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Do breast quadrants explain racial disparities in breast cancer outcomes?

Yunan Han[1,2] · Justin Xavier Moore[1,3] · Marvin Langston[1,4] · Lindsay Fuzzell[1,5] · Saira Khan[1,6] · Marquita W. Lewis[1] · Graham A. Colditz[1,7] · Ying Liu[1,7]

Abstract

Purpose Tumors of the inner quadrants of the breast are associated with poorer survival than those of the upper-outer quadrant. It is unknown whether racial differences in breast cancer outcomes are modified by breast quadrant, in addition to comparisons among Asian subgroups.

Methods Using the Surveillance, Epidemiology, and End Results database, we analyzed data among women diagnosed with non-metastatic invasive breast cancer between 1990 and 2014. We performed Cox proportional hazards regression models to assess the associations of race with breast cancer-specific survival and overall survival, stratified by breast quadrants. The models were adjusted for age, year of the diagnosis, tumor size, grade, histological type, tumor laterality, lymph node, estrogen receptor, progesterone receptor, and treatments.

Results Among 454,154 patients (73.0% White, 10.0% Black, 7.8% Asian/PI, and 9.2% Hispanic), 54.3% had tumors diagnosed in the upper-outer quadrant of the breast. Asian/PI women were more likely than White to have tumors diagnosed in the nipple/central portion of the breast and were less likely to have diagnosed in the upper-outer quadrant ($P < 0.001$), despite a similar distribution of breast quadrant between Black, Hispanic, and White women. Compared with White women, the multivariable-adjusted hazard ratios of breast cancer-specific mortality were 1.41 (95% CI 1.37–1.44) in Black women, 0.82 (95% CI 0.79–0.85) in Asian women, and 1.05 (95% CI 1.02–1.09) in Hispanic women. Among Asian subgroups, Japanese American women had a lower risk of breast cancer-specific mortality (HR = 0.68, 95% CI 0.62–0.74) compared with White women. Overall survival was similar to breast cancer-specific survival in each race group. The race-associated risks did not vary significantly by breast quadrants for breast cancer-specific mortality and all-cause mortality.

Conclusions Differences in breast cancer survival by race could not be attributed to tumor locations. Understanding the cultural, biological, and lifestyle factors that vary between White, African American, and ethnic subgroups of Asian American women may help explain these survival differences.

Abbreviations
BCS   Breast-conserving surgery
BCSM   Breast cancer-specific mortality
BCSS   Breast cancer-specific survival

✉ Ying Liu
  yliu3@wustl.edu

1   Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, 660 South Euclid Ave, Campus Box 8100, St. Louis, MO 63110, USA

2   Department of Breast Surgery, First Hospital of China Medical University, Shenyang, Liaoning, China

3   Division of Epidemiology, Department of Population Health Sciences, Augusta University, Augusta, GA, USA

4   Division of Research, Kaiser Permanente, Northern California, Oakland, CA 94612, USA

5   Department of Health Outcomes & Behavior, H. Lee Moffitt Cancer Center, Tampa, FL, USA

6   Epidemiology Program, College of Health Sciences, University of Delaware, Newark, DE, USA

7   Alvin J. Siteman Cancer Center, Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, MO, USA

CI   Confidence interval
ER   Estrogen receptor
HR   Hazard ratio
NOS   Not otherwise specified
OS   Overall survival
PI   Pacific Islander
PR   Progesterone receptor
SEER   Surveillance, Epidemiology, and End Results

Introduction

About one in eight American women will be diagnosed with breast cancer during their lifetime [1]. Incidence of breast cancer is higher among White women (130 per 100,000) compared with Black, Asian American/Pacific Islander (PI) and Hispanic women (126, 93, and 93 per 100,000, respectively) [1]. However, breast cancer mortality rates are higher in Black women [1–3] and lower in Asian American/PI and Hispanic American women compared with White women [1]. In addition, breast cancer is one of the leading causes of death among American women, accounting for over 41,000 deaths annually [1]. Tumor location in the breast is an important prognostic factor [4–7]. The upper-outer quadrant of the breast is the most prevalent site for breast cancer [8], likely due to the larger amount of epithelial tissue in this quadrant compared with other quadrants [9]. Tumors of the outer breast have shown more favorable outcomes than other sites [5, 6, 10, 11]. Specifically, women with tumors of the upper-outer quadrant have better survival compared to those with tumors of other quadrants [12]. Survival rates are diminished in patients with tumors of inner quadrant [6] and tumors of the medial breast [11], likely because these quadrants are more difficult to detect by mammography [13, 14]. Moreover, breast cancer lymphatic metastasis goes not only to the axillary lymph nodes but also to the internal mammary lymph nodes [15], especially for breast cancer located in inner quadrants of the breast. However, the importance of internal mammary lymph node biopsy in the accurate staging and management of breast cancer is controversial [16], thus lack of monitoring and timely treatment of internal mammary lymph nodes may lead to worse outcomes.

Race and ethnicity are also associated with breast cancer survival. Research on breast quadrants in relation to survival have failed to include race/ethnicity in their analyses [6, 11], have lumped races of small subpopulations together as "other", and/or have not differentiated ethnicities within Asian/PI populations [17]. The lumping of Asian subpopulations limits the generalizability to these minority groups as they are very heterogeneous and may have differing associations with breast cancer survival depending on cultural and social norms. For example, Iqbal et al. reported that Chinese had significant 45% reduced risk of death from breast cancer compared with non-Hispanic white women following early stage diagnosis, and Other Asians had significant 39% reduced risk of death from breast cancer, while Japanese and south Asians had no significant results [18]. It is plausible that tumor locations within the breast explain racial differences in breast cancer survival to some extents.

Therefore, we used nationally representative data of breast cancer to investigate if differences in breast cancer survival by race could be attributed to tumor locations. We did a further examination among subgroups of Asian/PI women. To our knowledge, no study to date has examined the association between specific Asian/PI American subpopulations, breast quadrants, and breast cancer survival.

Methods

Data source and patient population

From the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database released in April 2018 (November 2017 submission), we identified women 20–79 years old who were diagnosed with stages I–III breast cancer between 1 January 1990 and 31 December 2014, had no cancer history, and were followed through 31 December 2015 ($n = 714,472$). The SEER registries cover approximately 34.6% of the US population [19]. White, Black, Asian/PI, and Hispanic women accounted for 99% of eligible cases,therefore, we excluded patients of unknown race and American Indian/Alaska Natives if they were non-Hispanic ($n = 6,819$). Regarding the primary tumor sites categorized based on the International Classification of Diseases for Oncology (ICD-O-3) codes [20], we included tumors in the (1) nipple (C50.0) and central (C50.1) portion of breast, (2) upper-inner quadrant of breast (C50.2), (3) lower-inner quadrant of breast (C50.3), (4) upper-outer quadrant of breast (C50.4), (5) lower-outer quadrant of breast (C50.5), and (6) axillary tail of breast (C50.6) ($n = 465,118$). We excluded the cases whose tumors overlapped two or more contiguous sites or whose tumor point of origin could not be determined ($n = 242,535$). We excluded unknown laterality and bilateral cases ($n = 49$) and patients whose follow-up time was less than 12 months ($n = 10,915$). In total, 454,154 women were included in our study (Fig. 1). The SEER data contain de-identified information and were considered exempt by the institutional review board at Washington University in St. Louis.

Outcome, exposure, and covariates

The primary outcomes were breast cancer-specific survival (BCSS) and overall survival (OS). For patients who died during follow-up, follow-up began at the date of breast
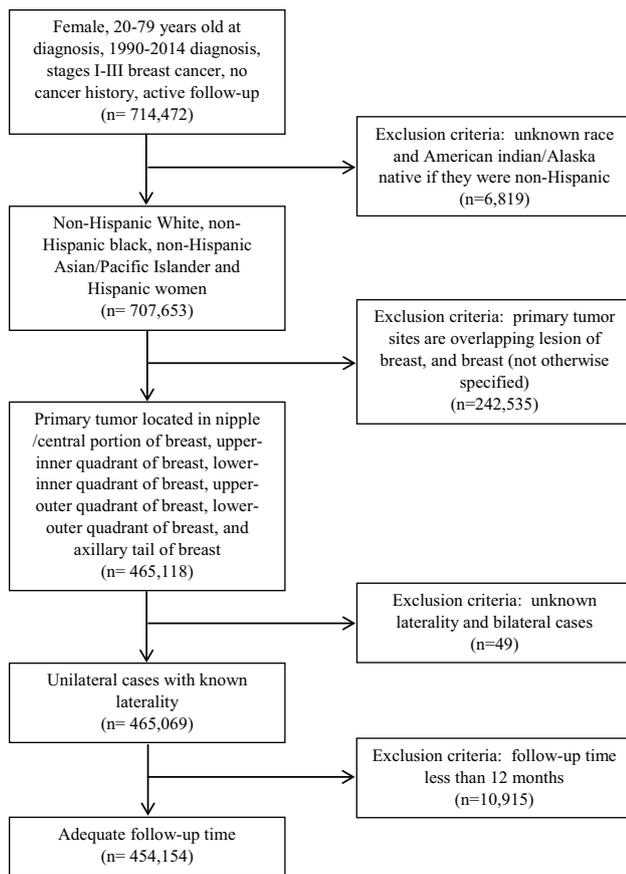
Fig. 1 Participants flow diagram of the study

cancer diagnosis and ended at the date of death. For patients that were alive at the study end, follow-up began on the date of breast cancer diagnosis and continued until the study end, 31 December 2015.

We classified race/ethnicity into four mutually exclusive categories of (1) non-Hispanic White (hereafter referred to as White, $n = 331,418$), (2) non-Hispanic Black (Black, $n = 45,218$), (3) non-Hispanic Asian/PI (Asian/PI, $n = 35,623$), and (4) Hispanic ($n = 41,895$). Since the exclusion of Hispanic non-Whites and PIs did not significantly change the race-associated survival outcomes, we combined all Hispanics, regardless of their race, as a single group and combined non-Hispanic Asians and PIs as a single group. Asian/PI Americans were further classified into eight categories similar as previously reported for these populations [21, 22]: (1) Chinese ($n = 6,605$), (2) Japanese ($n = 5,751$), (3) Filipino ($n = 9,080$), (4) Korean ($n = 2,192$), (5) Vietnamese ($n = 1,984$), (6) South Asian ($n = 2,693$), (7) other Asians ($n = 4,418$), and (8) PI ($n = 2,898$). South Asians consisted of Asian Indians and Pakistanis [21]. The "other Asians" consisted of Cambodians, Laotians, Hmong, Thai, and Asian and oriental not otherwise specified (NOS).

Covariates that were known risk factors for breast cancer survival [6, 7, 17] included personal characteristics, tumor characteristics, and treatment. Covariates included age (20–39, 40–49, 50–59, 60–69, or 70–79 years) and year of the diagnosis (1990–1994, 1995–1999, 2000–2004, or 2005–2009, 2010–2014), histopathological features including tumor size (≤ 2 cm, 2–5 cm, > 5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated and undifferentiated, or unknown), and histological type (IDC, ILC or other histology), laterality of the tumor (right, or left), lymph node status (negative, positive, or unknown), estrogen receptor (ER) status (negative, positive, or unknown), progesterone receptor (PR) status (negative, positive, or unknown), and treatments including surgery (no surgical treatment, breast-conserving surgery(BCS) alone, mastectomy, or unknown), radiation (no/unknown, yes), and chemotherapy (no/unknown, yes). The SEER registries collect information on radiation therapy and chemotherapy given as part of the first course of treatment. Radiation therapy data are classified by the types of radiation received or "no/unknown—no evidence of radiation was found in the medical records examined". Chemotherapy data are categorized as either "yes—patient had chemotherapy" or "no/unknown—no evidence of chemotherapy was found in the medical records examined". Because of the limitations in these variables, we could not distinguish between "no treatment" and "unknown".

Statistical analysis

BCSS and OS were compared across race groups using Kaplan–Meier plots and the log-rank test. We examined the proportional hazards assumption for BCSS and OS by race and did not observe any violation. Therefore, we utilized Cox Proportional Hazards regression models to assess the associations between race, breast quadrants, and survival outcomes, adjusted for the aforementioned covariates. We formally examined whether breast quadrants were an effect modifier on the association between race and survival outcomes by using an interaction term between race and breast quadrants in Cox Proportional Hazards models. We considered breast quadrant a non-modifiable factor and were not interested in the joint effect between breast quadrants and race [23]. Thus, we stratified all analyses by breast quadrants to examine whether breast quadrants modify the impact of race/ethnicity on breast cancer survival outcomes. We further examined the associations between Asian/PI ethnicity and survival outcomes by breast quadrants. Breast quadrants were collapsed into three categories: (1) nipple and central portion of breast, (2) inner quadrant (upper-inner quadrant and lower-inner quadrant), and (3) outer quadrant (upper-outer quadrant and lower-outer quadrant), to improve the statistical power of analysis in Asian/PI women.

We conducted several secondary analyses. First, we stratified the analysis by age at diagnosis (<50 years and ≥ 50 years) as a potential proxy for menopausal status. Second, we stratified the analysis by lymph node status as lymph node status varies by tumor quadrants (i.e., axillary tail of breast may be more likely to be lymph node positive) [17]. Prior studies have reported a poorer BCSS and OS for tumors of the axillary tail compared with those of the upper-outer quadrant [17]. Lastly, we performed analyses mining breast quadrants as the primary exposure for BCSS and OS, while controlling for race.

We used SAS statistical software (version 9.4; SAS Institute Inc) for analyses with the exception of the Kaplan–Meier plots, which was performed in Stata software (version 13; StataCorp LP). Statistical significance was suggested by two-sided $P < 0.05$.

Results

Among 454,154 patients, 331,418 (73.0%) were White, 45,218 (10.0%) were Black, 35,623 (7.8%) were Asian/PI, and 41,895 (9.2%) were Hispanic. Over half (54.3%) of the women were diagnosed with breast cancer in the upper-outer quadrant of the breast. Asian women were more likely than White women to have tumors diagnosed at the nipple/central portion of the breast and were less likely to have tumors diagnosed at the upper-outer quadrant of the breast ($P < 0.001$), while there was a similar distribution of breast quadrants between Black, Hispanic, and White women (Table 1). The mean age at diagnosis was 57.7 years. White women were more likely to be diagnosed at older ages than women from the other race groups ($P < 0.001$). Compared with White women, other racial/ethnic women were significantly more likely to have large tumors (tumor size > 2 cm), poorly differentiated and undifferentiated tumor. White women were more likely to have invasive lobular breast cancer (8.2%), while Asian/PI women were less likely to have invasive lobular breast cancer (4.9%) compared to other races (Black, 6.0%; Hispanic, 6.9%). Black and Hispanic women were more likely to have stages II–III breast cancer, and positive lymph node involvement. Black women (31.7%) were more likely than the other racial/ethnic women to have hormone receptor negative (ER− and PR−) breast cancer (White 17.4%, Asian/PI 17.9%, and Hispanic 20.9%; $P < 0.001$). Black women were more likely to undergo chemotherapy and a large proportion (45.4%) of Asian/PI women underwent mastectomy, while over half (56.5%) of White women received radiation therapy.

Survival outcomes

During the follow-up (mean: 105.5 months), 49,304 (10.9%) women died of breast cancer and 106,894 (23.5%) women died due to any cause. The 10-year BCSS was 87.7% and 10-year OS was 77.6%, based on the Kaplan–Meier estimator of the mortality-free survival probability (data not shown). There were significant differences by race in BCSS across all breast quadrants (log-rank test P value: < 0.001; Fig. 2). In general, Black women had the poorest BCSS rates, while Asian/PI women had the best survival rates across all breast quadrants (Supplementary Fig. 1). Similar to BCSS, there were significant differences in OS by race (data not shown).

Black women had an 81% (Hazard ratio [HR]: 1.81, 95% confidence interval [CI] 1.76–1.86), and Hispanic women had a 23% (HR: 1.23, 95% CI 1.19–1.27) increased risk of breast cancer-specific mortality (BCSM) when compared to White women in age-adjusted model. The results were attenuated but still significant after adjusted for patients' age, year of the diagnosis, laterality of the tumor, tumor histopathological features including tumor size, grade, histological type, lymph node status, estrogen receptor (ER) status, progesterone receptor (PR) status, and treatments including surgery, radiation, and chemotherapy. For examples, in multivariable-adjusted model, Black women had a 41% (HR: 1.41, 95% CI 1.37–1.44), and Hispanic women had a 5% (HR: 1.05, 95% CI 1.02–1.09) increased risk of BCSM when compared to White women. In contrast, Asian women had an 18% reduced risk of BCSM (HR: 0.82, 95% CI 0.79–0.85) when compared to White women. However, the association between race and BCSS did not significantly vary by breast quadrants (Table 2). We observed that Black women were at increased risk for BCSM as compared to White women (nipple and central portion of breast [HR: 1.33, 95% CI 1.22–1.44]; upper-inner quadrant [HR: 1.45, 95% CI 1.36–1.55]; lower-inner quadrant [HR: 1.34, 95% CI 1.23–1.46]; upper-outer quadrant [HR: 1.44, 95% CI 1.39–1.50], lower-outer quadrant [HR: 1.32, 95% CI 1.22–1.43], and axillary tail of breast [HR: 1.44, 95% CI 1.15–1.80]). By contrast, Asian/PI women had a consistently decreased risk of BCSM across breast quadrants as compared to White women (nipple and central portion of breast [HR: 0.82, 95% CI 0.74–0.91]; upper-inner quadrant [HR: 0.79, 95% CI 0.72–0.87]; lower-inner quadrant [HR: 0.80, 95% CI 0.70–0.91]; upper-outer quadrant [HR: 0.84, 95% CI 0.80–0.89]; lower-outer quadrant [HR: 0.77, 95% CI 0.69–0.87]; and axillary tail of breast [HR: 0.90, 95% CI 0.61–1.35]). Similar associations were observed for OS (Supplementary Table 1).

We next evaluated the associations between Asian/PI women and BCSS (Table 3). In multivariable analyses, the strongest reduction in risk of BCSM was seen among

Table 1 Age-standardized characteristics of breast cancer cases by race and ethnicity in the SEER Cancer Registries (n=454,154)

	Overall (N=454,154)	White (N=331,418)	Black (N=45,218)	Asian/PI (N=35,623)	Hispanic (N=41,895)
Breast quadrants					
Nipple/central portion of breast	8.6	8.5	7.7	10.3	8.9
Upper-inner quadrant	17.0	16.6	17.0	19.7	17.7
Lower-inner quadrant	8.4	8.3	9.8	8.3	8.2
Upper-outer quadrant	54.3	54.9	53.4	50.6	53.6
Lower-outer quadrant	10.7	10.7	10.8	10.4	10.7
Axillary tail of breast	1.0	1.0	1.3	0.7	0.8
Age at diagnosis, mean year[a] (SD)	57.7(11.9)	58.7(11.7)	55.2(11.9)	55.2(11.7)	54.4(12.1)
Age at diagnosis (%)					
20–39	6.3	5.1	9.4	8.7	10.8
40–49	20.7	18.8	24.6	26.1	26.9
50–59	27.4	27.1	28.9	28.7	27.5
60–69	26.2	27.6	23.0	23.1	21.6
70–79	19.3	21.4	14.1	13.5	13.2
Length of follow-up, mean month (SD)	105.5(68.4)	109.4(69.3)	90.8(63.7)	103.4(68.7)	93.9(64.2)
Length of follow-up (%)					
12–59	31.8	29.6	40.1	33.6	38.3
60–119	30.3	30.2	30.9	30.0	30.8
≥120	37.8	40.2	29.0	36.4	30.9
Year of diagnosis					
1990–1994	8.8	9.6	6.9	7.3	6.2
1995–1999	11.7	12.1	9.6	12.8	9.8
2000–2004	25.4	26.2	23.6	22.0	22.9
2005–2009	26.1	25.7	27.5	26.2	27.6
2010–2014	28.0	26.4	32.3	31.7	33.5
Laterality					
Right	49.1	49.3	48.7	49.3	48.5
Left	50.9	50.7	51.3	50.7	51.5
Histological subtype					
Invasive ductal carcinoma	74.7	74.1	76.5	78.6	74.8
Invasive lobular carcinoma	7.6	8.2	6.0	4.9	6.9
Other histology	17.7	17.7	17.6	16.6	18.3
Grade[b]					
Well differentiated	21.4	22.8	14.2	20.1	19.1
Moderately differentiated	42.1	43.0	36.1	43.7	41.1
Poorly differentiated and undifferentiated	36.5	34.2	49.7	36.1	39.8
Stage					
I	51.1	53.3	41.4	51.1	44.9
II	36.8	35.4	42.8	37.7	40.1
III	12.1	11.2	15.7	11.2	15.0
Tumor size (mm)[c]					
≤20	64.4	66.9	54.5	62.5	58.0
20–50	30.5	28.6	37.6	32.5	35.7
>50	5.1	4.5	7.9	5.0	6.3
Lymph nodes status[d]					
Negative	68.1	69.2	62.6	69.9	64.0

Table 1 (continued)

	Overall (N=454,154)	White (N=331,418)	Black (N=45,218)	Asian/PI (N=35,623)	Hispanic (N=41,895)
Positive	31.9	30.8	37.4	30.1	36.0
Estrogen receptor[e]					
Negative	20.8	18.9	33.7	19.4	22.5
Positive	79.2	81.1	66.3	80.6	77.5
Progesterone receptor[f]					
Negative	30.9	28.9	44.4	29.4	32.9
Positive	69.1	71.1	55.6	70.6	67.1
Hormone receptor[g]					
Negative (ER− and PR−)	19.2	17.4	31.7	17.9	20.9
Positive (ER+/PR+)	80.8	82.6	68.3	82.1	79.1
Surgery[h]					
None	1.3	1.0	2.7	1.4	2.1
Breast-conserving surgery[i]	59.3	60.4	57.0	53.2	57.1
Mastectomy[j]	39.4	38.5	40.2	45.4	40.9
Radiation					
No/unknown	44.7	43.5	47.4	48.4	49.1
Yes	55.3	56.5	52.6	51.6	50.9
Chemotherapy					
No/unknown	57.0	58.4	49.7	57.3	53.7
Yes	43.0	41.6	50.3	42.7	46.3

SD standard deviation

Values are means (SD) or percentages and are standardized to the age distribution of the overall study population in race/ethnicity groups

P values were calculated from a comparison across all groups except the groups with missing values

[a]Values were not age adjusted

[b]Overall missing: 35,403, White:26,563, Black:3,716, Asian/PI:2,325, Hispanic:2,799

[c]Overall missing: 5,250, White: 3,480, Black: 704, Asian/PI: 507, Hispanic: 559

[d]Overall missing: 509, White:348, Black:82, Asian/PI:24, hispanic:55

[e]Overall missing: 34,545, White:24,827, Black:3,831, Asian/PI:2,295, Hispanic:3,592

[f]Overall missing:40,300, White: 28,865, Black: 4,376, Asian/PI: 2,821, Hispanic: 4,238

[g]Overall missing: 40,572, White: 29,070, Black: 4,402, Asian/PI: 2,838, Hispanic: 4,262

[h]Overall missing: 606, White: 442, Black: 85, Asian/PI: 33, Hispanic: 46

[i]Breast-conserving surgery consisted of excisional biopsy, lumpectomy, nipple resection, wedge resection, quadrantectomy, segmental mastectomy, tylectomy, and partial mastectomy, NOS

[j]Mastectomy included total mastectomy, modified radical mastectomy, radical mastectomy, subcutaneous mastectomy and mastectomy, not otherwise specified

Japanese American women (HR: 0.68, 95% CI 0.62–0.74), and "other Asian" women (HR: 0.67, 95% CI 0.59–0.76) when compared to White women, and the risk also did not significantly vary by breast quadrants. Overall, Chinese American women had a 19% reduced risk of BCSM (HR: 0.81, 95% CI 0.75–0.88), and South Asian women displayed a 15% reduced risk of BCSM (HR: 0.85, 95% CI 0.74–0.97), while Filipino American women had a 12% reduced risk of BCSM (HR: 0.88, 95% CI 0.82–0.94). No significant association was observed in Korean or Vietnamese Asian subgroups and PI; however, sample sizes were small. Moreover, we observed significant inverse associations for BCSM among Chinese, Japanese, and other Asian women for each

breast quadrant. Test for heterogeneity of BCSM across the Asian subgroups was significant ($P_{heterogrnrity} < 0.0001$) (Table 3). Findings for OS by Asian subgroups were consistent (Supplementary Table 2).

Secondary analyses

In secondary analyses, we observed that our results were consistent with additional stratification by age (<50 vs. ≥50) and lymph node status for both BCSM and all-cause mortality (data not shown). In multivariable analyses of breast quadrants, controlling for race, we found that women with tumors in the nipple and central portion of the breast (HR:
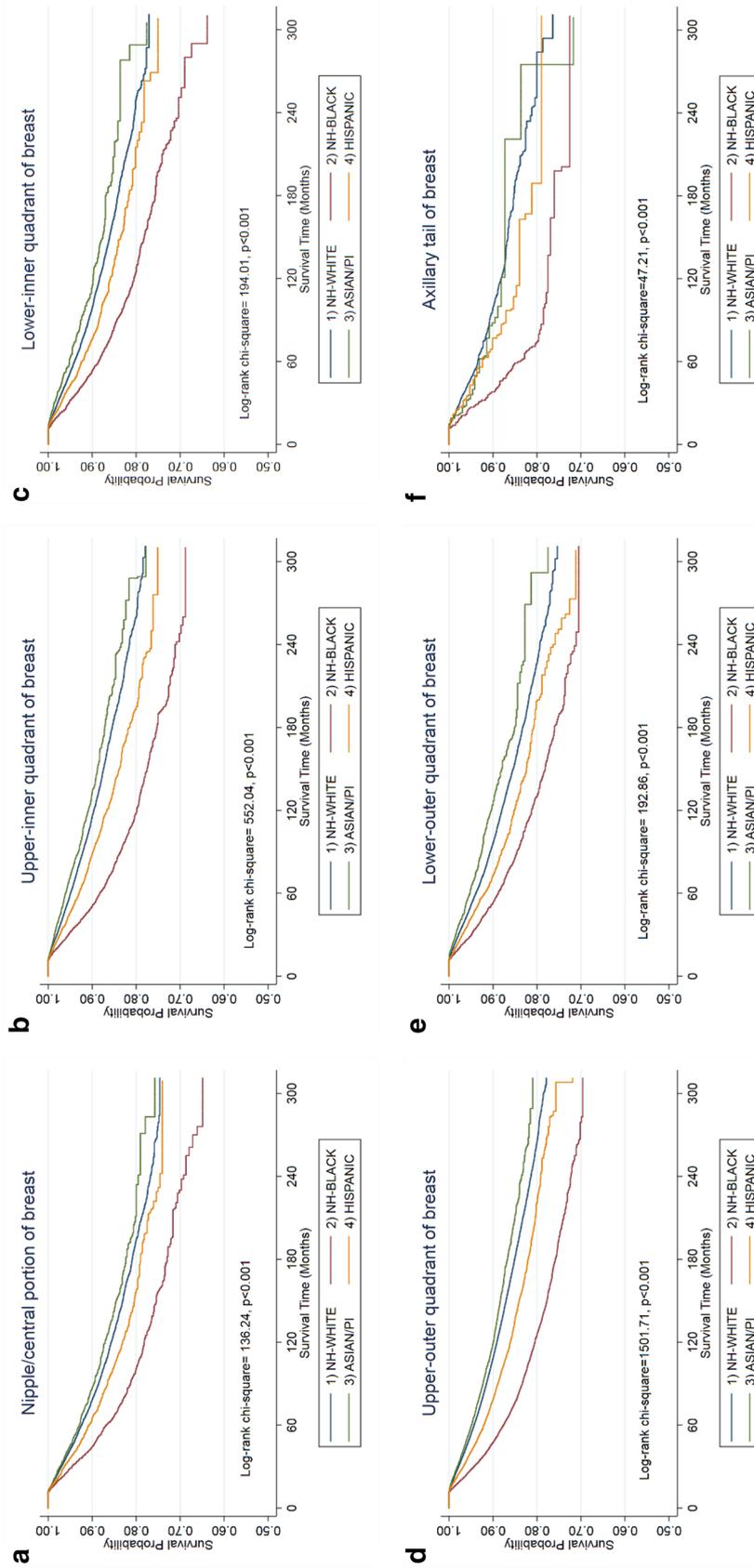
Fig. 2 Kaplan–Meier plots for breast cancer-specific survival associated with race and ethnicity in **a** nipple/central portion of breast, **b** upper-inner quadrant of breast, **c** lower-inner quadrant of breast, **d** upper-outer quadrant of breast, **e** lower-outer quadrant of breast and **f** axillary tail of breast

Table 2 Age-adjusted and multivariable-adjusted risk of breast cancer-specific mortality associated with race and ethnicity by breast quadrants ($n = 454,154$)

	Deaths from breast cancer	Person-years	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[a]
White	34,175	36,050,634	Reference	Reference
Black	7,298	4,170,530	1.81 (1.76–1.86)**	1.41 (1.37–1.44)**
Asian/PI	3,075	3,714,444	0.86 (0.83–0.90)**	0.82 (0.79–0.85)**
Hispanic	4,756	3,966,662	1.23 (1.19–1.27)**	1.05 (1.02–1.09)**
Breast quadrants				
Nipple/central portion of breast				
White	3,810	3,154,746	Reference	Reference
Black	626	321,451	1.59 (1.46–1.73)**	1.33 (1.22–1.44)**
Asian/PI	423	387,036	0.91 (0.82–1.00)	0.82 (0.74–0.91)**
Hispanic	511	359,686	1.15 (1.05–1.27)**	0.97 (0.88–1.06)
Upper-inner quadrant				
White	5,031	5,758,358	Reference	Reference
Black	1,204	687,462	1.96 (1.84–2.09)**	1.45 (1.36–1.55)**
Asian/PI	522	700,756	0.84 (0.77–0.92)**	0.79 (0.72–0.87)**
Hispanic	775	680,719	1.27 (1.18–1.37)**	1.09 (1.01–1.18)*
Lower-inner quadrant				
White	2,893	2,957,899	Reference	Reference
Black	680	401,115	1.69 (1.55–1.83)**	1.34 (1.23–1.46)**
Asian/PI	241	299,078	0.82 (0.71–0.93)**	0.80 (0.70–0.91)**
Hispanic	369	309,539	1.19 (1.07–1.32)**	1.03 (0.92–1.15)
Upper-outer quadrant				
White	18,290	20,081,992	Reference	Reference
Black	3,935	2,261,009	1.86 (1.80–1.93)**	1.44 (1.39–1.50)**
Asian/PI	1,553	1,918,629	0.88 (0.84–0.93)**	0.84 (0.80–0.89)**
Hispanic	2,535	2,169,691	1.24 (1.19–1.29)**	1.06 (1.02–1.11)**
Lower-outer quadrant				
White	3,775	3,701,406	Reference	Reference
Black	739	443,261	1.62 (1.50–1.76)**	1.32 (1.22–1.43)**
Asian/PI	310	381,388	0.79 (0.71–0.89)**	0.77 (0.69–0.87)**
Hispanic	526	413,895	1.23 (1.12–1.35)**	1.05 (0.96–1.16)
Axillary tail of breast				
White	376	396,233	Reference	Reference
Black	114	56,232	2.14 (1.73–2.65)**	1.44 (1.15–1.80)**
Asian/PI	26	27,557	1.03 (0.69–1.54)	0.90 (0.61–1.35)
Hispanic	40	33,132	1.28 (0.92–1.77)	0.97 (0.69–1.35)
			$P_{interaction}^{b} = 0.0007$	$P_{interaction}^{b} = 0.51$

CI confidence interval, *HR* hazard ratio, *PI* Pacific Islander

*Statistical significance difference at *P* value ≤ 0.05

**Statistical significance difference at *P* value ≤ 0.01

[a]Hazard ratios were adjusted for age (20–39, 40–49, 50–59, 60–69, or 70–79 years) and year of the diagnosis (1990–1994, 1995–1999, 2000–2004, or 2005–2009, 2010–2014), histopathological features including tumor size (≤ 2 cm, 2–5 cm, > 5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated and undifferentiated, or unknown), and histological type (IDC,ILC or other histology), laterality of the tumor (right, or left), lymph node status (negative, positive, or unknown), estrogen receptor (ER) status (negative, positive, or unknown), progesterone receptor (PR) status (negative, positive, or unknown), and treatments including surgery (no surgical treatment, breast-conserving surgery (BCS) alone, mastectomy, or unknown), radiation (no/unknown, yes), and chemotherapy (no/unknown, yes)

[b]In age-adjusted Cox regression model, the *P* value in the interaction effect (quadrant×race) is statistically significant ($P_{interaction} = 0.0007$). In adjusted Cox regression model, the *P* value in the interaction effect (quadrant×race) is statistically non-significant ($P_{interaction} = 0.51$)

Table 3 Age-adjusted and multivariable-adjusted risk of breast cancer-specific mortality associated with Asian/PI by breast quadrants

	Total cases	Deaths from breast cancer	Person-years	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[a]
White	331,418	34,175	36,050,634	Reference	Reference
Chinese	6,605	577	717,597	0.84 (0.77–0.91)**	0.81 (0.75–0.88)**
Japanese	5,751	438	735,515	0.63 (0.57–0.69)**	0.68 (0.62–0.74)**
Filipino	9,080	885	931,541	1.00 (0.93–1.07)	0.88 (0.82–0.94)**
Korean	2,192	203	221,352	0.96 (0.84–1.10)	0.90 (0.79–1.04)
Vietnamese	1,984	189	191,974	1.02 (0.88–1.18)	0.91 (0.79–1.05)
South Asian	2,693	207	227,486	0.93 (0.81–1.07)	0.85 (0.74–0.97)*
Other Asian	4,418	252	395,461	0.66 (0.58–0.75)**	0.67 (0.59–0.76)**
PI	2,898	324	292,909	1.17 (1.05–1.30)**	1.05 (0.94–1.17)
$P_{heterogrnrity}$[b] < 0.0001					
Breast quadrants					
Nipple/central portion of breast					
White	28,541	3,810	3,154,746	Reference	Reference
Chinese	595	67	65,684	0.84 (0.66–1.07)	0.79 (0.62–1.01)
Japanese	567	59	75,119	0.66 (0.51–0.86)**	0.65 (0.50–0.84)**
Filipino	1,094	144	115,796	1.04 (0.88–1.23)	0.84 (0.71–0.99)*
Korean	181	24	21,051	0.95 (0.63–1.42)	0.87 (0.58–1.29)
Vietnamese	183	26	18,298	1.21 (0.82–1.78)	1.09 (0.74–1.61)
South Asian	235	32	20,666	1.26 (0.89–1.79)	1.17 (0.83–1.66)
Other Asian	411	30	38,452	0.63 (0.44–0.91)*	0.63 (0.44–0.91)*
PI	317	41	31,970	1.06 (0.78–1.45)	0.98 (0.72–1.34)
Inner quadrants[c]					
White	82,692	7,924	8,716,257	Reference	Reference
Chinese	1,852	134	192,775	0.75 (0.63–0.89)**	0.76 (0.64–0.91)**
Japanese	1,612	108	197,340	0.60 (0.50–0.73)**	0.66 (0.55–0.80)**
Filipino	2,523	242	250,473	1.07 (0.94–1.22)	0.89 (0.78–1.01)
Korean	600	38	58,394	0.70 (0.51–0.96)*	0.67 (0.49–0.93)*
Vietnamese	560	41	50,448	0.85 (0.63–1.16)	0.77 (0.56–1.04)
South Asian	730	52	60,014	0.94 (0.71–1.23)	0.85 (0.65–1.12)
Other Asian	1,297	70	114,142	0.66 (0.52–0.83)**	0.66 (0.52–0.84)**
PI	773	78	76,248	1.12 (0.90–1.40)	1.05 (0.84–1.31)
Outer quadrants[d]					
White	220,185	22,441	24,179,631	Reference	Reference
Chinese	4,158	376	459,138	0.88 (0.79–0.97)**	0.84 (0.75–0.93)**
Japanese	3,572	271	463,056	0.63 (0.56–0.71)**	0.69 (0.61–0.78)**
Filipino	5,463	499	565,272	0.96 (0.87–1.04)	0.88 (0.80–0.96)**
Korean	1,411	141	141,907	1.07 (0.91–1.27)	1.00 (0.85–1.18)
Vietnamese	1,241	122	123,228	1.05 (0.88–1.26)	0.94 (0.79–1.12)
South Asian	1,728	123	146,806	0.87 (0.73–1.04)	0.79 (0.66–0.94)**
Other Asian	2,710	152	242,867	0.66 (0.57–0.78)**	0.68 (0.58–0.79)**
PI	1,808	205	184,691	1.21 (1.05–1.38)**	1.07 (0.93–1.22)
				$P_{interaction}$[e] = 0.46	$P_{interaction}$[e] = 0.73

CI Confidence interval, HR Hazard ratio, PI Pacific Islander

* Statistical significance difference at P value ≤ 0.05

** Statistical significance difference at P value ≤ 0.01

[a] Hazard ratios were adjusted for age (20–39, 40–49, 50–59, 60–69, or 70–79 years) and year of the diagnosis (1990–1994, 1995–1999, 2000–2004, or 2005–2009, 2010–2014), histopathological features including tumor size (≤ 2 cm, 2–5 cm, > 5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated and undifferentiated, or unknown), and histological type (IDC,ILC or other histology), laterality of the tumor (right, or left), lymph node status (negative, positive, or unknown), estrogen receptor (ER) status (negative, positive, or

Table 3 (continued)

unknown), progesterone receptor (PR) status (negative, positive, or unknown), and treatments including surgery (no surgical treatment, breast-conserving surgery(BCS) alone, mastectomy, or unknown), radiation (no/unknown, yes), and chemotherapy (no/unknown, yes)

[b]Heterogeneity for the breast cancer-specific mortality across the Asian/PI subgroups

[c]Inner quadrants includes upper-inner quadrant and lower-inner quadrant

[d]Outer quadrants includes upper-outer quadrant, lower-outer quadrant and axillary tail of breast

[e]In age-adjusted Cox regression model, the P value in the interaction effect (quadrant×race) is statistically non-significant ($P_{interaction} = 0.46$). In adjusted Cox regression model, the P value in the interaction effect (quadrant×race) is statistically non-significant ($P_{interaction} = 0.73$)

1.13, 95% CI 1.10–1.17), upper-inner quadrant (HR: 1.20, 95% CI 1.17–1.23), lower-inner quadrant (HR: 1.28, 95% CI 1.24–1.33), and lower-outer quadrant (HR: 1.15, 95% CI 1.11–1.18) were all at increased risk of BCSM as compared to women with breast cancer in the upper-outer quadrant. No increased risk for BCSM was observed for breast cancer in the axillary tail of the breast as compared to breast cancer in the upper-outer quadrant (HR: 1.03, 95% CI 0.95–1.12). Analyses of breast quadrant yielded similar results for OS (data not shown).

Discussion

Tumor location in the breast has prognostic importance and is useful in the clinical setting. Tumors originating in the inner quadrant and nipple/central portion have poorer outcomes than the upper-outer quadrant of the breast [6, 11, 12, 24]. However, few studies have investigated racial differences in breast quadrants and whether this explains well documented racial/ethnic inequities in breast cancer survival as far as we know. We addressed this important gap of knowledge in a nationally representative, racially diverse cohort of women with breast cancer. Consistent with prior studies [18, 25], we observed that Black women exhibited the lowest BCSS and OS, and Asian women had the highest survival probabilities. This relationship was not modified by breast quadrants. Among Asian American women, Japanese and "other Asian" women had the highest BCSS, while Filipino had the lowest BCSS, which did not vary by breast quadrants. Our findings suggest that racial differences in breast cancer survival are not explained by breast quadrants.

A survival advantage for breast cancer has been well documented for Asian/PI women compared to White women [13, 14], with high survival rates for Japanese and Chinese women likely driving this advantage [15, 16]. We observed that Japanese and "other Asian" Americans had at least a 30% reduced risk of death, regardless of breast quadrants, than Whites. Studies suggest that Japanese women may exhibit a more vigorous host response to breast cancer which results in smaller tumor size, less aggressive cancer, and fewer lymph node metastases [26, 27]. However, the survival advantage remained even after adjusting for ER status, PR status, lymph node status,

stage, and intended primary treatment. Other sociodemographic and economic factors could contribute to the reduced risk observed among the Asian subpopulations. However, personal-level information on income, education, insurance status, and other indicators of wealth and health behaviors were not available among SEER patients. Conversely, previous studies have shown that Black women have a lower incidence of breast cancer [28], but are often diagnosed with breast cancer at more advanced stages [3, 28, 29] and have poorer survival rates after diagnosis than White women [3, 29–31]. We observed that Black women were more likely to have hormone receptor negative breast cancer subtypes when compared with all other races, of note, as this subtype is associated with poorer survival and prognosis due to lack of endocrine therapy [32, 33]. Furthermore, Iqbal et al. observed that Black women were significantly more likely to die within seven years of a breast cancer diagnosis than non-Hispanic White or Asian women [18]. In line with prior research, the current study revealed that Black women had at least 30% increased risk of BCSM and all-cause mortality compared to other racial and ethnic groups, regardless of breast quadrants.

A recent study reported a poorer BCSS (HR: 1.20, 95% CI 1.07–1.34) and OS (HR: 1.11, 95% CI 1.02–1.22) for tumors of the axillary tail (an extension of the upper-outer quadrant) compared with those of the upper-outer quadrant [17]. However, in our secondary analysis, no increased risk for BCSM and all-cause mortality was observed for breast cancer in the axillary tail of the breast as compared to upper-outer quadrant, likely due to the different participants and their different race/ethnicity distributions.

Our findings expand on the literature by investigating the association between tumor characteristics and racial/ethnic breast cancer survival disparities primarily through the analysis of breast quadrants among women of different races and also in Asian/PI Americans subpopulations. Previous studies have reported that inequalities in survival still persist after accounting for socioeconomic status [34], body mass index [35], hormone receptor [36], stage [37], access to care [38], treatments [39], and immigration among Asian subpopulations [40]. Our findings suggest that racial/ethnic survival differences are not accounted for by breast quadrants. Understanding the contributors

to racial disparities in breast cancer survival have implications for health policies and programs aimed at reducing cancer survival disparities for the most vulnerable populations.

Misclassification of race/ethnicity may impact our finding. However, previous analysis using SEER data has shown that misclassification is minimal for non-Hispanic Whites and Blacks, and moderate for Hispanics and Asians [41]. Asian subpopulations may be miss-specified by our methods if tumor biology differences exist across Asian subpopulation groupings [18]. Although misclassification of Asian subgroup status has been documented in the SEER [42], the lack of research on survival among these populations renders reporting of these subgroups a high priority. Since the breast quadrants were not specified by a single and dedicated physician, inconsistencies in classification of the breast quadrants may impact our results. Misclassification of breast quadrants may be most severe for the upper-outer quadrant and the axillary tail due to their continuity [17]. In addition, there is a lack of specific details on the type, dose and duration of chemotherapy, radiation therapy, and the use of hormonal therapy [43]. Further, data related to comorbidity and other health information are lacking [43], and comorbidity is an important factor for treatment received and cancer outcomes [44].

Our analysis is strengthened through the use of the large SEER population-based database, which covers approximately 34.6% of the U.S. population. Use of SEER limits the likelihood of selection bias and increases the likelihood of detecting statistically significant differences given the large sample size. Further, our study provides a more comprehensive examination of racial/ethnic differences, especially among Asian/PI Americans, in breast cancer outcomes than prior studies.

Conclusion

In conclusion, using the large and racially representative SEER database we were the first to examine breast quadrants by race and observed that the lower BCSS in Black women and the higher BCSS in Asian American women compared with White women were not attributed to breast quadrants. Among Asian American women, Japanese and "other Asian" group women had the greatest BCSS, and Filipino American women had the poorest survival, which was also not explained by breast quadrants. Further investigations in understanding the cultural, biological, and lifestyle factors that vary between White, African American, and specific subtypes of Asian American women may help explain these survival differences.

Data availability The datasets analyzed during the current study are available from the first author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

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