and tumor characteristics of the breast cancer subtypes in Hispanic women with invasive breast cancer, California, 2005–2010

Characteristics	Total $n = 16,380$	HR+/HER2− $n = 10,247$	Triple negative $n = 2,549$	HR+/HER2+ $n = 2,265$	HR−/HER2+ $n = 1,319$
Nativity					
US-born	7,633 (46.6)	4,932 (48.1)	1,193 (46.8)	976 (43.1)	532 (40.3)
Foreign-born	8,747 (53.4)	5,315 (51.9)	1,356 (53.2)	1,289 (56.9)	787 (59.7)
Socioeconomic status					
Quintile 1 (low)	4,261 (26.0)	2,478 (24.2)	713 (28.0)	645 (28.5)	425 (32.2)
Quintile 2	3,723 (22.7)	2,302 (22.5)	608 (23.9)	511 (22.6)	302 (22.9)
Quintile 3	3,027 (18.5)	1,915 (18.7)	485 (19.0)	394 (17.4)	233 (17.7)
Quintile 4	2,484 (15.2)	1,625 (15.9)	348 (13.7)	344 (15.2)	167 (12.7)
Quintile 5 (high)	1,683 (10.3)	1170 (11.4)	204 (8.0)	207 (9.1)	102 (7.7)
Unknown/missing	1,433 (7.3)	757 (7.4)	191 (7.5)	164 (7.2)	90 (6.8)
Hispanic enclave					
Quintile 1 (low)	1,359 (8.3)	903 (8.8)	197 (7.7)	162 (7.2)	97 (7.4)
Quintile 2	2,217 (13.5)	1,472 (14.4)	333 (13.1)	253 (11.2)	159 (12.1)
Quintile 3	2,810 (17.2)	1,793 (17.5)	440 (17.3)	376 (16.6)	201 (15.2)
Quintile 4	3,992 (24.4)	2,544 (24.8)	605 (23.7)	540 (23.8)	303 (23.0)
Quintile 5 (high)	5,261 (32.1)	3,062 (29.9)	861 (33.8)	837 (37.0)	501 (38.0)
Unknown/missing	917 (4.5)	473 (4.6)	113 (4.4)	97 (4.3)	58 (4.4)
Age at diagnosis (years)					
<45	3,633 (22.2)	1,867 (18.2)	771 (30.2)	641 (28.3)	354 (26.8)
45–49	2,444 (14.9)	1,529 (14.9)	373 (14.6)	357 (15.8)	185 (14.0)
50–54	2,348 (14.3)	1,380 (13.5)	405 (15.9)	336 (14.8)	227 (17.2)
55–59	2,024 (12.4)	1,246 (12.2)	308 (12.1)	284 (12.5)	186 (14.1)
60–64	1,720 (10.5)	1,179 (11.5)	233 (9.1)	197 (8.7)	111 (8.4)
≥65	4,211 (25.7)	3,046 (29.7)	459 (18.0)	450 (19.9)	256 (19.4)
Marital status at diagnosis					
Married	9,293 (56.7)	5,773 (56.3)	1,460 (57.3)	1,299 (57.4)	761 (57.7)
Never married	2,917 (17.8)	1,771 (17.3)	463 (18.2)	453 (20.0)	230 (17.4)
Previously married	3,598 (22.0)	2,351 (22.9)	529 (20.8)	453 (20.0)	265 (20.1)
Unknown	793 (3.5)	352 (3.4)	97 (3.8)	60 (2.6)	63 (4.8)
Insurance status[a]					
Private/military	8,199 (50.1)	5,260 (51.3)	1,272 (49.9)	1,058 (46.7)	609 (46.2)
Public	6,825 (41.7)	4,161 (40.6)	1,062 (41.7)	1,020 (45.0)	582 (44.1)
Uninsured	235 (1.4)	142 (1.4)	37 (1.5)	36 (1.6)	20 (1.5)
Unknown	1,489 (6.8)	684 (6.7)	178 (7.0)	151 (6.7)	108 (8.2)
Clinical characteristics					
AJCC tumor stage					
I	6,034 (36.8)	4,379 (42.7)	680 (26.7)	667 (29.4)	308 (23.4)
II	6,186 (37.8)	3,644 (35.6)	1,170 (45.9)	860 (38.0)	512 (38.8)
III	2,768 (16.9)	1,473 (14.4)	472 (18.5)	492 (21.7)	331 (25.1)
IV	778 (4.7)	409 (4.0)	127 (5.0)	141 (6.2)	101 (7.7)
Unknown	1,137 (3.7)	342 (3.3)	100 (3.9)	105 (4.6)	67 (5.1)
Tumor grade					
Low	9,053 (55.3)	7,321 (71.4)	403 (15.8)	1,054 (46.5)	275 (20.8)
High	6,659 (40.7)	2,501 (24.4)	2,065 (81.0)	1,115 (49.2)	978 (74.1)
Unknown	1,356 (4.1)	425 (4.1)	81 (3.2)	96 (4.2)	66 (5.0)
Tumor size (cm)					
0–2.00	8,111 (49.5)	5,793 (56.5)	910 (35.7)	947 (41.8)	461 (35.0)

Table 1 continued

Characteristics	Total $n = 16,380$	HR+/HER2− $n = 10,247$	Triple negative $n = 2,549$	HR+/HER2+ $n = 2,265$	HR−/HER2+ $n = 1,319$
2.01–5.00	6,065 (37.0)	3,370 (32.9)	1,188 (46.6)	961 (42.4)	546 (41.4)
>5.00	1,493 (9.1)	743 (7.3)	317 (12.4)	227 (10.0)	206 (15.6)
Microinvasion	132 (0.8)	44 (0.4)	32 (1.3)	29 (1.3)	27 (2.0)
Diffuse	85 (0.5)	45 (0.4)	11 (0.4)	16 (0.7)	13 (1.0)
Unknown	990 (3.0)	252 (2.5)	91 (3.6)	85 (3.8)	66 (5.0)
Lymph node involvement					
Negative	9,241 (56.4)	6,117 (59.7)	1,423 (55.8)	1,098 (48.5)	603 (45.7)
Positive	6,840 (41.8)	3,965 (38.7)	1,083 (42.5)	1,109 (49.0)	683 (51.8)
Unknown	640 (1.8)	165 (1.6)	43 (1.7)	58 (2.6)	33 (2.5)
Metastasis					
Negative	15,255 (93.1)	9,644 (94.1)	2,368 (92.9)	2,055 (90.7)	1,188 (90.1)
Positive	778 (4.7)	409 (4.0)	127 (5.0)	141 (6.2)	101 (7.7)
Unknown	637 (2.1)	194 (1.9)	54 (2.1)	69 (3.0)	30 (2.3)

Column percentages based on individuals with valid, non-missing information on risk factor

[a] Insurance status is based on payer source at diagnosis. Public insurance included Medicaid and other government-assisted programs; and private insurance included health maintenance organizations, preferred provider organizations, managed care not otherwise specified, and military care

Adjusted Cox proportional hazard modeling was performed to estimate the risk of death from breast cancer for all subtypes adjusted for patient sociodemographic and clinical characteristics. Survival time, in months, was defined as time from diagnosis to whichever of the following occurred first: death from breast cancer, last known contact, death due to other causes, or end of study follow-up (December 31, 2010). We tested the proportionality assumption using scaled Schoenfeld residuals. AJCC stage levels were included in the models as a stratifying variable, allowing the underlying hazard function to vary by stage.

Results

HR+/HER2− was the most common subtype (62.6 %), followed by triple negative (15.6 %), HR+/HER2+ (13.8 %) and HR−/HER2+ (8.1 %) (Table 1) . Over 50 % of breast cancers were diagnosed among foreign-born Hispanics, overall and within each subtype, compared with US-born Hispanics. Women in the lowest SES and highest Hispanic enclave neighborhoods comprised the greatest proportions of participants among all breast cancer subtypes.

Association between breast cancer subtypes and patient attributes

Foreign-born Hispanic women were significantly more likely than US-born Hispanic women to be diagnosed with HR−/HER2+ versus HR+/HER2− breast cancer (OR = 1.17, 95 % CI 1.02–1.35); other subtypes did not differ by nativity (Table 2). Compared to women living in the highest SES neighborhoods, those in lower SES neighborhoods had a 1.32–1.42 fold greater risk of triple negative ($p < 0.05$) and 1.17–1.43 fold greater risk of HR−/HER2+ relative to HR+/HER2− breast cancer ($p < 0.05$). Hispanic women aged 45–49 years had a lower risk of the triple negative (OR = 0.72, 95 % CI 0.60–0.87) and HR-/HER2+ (OR = 0.59, 95 % CI 0.47–0.75) subtypes, compared with women aged 50–54 years.

Breast cancer-specific survival and mortality by breast cancer subtype

Breast cancer-specific survival significantly differed between tumor subtypes ($p < 0.0001$; Fig. 1). Over the approximately 5.5 years of follow-up, Hispanic women with triple negative and HR−/HER2+ breast cancer had the lowest probability of survival. After multivariate adjustment (Table 3), Hispanic women diagnosed with triple negative breast cancer were four times more likely to die from the disease compared to those diagnosed with the HR+/HER2− subtype (HR = 4.05, 95 % CI 3.35–4.90). Overall, the risk of death from breast cancer followed a step-wise pattern by neighborhood SES, such that the risk of death from breast cancer increased as a woman's neighborhood SES level decreased; compared to quintile 5 (highest SES), HRs were 1.38 (95 %CI 0.98–1.94) for quintile 4 and 1.76 (95 % CI 1.25–2.49) for quintile 1.

For US-born Hispanic women, the risk of breast cancer-specific mortality was significantly greater for all subtypes compared with HR+/HER2− tumors (Table 4), whereas among foreign-born Hispanic women, only those diagnosed

Table 2 Adjusted odds ratios of sociodemographic and tumor characteristics associated with breast tumor subtypes (vs. HR+/HER2−) in Hispanic Women, California, 2005–2010

Characteristics	HR+/HER2− %	Triple negative		HR+/HER2+		HR−/HER2+	
		%	OR [95 % CI]	%	OR [95 % CI]	%	OR [95 % CI]
Sociodemographic							
Nativity							
US-born	48.1	46.8	Ref.	43.1	Ref.	40.3	Ref.
Foreign-born	51.9	53.2	0.97 (0.87–1.09)	56.9	1.06 (0.95–1.18)	59.7	**1.17 (1.02–1.35)**
Socioeconomic status							
Quintile 1 (low)	24.2	28.0	**1.42 (1.13–1.79)**	28.5	0.96 (0.77–1.20)	32.2	**1.43 (1.07–1.92)**
Quintile 2	22.5	23.9	**1.40 (1.12–1.74)**	22.6	0.93 (0.76–1.15)	22.9	1.21 (0.91–1.60)
Quintile 3	18.7	19.0	**1.39 (1.12–1.72)**	17.4	1.01 (0.82–1.24)	17.7	1.27 (0.96–1.68)
Quintile 4	15.9	13.7	**1.32 (1.06–1.64)**	15.2	1.15 (0.94–1.41)	12.7	1.17 (0.89–1.56)
Quintile 5 (high)	11.4	8.0	Ref.[†]	9.1	Ref.	7.7	Ref.[†]
Hispanic enclave							
Quintile 1 (low)	8.8	7.7	Ref.	7.2	Ref.[‡]	7.4	Ref.
Quintile 2	14.4	13.1	0.98 (0.78–1.23)	11.2	0.89 (0.70–1.12)	12.1	1.04 (0.77–1.41)
Quintile 3	17.5	17.3	0.97 (0.77–1.21)	16.6	1.07 (0.86–1.34)	15.2	0.96 (0.71–1.29)
Quintile 4	24.8	23.7	0.88 (0.70–1.10)	23.8	1.07 (0.86–1.34)	23.0	0.91 (0.68–1.22)
Quintile 5 (high)	29.9	33.8	0.98 (0.77–1.23)	37.0	**1.34 (1.06–1.68)**	38.0	1.12 (0.83–1.52)
Age at diagnosis (years)							
<45	18.2	30.2	1.03 (0.87–1.22)	28.3	1.15 (0.98–1.36)	26.8	0.86 (0.70–1.06)
45–49	14.9	14.6	**0.72 (0.60–0.87)**	15.8	0.87 (0.73–1.05)	14.0	**0.59 (0.47–0.75)**
50–54	13.5	15.9	Ref.	14.8	Ref.	17.2	Ref.
55–59	12.2	12.1	0.93 (0.76–1.14)	12.5	0.97 (0.79–1.17)	14.1	0.95 (0.75–1.21)
60–64	11.5	9.1	0.83 (0.67–1.03)	8.7	**0.79 (0.64–0.97)**	8.4	**0.71 (0.54–0.93)**
≥65	29.7	18.0	**0.81 (0.67–0.97)**	19.9	**0.78 (0.65–0.94)**	19.4	**0.78 (0.62–0.98)**
Marital status							
Married	56.3	57.3	Ref.	57.4	Ref.	57.7	Ref.
Never married	17.3	18.2	0.91 (0.79–1.05)	20.0	1.02 (0.89–1.17)	17.4	0.85 (0.71–1.02)
Previously married	22.9	20.8	1.10 (0.96–1.27)	20.0	1.05 (0.91–1.20)	20.1	1.02 (0.85–1.21)
Insurance status							
Private/military	51.3	49.9	Ref.	46.7	Ref.	46.2	Ref.
Public	40.6	41.7	1.06 (0.94–1.20)	**45.0**	**1.24 (1.10–1.39)**	44.1	1.13 (0.97–1.31)
Uninsured	1.4	1.5	0.89 (0.57–1.39)	1.6	1.00 (0.66–1.52)	1.5	1.00 (0.59–1.69)
Clinical							
Tumor grade							
Low	71.4	15.8	Ref.	46.5	Ref.	20.8	Ref.
High	24.4	81.0	**12.26 (10.79–13.93)**	49.2	**2.46 (2.21–2.74)**	74.1	**8.43 (7.21–9.86)**
Metastasis							
Negative	94.1	92.9	Ref.	90.7	Ref.	90.1	Ref.
Positive	4.0	5.0	0.91 (0.70–1.20)	6.2	1.27 (0.99–1.64)	**7.7**	1.00 (0.73–1.36)
Tumor size (cm)							
0–2.00	56.5	35.7	Ref.	41.8	Ref.	35.0	Ref.
2.01–5.00	32.9	46.6	**1.29 (1.14–1.45)**	42.4	**1.18 (1.05–1.32)**	41.4	1.08 (0.92–1.26)
>5.00	7.3	12.4	**1.59 (1.31–1.91)**	10.0	1.14 (0.94–1.38)	15.6	**1.64 (1.31–2.05)**
Microinvasion	0.4	1.3	**2.38 (1.37–4.12)**	1.3	**1.99 (1.19–3.35)**	2.0	**3.14 (1.81–5.46)**
Diffuse	0.4	0.4	1.90 (0.92–3.90)	0.7	**2.43 (1.30–4.55)**	1.0	**4.41 (2.24–8.71)**
Lymph nodes involved							
Negative	59.7	55.8	Ref.	90.7	Ref.	45.7	Ref.

Table 2 continued

Characteristics	HR+/HER2− %	Triple negative		HR+/HER2+		HR−/HER2+	
		%	OR [95 % CI]	%	OR [95 % CI]	%	OR [95 % CI]
Positive	38.7	42.5	**0.54 (0.48–0.60)**	**6.2**	**0.86 (0.77–0.97)**	**51.8**	**0.82 (0.71–0.94)**

Ref. referent category, *OR* odds ratio, *CI* confidence interval

Models adjusted for all variables listed in the table. Bold text signifies statistically significant associations

† p for trend <0.05; ‡ p for trend <0.01

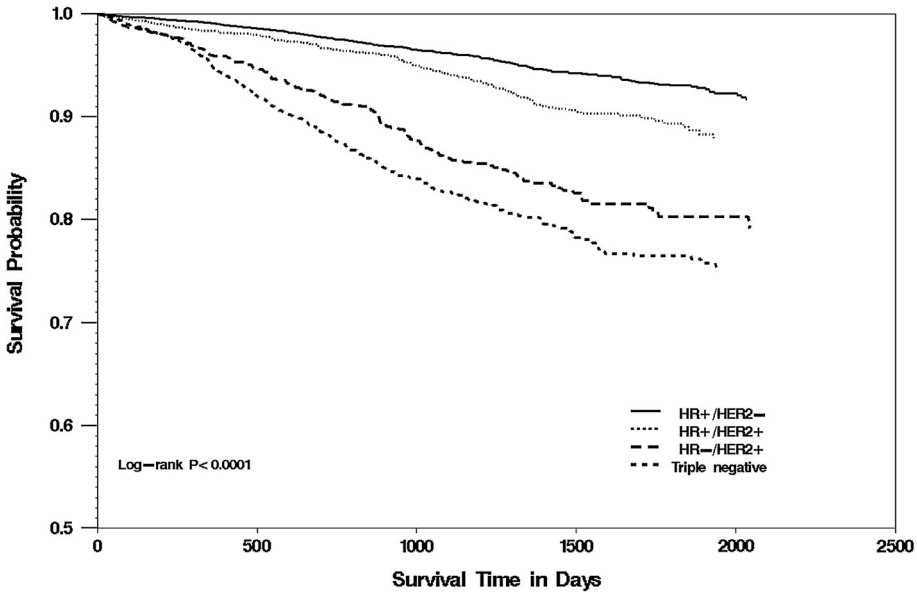

Fig. 1 Kaplan–Meier curve of Hispanic women by breast cancer subtype, California 2005–2010

with triple negative and HR−/HER2+ subtypes had significantly increased risk of death from breast cancer.

Discussion

Our study is among the first, certainly the most comprehensive with 16,380 participants, population-based analyses of breast cancer subtypes among US Hispanic women. These results confirm and extend emerging patterns for the molecular breast cancer subtypes. Similar to other racial/ethnic groups [13, 18–20], residence in a low SES neighborhood was significantly associated with an increased risk of diagnosis and dying from HR−/HER2+ and triple negative breast cancers. Foreign-born Hispanics were at greater risk of diagnosis with HR−/HER2+, compared with US-born Hispanics. The risk of death from triple negative breast cancer was substantial, as both US- and foreign-born Hispanic women diagnosed with this subtype had an approximately fourfold greater risk of death than those with HR+/HER2− breast cancer.

Although our case-only analyses cannot speak directly to cancer etiology or risk, these data underscore the potential impact of SES, a social determinant of health, on risk factors that may be etiologically important in increasing women's risk of developing poor prognostic breast cancer subtypes. For instance, women of low SES status, or residing in low SES neighborhoods, may have lower access to and consume fewer healthy foods (i.e., vegetables and nutrient-rich foods), fewer opportunities to engage in physical activity, and higher levels of obesity [21, 22], as indicated by studies, are associated with increased risk of ER− [23–25] or triple negative breast cancers [26]. Moreover, low SES may be related to younger age at first birth and lack of breastfeeding [27, 28], factors associated with an elevated risk of triple negative or basal-like breast cancers [29–31].

Importantly, if socioeconomic differences play a role in the risk of developing certain tumor subtypes, then the breast cancer-specific mortality disadvantage observed among Hispanic and other racial/ethnic women may be partly due to the intrinsic aggressiveness of the tumor

Table 3 Breast cancer-specific mortality, by tumor subtype, in Hispanic Women in California, 2005–2010

	All subtypes		HR+/HER2−		Triple negative		HR+/HER2+		HR-/HER2+	
	Deaths ($n = 993$)	HR (95 % CI)	Deaths ($n = 345$)	HR (95 % CI)	Deaths ($n = 357$)	HR (95 % CI)	Deaths ($n = 133$)	HR (95 % CI)	Deaths ($n = 158$)	HR (95 % CI)
Nativity										
US-born	426	Ref.	138	Ref.	153	Ref.	66	Ref.	69	Ref.
Foreign-born	567	0.97 (0.83–1.13)	207	1.12 (0.86–1.47)	204	0.99 (0.76–1.28)	67	0.68 (0.43–1.06)	89	0.72 (0.48–1.08)
Socioeconomic status										
Quintile 1 (low)	336	**1.76 (1.25–2.49)**	117	1.62 (0.91–2.88)	120	1.21 (0.69–2.13)	41	2.85 (0.90–9.00)	58	**4.02 (1.35–11.99)**
Quintile 2	230	**1.67 (1.19–2.36)**	77	1.32 (0.74–2.34)	76	1.14 (0.65–1.98)	31	2.84 (0.91–8.86)	46	**4.95 (1.70–14.40)**
Quintile 3	179	**1.54 (1.10–2.15)**	58	1.31 (0.74–2.32)	79	1.44 (0.85–2.44)	22	2.34 (0.79–6.93)	20	1.79 (0.59–5.38)
Quintile 4	127	1.38 (0.98–1.94)	43	1.04 (0.59–1.83)	40	1.02 (0.59–1.79)	23	2.46 (0.83–7.30)	21	**3.01 (1.03–8.77)**
Quintile 5 (high)	69	Ref.[†]	29	Ref.	23	Ref.	8	Ref.	9	Ref.[†]
Hispanic enclave										
Quintile 1 (low)	63	Ref.	19	Ref.	25	Ref.	9	Ref.	10	Ref.
Quintile 2	117	1.05 (0.75–1.48)	37	0.79 (0.43–1.46)	47	1.25 (0.73–2.13)	15	0.68 (0.24–1.90)	18	1.65 (0.65–4.20)
Quintile 3	161	0.98 (0.71–1.36)	56	1.01 (0.57–1.80)	58	1.05 (0.62–1.80)	24	0.70 (0.27–1.78)	23	1.11 (0.44–2.83)
Quintile 4	238	0.92 (0.66–1.27)	88	1.01 (0.57–1.80)	84	0.98 (0.58–1.66)	32	0.83 (0.33–2.09)	34	0.84 (0.33–2.14)
Quintile 5 (high)	382	0.92 (0.66–1.28)	133	0.98 (0.55–1.77)	128	1.11 (0.65–1.89)	51	0.59 (0.22–1.60)	70	0.94 (0.37–2.40)
Age at diagnosis (years)										
<45	245	0.94 (0.73–1.20)	60	0.65 (0.42–1.03)	116	1.35 (0.88–2.08)	29	**0.49 (0.25–0.96)**	40	1.37 (0.76–2.46)
45–49	130	0.96 (0.73–1.27)	48	0.79 (0.49–1.27)	53	1.25 (0.77–2.03)	12	0.55 (0.25–1.20)	17	1.33 (0.66–2.67)
50–54	149	Ref.	51	Ref.	43	Ref.	28	Ref.	27	Ref.
55–59	105	0.94 (0.70–1.26)	40	0.98 (0.59–1.60)	36	1.16 (0.69–1.95)	9	**0.33 (0.13–0.82)**	20	1.02 (0.50–2.07)
60–64	81	0.90 (0.65–1.24)	28	0.72 (0.42–1.26)	30	1.45 (0.83–2.54)	13	0.71 (0.29–1.70)	10	0.90 (0.40–2.07)
≥65	283	**1.30 (1.01–1.67)**	118	1.09 (0.71–1.69)	79	1.55 (0.95–2.52)	42	1.01 (0.54–1.90)	44	1.55 (0.84–2.86)
Marital status at diagnosis										
Married	507	Ref.	155	Ref.	204	Ref.	68	Ref.	80	Ref.
Never married	192	1.06 (0.87–1.29)	72	**1.40 (1.00–1.96)**	64	0.94 (0.67–1.32)	24	0.89 (0.50–1.58)	32	1.16 (0.70–1.93)
Prev. married	248	1.14 (0.95–1.37)	93	**1.44 (1.05–1.98)**	79	0.86 (0.63–1.19)	38	1.16 (0.71–1.89)	38	1.42 (0.86–2.34)
Insurance status										
Private	394	Ref.	139	Ref.	146	Ref.	46	Ref.	63	Ref.
Public	500	1.13 (0.96–1.34)	170	0.99 (0.74–1.33)	180	1.23 (0.92–1.64)	75	1.25 (0.77–2.01)	75	1.12 (0.73–1.70)
Uninsured	24	1.41 (0.88–2.26)	9	1.58 (0.72–3.45)	7	1.53 (0.68–3.43)	<5	3.11 (0.91–10.65)	5	0.57 (0.14–2.35)
Subtype										
HR+/HER2−	345	Ref.								
Triple negative	357	**4.05 (3.35–4.90)**								

Table 3 continued

	All subtypes		HR+/HER2−		Triple negative		HR+/HER2+		HR-/HER2+	
	Deaths ($n = 993$)	HR (95 % CI)	Deaths ($n = 345$)	HR (95 % CI)	Deaths ($n = 357$)	HR (95 % CI)	Deaths ($n = 133$)	HR (95 % CI)	Deaths ($n = 158$)	HR (95 % CI)
HR+/HER2+	133	1.20 (0.95–1.52)								
HR−/HER2+	158	**2.26 (1.80–2.84)**								

Ref. referent category, *HR* hazard ratio, *CI* confidence interval

Cox models were adjusted for all variables presented in addition to year of diagnosis, tumor size (continuous), lymph node (yes/no), and first course of treatment (surgery, chemotherapy, and radiation therapy); Public insurance included Medicaid and other government-assisted programs; and private insurance included health maintenance organizations, preferred provider organizations, managed care not otherwise specified, and military care AJCC stage levels I–IV and unknown was included as a stratifying variable. Bold text signifies statistically significant associations

† p for trend <0.05

Table 4 Breast cancer-specific mortality by Hispanic nativity

Breast cancer subtype	US-born hispanic		Foreign-born	
	Deaths	HR [95 % CI]	Deaths	HR [95 % CI]
HR+/HER2−	138	Ref.	207	Ref.
Triple negative	153	**4.38 (3.25–5.95)**	204	**4.10 (3.20–5.26)**
HR+/HER2+	66	**1.57 (1.11–2.22)**	67	0.93 (0.67–1.31)
HR−/HER2+	69	**3.22 (2.25–4.61)**	89	**1.91 (1.41–2.58)**

Ref. referent category, *HR* hazard ratio, *CI* confidence interval

Cox models were adjusted for socioeconomic status (quintiles), Hispanic enclave (quintiles), age at diagnosis (continuous), marital status (married, never married, previously married), insurance status (private, public, uninsured, unknown), tumor size (continuous), lymph node (yes/no), tumor grade (low/high/unknown), and first course of treatment (surgery, chemotherapy, and radiation therapy); AJCC stage levels I–IV and unknown was included as a stratifying variable. Bold text signifies statistically significant associations

subtype, and the more commonly recognized factors associated with low SES or living in low SES neighborhoods [32]. Consistent with studies among other racial/ethnic groups [4, 5, 33, 34], our study confirms the adverse characteristics of certain breast cancers, such that compared with the HR+/HER2− subtype, Hispanic women diagnosed with HR+/HER2+, HR−/HER2+, and triple negative subtypes had significantly greater risk of death.

While our study adds valuable information on breast cancer subtypes among Hispanic women, it has some limitations. Tumor subtype information was missing for approximately 16.6 % of potentially eligible participants, although the magnitude and direction of biases related to missing data are unknown. We did not have individual-level data on income or education; nevertheless, neighborhood-level measures may capture information on environmental factors that occur as a result of its socioeconomic condition and deprivation [20]. The distribution of breast cancer subtypes among Hispanic women in California may not reflect distributions among other US Hispanic women; accordingly, our findings may be most generalizable to women of primarily Mexican descent, the largest Hispanic subgroup in California [35]. The imputation method used to classify nativity is subject to error and may have led to some misclassification; however, most participants (about 65 %) were classified based on cancer registry birthplace data, previously shown to have high accuracy [11, 36]. Similarly, Hispanic ethnicity may be subject to misclassification [37, 38], although classification should have improved with application of a registry-wide algorithm [9]. While Hispanics are a diverse population, we could not include information on Hispanic origin

because it was missing for approximately 40 % of participants. Breast cancer-specific survival analyses are subject to the accuracy of the underlying cause of death code, which has been shown to be 84–90 % accurate [39, 40]. Finally, those tumor characteristics associated with aggressive breast cancer subtypes, including HR- and younger age at diagnosis, are also associated with interval-detected cancers, which may lead to length bias and lower survival than screen-derived cancers [41, 42].

Conclusion

In the largest population-based study of breast cancer subtypes among US Hispanic women conducted to date, we found that residing in a low SES neighborhood was significantly associated with increased risk of developing and dying from HR− breast cancers. Foreign-born women were at greater risk of HR−/HER2+ tumors, although nativity was not associated with other subtypes. Similarity in the distribution and prognosis of breast cancer subtypes among California Hispanic women and previous studies in other racial/ethnic groups underscores the need to understand how sociodemographic factors, such as SES, contribute to the distinct patterns of breast cancer subtype incidence and mortality among women of all racial/ethnic backgrounds.

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Conflict of interest The authors have no conflicts of interest to disclose

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