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Breast Cancer Outcomes in a Racially and Ethnically Diverse Cohort of Insured Women

Reina Haque, PhD[1]; Xiaoqing Xu, PhD[1]; Jiaxiao Shi, PhD [1]; Marilyn L. Kwan, PhD [2]; Rowan T. Chlebowski, MD, PhD[3]

Background: It is unknown how subsequent breast cancer outcomes vary by biologic subtype and race/ethnicity in a diverse cohort of breast cancer survivors.

Methods: We conducted a prospective cohort study of 6,154 insured breast cancer survivors (AJCC TNM stages 0–IV) diagnosed between 1996-2007 and followed them through 1/1/2010 for subsequent breast cancer events (recurrence, contralateral breast cancer, metastasis, mortality). We compared subsequent breast cancer rates by race/ethnicity groups and biologic subtype (luminal A, luminal B, HER2-enriched, and triple negative). We calculated hazard ratios (HRs) with 95% CIs using multivariable Cox proportional hazards models, adjusted for sociodemographics, cancer treatments, and tumor characteristics.

Results: The cohort was diverse: 62.4% non-Hispanic White, 13.2% Hispanic, 14.9% African American, and 9.5% Asian. We identified 1,456 subsequent breast cancer events over 22,830 person-years. Although certain Asian women had higher crude subsequent breast cancer rates compared with Whites, within each biologic subtype category, these disparities disappeared in the multivariable analyses. After accounting for race/ethnicity, compared with women with luminal A tumors (reference), women with luminal B (adjusted HR=3.65, 95% CI: 3.08-4.32), HER2-enriched (adjusted HR=2.81, 95% CI: 2.25-3.51) and triple negative (adjusted HR=1.25, 95% CI: 1.01-1.54) tumors had statistically increased risks of subsequent breast cancer. Factors that were statistically significantly associated with increased risk included higher stage, larger tumor size, positive lymph nodes, and no adjuvant endocrine or chemotherapy (all $P<.025$).

Discussion: Our data suggest that disparities in subsequent breast cancer outcomes were more strongly associated with tumor characteristics and non-use of adjuvant treatments than race/ethnicity. *Ethn Dis*. 2018;28(4):565-574; doi:10.18865/ed.28.4.565.

Keywords: Breast Cancer; Race/Ethnicity; Repeat Breast Cancer Risk

[1] Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

[2] Division of Research, Kaiser Permanente Northern California, Oakland, CA

[3] Department of Medical Oncology and Therapeutics Research, City of Hope National Medical Center, Duarte, CA

Address correspondence to Reina Haque, PhD, MPH; Kaiser Permanente Southern California Research & Evaluation; 100 S. Los Robles, 2nd Floor; Pasadena, CA 91101; 626.564.5707; Reina.Haque@kp.org

Introduction

Sparse data exist about breast cancer outcomes in minority women. Despite improvements in early detection and treatment strategies based on consideration of biologic subtype classifications of breast tumors, differences in breast cancer mortality persist when comparing African American and White patients,[1] and even fewer studies include Asian women. Current breast cancer therapy is based on breast cancer subtyping via tumor receptors for estrogen (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER2).[2-5] These subtypes include luminal A (ER+ and/or PR+, HER2-), luminal B (ER+ and/or PR+, HER2+), triple negative (ER-/PR-/HER2-) and HER2-enriched (HER2+/ER-/PR-).[4-6] Racial disparities in survival may be attributed to both biologic (eg, subtype, tumor characteristics, molecular abnormalities that accelerate progression) and non-biologic factors (eg, socioeconomic status, insurance coverage).[7-9]

Although recurrence risk by breast cancer subtypes has been examined, surprisingly few studies have included adequate numbers of minority women, particularly from Asian subgroups, precluding evaluation of potential racial/ethnic disparities by biologic subtypes. Previous studies that examined racial/ethnic disparities in breast cancer prognosis were limited by small numbers of breast cancer events,[10] or lacked comprehensive information on breast cancer therapy.[1,11] Several studies included breast cancer survivors with inad-

equate health insurance coverage, a major contributor to suboptimal care correlated with poor breast cancer outcomes. Thus, our goal was to examine the risk of subsequent breast cancer events (recurrence, new contralateral breast cancer, metastases development, or breast cancer death) in an insured group of diverse women to better understand the role of patient, treatment and clinical factors on breast cancer progression.

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Methods

Study Population and Setting

Our study was based in a large integrated health care delivery system, Kaiser Permanente Southern California, which serves 4.3 million members (approximately 25% of the southern California population) with equal access to health care. We identified 6,154 women diagnosed with their first breast cancer (American Joint Commission on Cancer TNM stages 0-IV classification) between January 1996 and December 2007. The cohort was followed through January 1, 2010. All subjects were identified through KPSC's Surveillance Epidemiology and End Results (SEER)-affiliated cancer registry.

Biologic Subtypes and Data Elements

Data elements were extracted from medical records review, cancer registry, electronic health records, and state and national mortality databases. Biologic subtype was determined by immunohistochemical (IHC) staining of ER and PR of formalin fixed paraffin embedded tumor tissue and HER2 status of the initial breast tumor; this information was extracted from pathology reports. These marker assays were completed at a single KPSC Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. These markers were classified into the four main biologic subtypes: luminal A [ER+ and/or PR+, HER2-]; luminal B [ER+ and/or PR+, HER2+]; triple negative [ER-/PR-/HER2-]; and HER2-enriched [HER2+/ER-/PR-]).[2-5]

Information on sociodemographics, tumor characteristics, primary cancer treatments (surgery type, radiotherapy, chemotherapy), and co-morbidity, were collected from electronic health records and cancer registry. Use of adjuvant endocrine therapy, tamoxifen and aromatase inhibitors was extracted from electronic pharmacy records. Date and cause of death were ascertained using KPSC membership records, and State of California and national Social Security Administration's mortality databases. Socioeconomic status (SES) information was based on California's 2000 census. Women were classified according to the median family household income of their census block at the time of diagnosis.

Study Outcome

Local or regional recurrence, development of metastasis, new contralateral breast cancer, and breast cancer-specific death (deaths attributed to the breast cancer) were combined into one composite outcome, subsequent breast cancer, based on whichever event occurred first. New second primary tumors (ipsilateral and contralateral breast) cancers were identified from the cancer registry, and included noninvasive or invasive cancers, and must have occurred at least six months after initial breast cancer surgery. Recurrences included lesions occurring in the ipsilateral breast at least six months after initial breast cancer surgery, with or without spread to regional areas (eg, nearby axillary lymph nodes), or distant metastasis. Recurrences were identified through manual review of all available pathology reports (two-thirds of the cohort), and by electronic health record review when pathology reports were unavailable.[12] Our hybrid approach of manually reviewing pathology text supplemented with an automated data algorithm applied to the electronic health record databases was validated (sensitivity 96.9%; specificity 92.4%).[12] We examined these outcomes as a composite because new second pri-

mary cancer in the contralateral breast (1.5% of outcomes) were rare.

Statistical Analysis

We initially examined the overall rates of subsequent breast cancer events stratified by race/ethnicity and biologic subtype. Demographic characteristics, tumor characteristics and treatment for the primary breast cancer were categorized and compared using chi-square or Fisher's exact tests, and a P<.05 (two-sided) was considered statistically significant. Follow-up commenced on the date of the primary breast cancer diagnosis and ended on the date of a subsequent breast cancer, date of death, termination of health plan membership, or study's end (January 1, 2010), whichever occurred first. Hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models with time-dependent primary treatment variables (adjuvant tamoxifen and/or aromatase inhibitors, radiation, and chemotherapy), and adjustment for covariates (age and stage at diagnosis; Charlson comorbidity index; geocoded income; histology; grade; lymph node status; surgery; number of healthcare visits during follow-up). We also conducted a sensitivity analysis excluding the few who developed a new second primary cancer in the contralateral breast (n=96 or 1.5%). The proportionality assumption was examined through both residual analysis and testing interactions between time and the main variables of subtype and race/ethnicity; we observed no deviations. All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, North Carolina).

Results

The cohort of 6,154 women with incident breast cancer with median age of 59 years (SD=12.9 years) was followed a maximum of 13 years

Table 1. Demographics characteristics at initial breast cancer diagnosis by race/ethnicity, N=6,154

	Non-Hispanic White		African American		Hispanic		Asian		Total	
	N=3,842		N=915		N=812		N=585		N=6,154	
	n	%	n	%	n	%	n	%	n	%
Age at diagnosis, years										
<40	174	4.53	69	7.54	80	9.85	39	6.67	362	5.88
40-49	579	15.07	198	21.64	226	27.83	124	21.20	1127	18.31
50-59	1067	27.77	250	27.32	240	29.56	182	31.11	1739	28.26
60-69	1044	27.17	236	25.79	171	21.06	163	27.86	1614	26.23
70-79	637	16.58	113	12.35	76	9.36	60	10.26	886	14.40
80+	341	8.88	49	5.36	19	2.34	17	2.91	426	6.92
Year of breast cancer diagnosis										
1996-1997	5	.13	1	.11	2	.25	2	.34	10	.20
1998-1999	142	3.70	23	2.51	27	3.33	25	4.27	217	3.50
2000-2001	422	10.98	67	7.32	75	9.24	50	8.55	614	10.00
2002-2003	755	19.65	193	21.09	174	21.43	121	20.68	1243	20.20
2004-2005	946	24.62	265	28.96	209	25.74	158	27.01	1578	25.60
2006-2007	1572	40.92	366	40.00	325	40.02	229	39.15	2492	40.50
Charlson Comorbidity Index [a]										
0	2738	71.26	596	65.14	620	76.35	428	73.16	4382	71.21
1 or 2	854	22.23	231	25.25	156	19.21	131	22.39	1372	22.29
≥3	250	6.51	88	9.62	36	4.43	26	4.44	400	6.50
Income group [b]										
Lower 25%	720	20.41	385	44.25	259	36.02	108	20.61	1472	26.10
>25-50%	857	24.30	222	25.52	195	27.12	118	22.52	1392	24.68
>50-75%	979	27.76	160	18.39	178	24.76	147	28.05	1464	25.96
Top 25%	971	27.53	103	11.84	87	12.1	151	28.82	1312	23.26
Unknown/Missing	315	-	45	-	93	-	61	-	514	-

a. One year prior to breast cancer diagnosis
b. Income group: lower 25%: <$37,738; >25%-50%: $37,739 - $50,417; >50%-75%: $50,418 - $66,250; Top 25%: >66,251

Table 2. Follow up, tumor and treatment characteristics at breast cancer diagnosis by race/ethnicity, N=6,154

	Non-Hispanic White		African American		Hispanic		Asian		Total	
	N=3,842		N=915		N=812		N=585		N=6,154	
	n	%[a]	n	%[a]	n	%[a]	n	%[a]	n	%[a]
Follow-up status										
End of study	2332	60.70	512	55.96	481	59.24	345	58.97	3670	59.64
Recurrence/metastasis	621	16.16	176	19.23	166	20.44	124	21.20	1087	17.66
Contralateral BC	56	1.46	20	2.19	13	1.60	7	1.20	96	1.56
Ipsilateral BC	11	.29	3	.33	1	.12	2	.34	17	.28
BC death	157	4.09	59	6.45	23	2.83	17	2.91	256	4.16
Other cause of death	192	5.00	43	4.70	13	1.60	18	3.08	266	4.32
Disenrolled	473	12.31	102	11.15	115	14.16	72	12.31	762	12.38
AJCC stage at diagnosis										
Stage 0	14	.37	4	.44	4	.50	7	1.22	29	.48
Stage I	1554	40.75	309	33.96	275	34.03	219	38.02	2357	38.59
Stage II	1609	42.00	413	45.38	382	47.28	270	46.88	2674	43.78
Stage III	510	13.37	136	14.95	118	14.6	63	10.94	827	13.54
Stage IV	127	3.33	48	5.28	29	3.59	17	2.95	221	3.62
Other/unknown/missing	28	-	5	-	4	-	9	-	46	-
Lymph node status										
Negative	2071	58.60	475	57.51	415	54.53	316	57.35	3277	57.78
Positive	1463	41.40	351	42.49	346	45.47	235	42.65	2395	42.22
Other/unknown/missing	308	-	89	-	51	-	34	-	482	-
Breast cancer subtype										
Luminal A	2443	63.59	387	42.30	450	55.42	331	56.58	3611	58.68
Luminal B	257	6.69	64	6.99	61	7.51	66	11.28	448	7.28
Triple negative	815	21.21	369	40.33	225	27.71	115	19.66	1524	24.76
HER2-enriched	327	8.51	95	10.38	76	9.36	73	12.48	571	9.28
Primary therapy [b]										
BCS with RT	1213	32.84	279	32.33	227	29.33	180	31.25	1899	32.21
BCS, no RT	772	20.9	228	26.42	154	19.90	92	15.97	1246	21.13
Mastectomy [c]	1709	46.26	356	41.25	393	50.78	293	50.87	2751	46.66
Other/unknown/missing	37	-	15	-	10	-	9	-	71	-
Chemotherapy										
No	1742	45.77	348	38.24	254	31.87	195	34.27	2539	41.75
Yes	2064	54.23	562	61.76	543	68.13	374	65.73	3543	58.25
Unknown/missing	36	-	5	-	15	-	16	-	72	-
Tamoxifen/AI use										
No	1340	34.88	497	54.32	339	41.75	215	36.75	2391	38.85
Yes	2502	65.12	418	45.68	473	58.25	370	63.25	3763	61.15
Histology/behavior										
DCIS	8	.21	2	.22	2	.25	2	.34	14	.23
LCIS	0	.00	0	.00	1	.12	0	.00	1	.02
IDC	2555	66.50	709	77.49	557	68.6	410	70.09	4231	68.75
ILC	249	6.48	30	3.28	41	5.05	20	3.42	340	5.52
Other/mixed	1030	26.81	174	19.02	211	25.99	153	26.15	1568	25.48

BC, breast cancer; BCS, breast conserving surgery; RT, radiation therapy; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; AI, aromatase inhibitor

a. Prevalence may not add up to 100% due to rounding; [b]Numbers do not add up to the total due to 3%-4% of the members receive the primary therapy outside Kaiser network; [c]with or without radiation therapy

(median 3.1 years [SD=2.3 years]). The cohort was diverse: 3,842 (62.4%) were non-Hispanic White, 812 (13.2%) were Hispanic, 915 (14.9%) were African American, and 585 (9.5%) were Asian (Table 1). Asian women, particularly South Asians, were diagnosed with breast cancer at younger ages compared with Whites and were more likely to be in higher socioeconomic status (SES) groups. African American women were more likely to be in the lower SES group. More than 70% of the cohort had no major comorbidity. More African American women (34.9%) had a Charlson comorbidity index >1 than White women (28.7%).

The distribution of tumor characteristics and cancer treatment by race/ethnicity are displayed in Table 2. Overall, luminal A breast cancer was the most common (58.7%), followed by triple negative cancer (24.8%), HER-2 enriched (9.3%) and luminal B (7.3%). Fractions of each subtype varied by race/ethnicity (P<.01). Triple-negative breast cancer was more common in African American women (40.3%) than in White women (21.2%). The fraction of luminal B was higher in South Asians (10.7%), Chinese (13.9%), and Other Asians (14.2%) compared with White women (6.7%). Filipina women (14.5%) and Other Asian (13.0%) women had the highest fractions of HER2-enriched disease. Nearly 83% of the cohort was diagnosed with early stage disease (AJCC TNM stages 0-II). Invasive histology was more common in African American, South Asian, and Other Asian women (P<.01). Minority women, particularly African Americans and Other Asians, had higher grade tumors. A higher proportion of minority women, in general, underwent chemotherapy (P<.01). Use of adjuvant tamoxifen or aromatase inhibitors was similar across all groups in women who were ER+ or PR+, except among African American women who were less likely to use this adjuvant therapy.

Subsequent Breast Cancer Events

In the cohort of 6,154 women, we identified 1,456 subsequent breast cancer events over 22,830 person-years total (median 3.1 years) (Table 2). Of the 1,456 subsequent breast cancer events, 1087 (74.6%) were recurrences, 96 (6.6%) were new contralateral breast tumors, 17 (1.2%) were second primary tumors (ipsilateral breast), and 256 (17.6%) were breast cancer deaths. A large fraction of the cohort survived through the end of study, N=3670 (59.6%). The median time to subsequent breast cancer was 22 months (interquartile range [IQR]: 13-38 months) in women with luminal A tumors; 13 months (IQR: 12-19 months) for luminal B; 16 months (IQR: 12-26 months) for triple negative; and 14 months for HER-2 enriched (IQR: 12-22 months). The median times to subsequent breast cancer events did not vary substantially by race/ethnicity (data not shown).

Figure 1 and Table 3 show the absolute subsequent breast cancer rates stratified by race/ethnicity and subtype. Overall, the absolute subsequent breast cancer rate was greatest among those with HER-2 enriched, followed by luminal B, triple-negative, and luminal A, respectively (Figure 1). In women with luminal A subtype, crude subsequent breast cancer rates were highest among African American (48/1,000 person-years, PY) and Chinese women (47/1,000 PY), respectively, vs Whites (34/1,000 PY). In women with luminal B tumors, minority groups had higher rates of subsequent breast cancer compared with Whites (147/1,000 PY): 192/1,000 PY for Hispanics, 191/1,000 PY for African Americans, and 172/1,000 PY for Asians. In women with triple negative tumors, the subsequent cancer rates were higher among Filipinas (103/1,000 PY), Japanese (154/1,000 PY) and African American women (89/1,000), than in Whites (68/1,000 PY) or Hispanics (70/1,000 PY). In contrast, in women with HER2-enriched subtype, Hispanics (212/1,000 PY) and Filipinas (236/1,000 PY) had higher subsequent breast cancer rates, while African American (140/1,000 PY) women had a lower rate than Whites (181/1,000 PY).

Although we observed disparities in crude person-year rates within each biologic subtype by race/ethnicity, these differences attenuated when examining the adjusted hazard ratios (HR) for each minority group as compared with Whites (Table 3). Interestingly, in women with HER2-enriched tumors, African Americans were 42% less likely (adjusted HR = .58, 95% CI: .41-.81) to develop subsequent breast cancer than Whites after adjusting for age at diagnosis, stage of diagnosis, geocoded median

Table 3. Hazard ratios for subsequent breast cancer stratified by stage and major breast cancer subtypes, N=6,154, diagnosed 1996-2007, followed through 2010

	Number of subsequent breast cancer	Person years of follow-up	Rate/1,000 person years	Overall HR	95% CI	Adjusted HR [a]	95% CI
Luminal A							
Whites	326	9,507	34	1.00	reference	1.00	reference
Hispanic	64	1,763	36	1.06	(.81, 1.38)	.84	(.64, 1.10)
African American	67	1,398	48	1.37	(1.05, 1.78)	1.10	(.84, 1.45)
Asian [b]	44	1,336	33	.97	(.71, 1.33)	1.01	(.73, 1.39)
South Asian	3	78	38	1.25	(.40, 3.90)	1.22	(.39, 3.83)
Filipina	22	625	35	1.05	(.68, 1.61)	1.08	(.70, 1.67)
Other Asian	11	345	32	0.93	(.51, 1.70)	.99	(.54, 1.82)
Chinese	7	149	47	1.28	(.61, 2.72)	1.27	(.59, 2.73)
Japanese	1	138	7	.22	(.03, 1.53)	.25	(.03, 1.77)
Luminal B							
Whites	122	828	147	1.00	reference	1.00	reference
Hispanic	34	177	192	1.28	(.87, 1.87)	1.18	(.80, 1.74)
African American	34	178	191	1.27	(.87, 1.86)	.96	(.64, 1.43)
Asian [b]	33	192	172	1.19	(.81, 1.75)	1.27	(.85, 1.88)
South Asian	3	4	774	3.90	(1.24, 12.27)	5.58	(1.74, 17.92)
Filipina	12	68	176	1.19	(.66, 2.16)	1.30	(.71, 2.39)
Other Asian	11	63	174	1.16	(.62, 2.14)	1.16	(.62, 2.17)
Chinese	4	49	82	.68	(.25, 1.83)	.64	(.24, 1.77)
Japanese	3	8	361	2.17	(.69, 6.84)	5.47	(1.70, 17.60)
Triple negative							
Whites	213	3,151	68	1.00	reference	1.00	reference
Hispanic	59	849	70	1.03	(.77, 1.37)	.94	(.70, 1.26)
African American	110	1,239	89	1.26	(1.00, 1.58)	1.05	(.82, 1.35)
Asian [b]	33	430	77	1.10	(.76, 1.59)	1.11	(.76, 1.61)
South Asian	1	24	42	.57	(.08, 4.07)	.57	(.08, 4.10)
Filipina	16	155	103	1.43	(.86, 2.38)	1.45	(.86, 2.44)
Other Asian	7	169	42	.64	(.30, 1.37)	.61	(.29, 1.31)
Chinese	3	45	67	.94	(.30, 2.93)	1.58	(.50, 4.98)
Japanese	6	39	154	2.00	(.89, 4.50)	1.76	(.77, 4.00)
HER2 enriched							
White	184	1,018	181	1.00	reference	1.00	reference
Hispanic	46	217	212	1.22	(.88, 1.68)	1.00	(.71, 1.40)
African American	47	336	140	.77	(.56, 1.07)	.58	(.41, 0.81)
Asian [b]	40	211	190	1.01	(.71, 1.42)	.79	(.56, 1.13)
South Asian	0	9	-	-	-	-	-
Filipina	21	89	236	1.19	(.76, 1.87)	1.09	(.69, 1.73)
Other Asian	13	62	209	1.10	(.63, 1.93)	.59	(.33, 1.06)
Chinese	3	26	114	.67	(.21, 2.10)	.57	(.18, 1.81)
Japanese	3	24	124	.73	(.23, 2.29)	.73	(.23, 2.31)

a. Adjusted for age at diagnosis, year of diagnosis, years since first breast cancer diagnosis, TAM/AI (binary time-dependent variable), lymph node status, stage at diagnosis, primary and adjuvant cancer therapy, tumor grade, histology, tumor size, medical center, and geocoded median household income, Charlson Comorbidity Index, number of health care visits during follow-up.
b. HRs for all the Asian subgroups combined were based on separate models

household income, years since breast cancer diagnosis, lymph node status, primary cancer therapy and time-dependent adjuvant therapy (radiation, chemo, endocrine), tumor characteristics, hospital location, number of health care visits during follow-up, and the Charlson Comorbidity Index. As a combined group, Asian women with the luminal B subtype (HR=1.27, 95% CI: .85-1.88) were more likely to develop subsequent

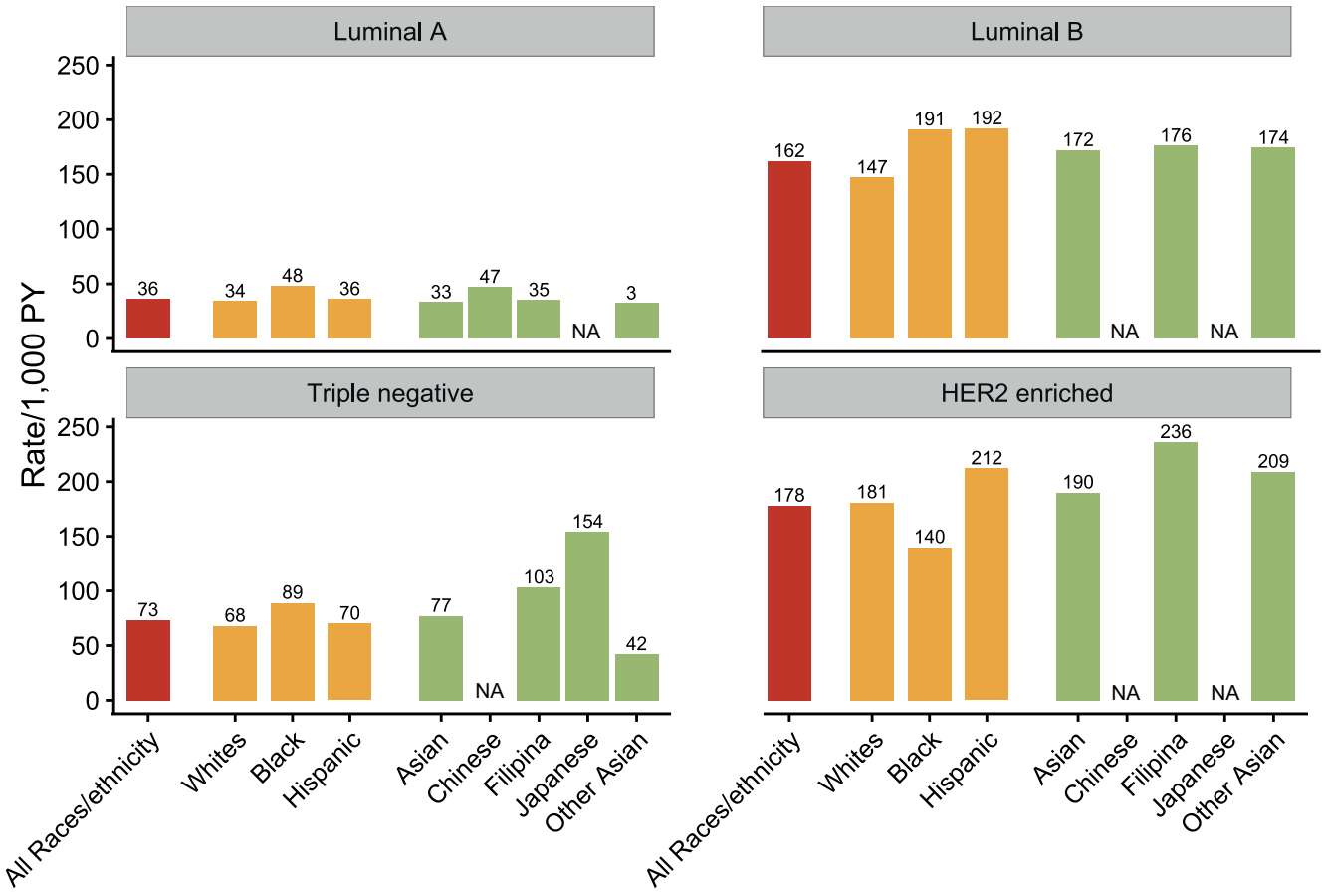

Figure 1. Rates of subsequent breast cancer by race/ethnicity; PY, person years

breast cancer while Asian women with HER2-enriched tumors (HR=.79, 95% CI: .56-1.13) were less likely to develop subsequent breast cancer versus Whites, but the confidence intervals included the null. There was a suggestion of an increased risk of subsequent breast cancer among South Asians (HR=5.58, 95% CI: 1.74-17.92) and Japanese (HR=5.47, 95% CI: 1.70-17.60) with luminal B tumors vs Whites, but these results were based on very small numbers. We found no increased risks in other subgroups of Asian women, possibly due to the small number of events.

In the sensitivity analysis in which we excluded few women who developed a new second primary in the contralateral breast (N=96 out of 1,456 SBC events or 1.5%), the HRs remained the same (data not shown).

Table 4 displays the independent association of tumor characteristics (biologic subtype, stage, grade, lymph nodes), race/ethnicity, primary cancer treatments, and adjuvant therapy with the risk of subsequent breast cancer. In terms of adjusted relative risks, the risk of subsequent breast cancer was 3.65 times greater (adjusted HR=3.65, 95% CI: 3.08-4.32) in women with luminal B tumors as compared with luminal A (reference group) after accounting for sociodemographics, tumor characteristics, cancer treatments, and comorbidity. Women with HER-2 enriched tumors had a risk 2.81 times greater (adjusted HR=2.81, 95% CI: 2.25-3.51) than with luminal A tumors. Women with triple-negative tumors had a risk 1.25 times greater (adjusted HR=1.25, 95% CI: 1.01-1.54) than with luminal A tumors. Consistent with the lack of racial/ethnic disparities within each biologic subtype group implied in Table 3, the risk of subsequent breast

Table 4. Hazard ratios for subsequent breast cancer stratified by key predictive factors, N=6,154, diagnosed 1996-2007, followed through 2010

	Adjusted HR [a]	95% CI
Biologic subtypes		
Luminal A	1.00	reference
Luminal B	3.65	(3.08, 4.32)
Triple negative	1.25	(1.01, 1.54)
HER2 enriched	2.81	(2.25, 3.51)
Race/ethnicity		
Whites	1.00	reference
Hispanic	.95	(.81, 1.12)
African American	.93	(.79, 1.09)
Asian	1.01	(.85, 1.21)
South Asian	1.32	(.62, 2.79)
Filipina	1.20	(.93, 1.54)
Other Asian	.80	(.58, 1.10)
Chinese	.90	(.55, 1.48)
Japanese	1.09	(.63, 1.91)
Primary therapy		
BCS with RT	1.00	reference
BCS, No RT	1.21	(1.01, 1.44)
Mastectomy [b]	1.16	(.83, 1.35)
Chemotherapy		
Yes	1.00	reference
No	.86	(.74, 1.00)
AJCC stage at diagnosis		
Stage 0	1.00	reference
Stage I	3.53	(.48, 25.64)
Stage II	4.85	(.66, 35.71)
Stage III	8.00	(1.09, 58.82)
Stage IV	20.83	(2.82, 142.85)
Lymph node status		
Positive	1.00	reference
Negative	.70	(.60, .81)
Tamoxifen/AI use [c]		
No	1.00	reference
Yes	.73	(.60, .87)

BCS: breast conserving surgery; RT: radiation therapy; AI: aromatase inhibitor.
a. Model included all variables listed in table plus age at diagnosis, year of diagnosis, years since first breast cancer diagnosis, histology, tumor size, medical center, geocoded median household income, Charlson index, number of healthcare visits during follow-up.
b. With or without radiation therapy.
c. AI/Tamoxifen use and chemotherapy were treated as time-dependent variables.

cancer was comparable in each race/ethnic group after adjusting for biologic subtype, tumor characteristics, and cancer treatments. Of note, factors that were statistically significantly associated with increased risk of subsequent breast cancer included luminal B, HER2-enriched, or triple negative subtype, higher tumor grade, larger tumor size, positive lymph nodes, and non-use of adjuvant treatments (chemotherapy or endocrine treatments) (all P <.025 from the aforementioned multivariable model, Table 4).

Discussion

In this diverse cohort of insured breast cancer survivors, we found that crude risk of subsequent breast cancer was greater in some racial/ethnic groups compared with White women. For example, in women with triple negative tumors, Filipina, Japanese and Hispanic women had the highest rates of subsequent breast cancer as compared with Whites. Similarly, in women with luminal B tumors, African American and Hispanic had higher rates of subsequent breast cancer than Whites. However, within each biologic subtype, the racial/ethnic differences in developing subsequent breast cancer disappeared after multivariable adjustment for tumor characteristics, primary and adjuvant cancer treatments, and sociodemographics. Interestingly, we found a statistically significant 42% lower risk of subsequent breast cancer events in African American women with HER2-enriched tumors as compared with White women with HER2-enriched tumors. This reduced risk may reflect differences in reproductive risk factors or lifestyle factors that we could not assess. Our combined results suggest that biologic subtype, tumor characteristics at diagnosis, and cancer treatments play a greater role in predicting breast cancer outcomes, rather than race/ethnicity, at least in this managed care population in which bias due to variable medical coverage was reduced. Although prior reports suggest that women with triple negative breast cancer have worse outcomes,[2,8] the risk of subsequent breast cancer was even greater in women

with luminal B and HER2-enriched tumors vs luminal A tumors.

Our finding of a greater risk of subsequent breast cancer in women with luminal B tumors compared with luminal A tumors is consistent with a previous report of a higher recurrence score (as defined by gene predictor of distant relapse).[5] The lower risk of subsequent breast cancer events in ER-negative tumors (ie, triple negative and HER2-enriched), may reflect that these two biologic subtypes respond better to chemotherapy, as compared with luminal B tumors.[13]

Our study has several strengths. The cohort was diverse and of the 6,154 women, 37% were from minority backgrounds, thus enhancing generalizability of our study. Importantly, given that all women were insured, this decreased the bias that stemmed from variable medical coverage often correlated with poor outcomes. Also, due to the comprehensive data from the electronic health records, we examined risks accounting for a broad set of key potential confounders, including number of health care visits during the follow-up which includes breast cancer surveillance. Further, we examined chemotherapy and endocrine therapy captured from electronic pharmacy dispensing records as time-dependent variables ensuring that women were exposed to the treatment, and the treatment effect estimates were valid. Moreover, we identified the majority of recurrences using medical chart review supplemented by information from the cancer registry or a validated computerized algorithm applied to the electronic health record.[12]

However, certain limitations must be considered. We were not able to further adjust for birth place of the patients; birth place may influence subsequent breast cancer risk due to early life environmental exposures and behaviors related to residency.[14] Although the median follow-up of 3.1 years suggests the findings are most reliable for subsequent breast cancer events that occur close to diagnosis, our study nonetheless had 22,830 person-years of follow-up. Although we examined IHC markers (ER and PR status), the use of IHC is more common in community hospitals, and prior studies have demonstrated the high concordance between IHC and gene expression profiles to approximate biologic subtype leading to the classification into luminal A and B, HER-2 enriched and triple negative.[15-17] Further, adjuvant therapies have changed over time since the end of the study; however, oral tamoxifen and aromatase inhibitors remain the cornerstone treatment for women with ER+ and/or PR+ (Luminal A and B) tumors, and we considered those medications in our analysis. Nonetheless, our results may not apply to women treated with newer chemotherapies.

Our combined results suggest that biologic subtype, tumor characteristics at diagnosis, and cancer treatments play a greater role in predicting breast cancer outcomes, rather than race/ethnicity…

Conclusions

We determined that biologic subtype, worse tumor characteristics, and lack of adjuvant endocrine or chemotherapy are more strongly correlated with the risk of subsequent breast cancer than women's race/ethnicity in a cohort of insured women. Women with luminal B tumors were more than three times likely to develop subsequent breast cancer events vs those with luminal A tumors. Women with HER2-enriched tumors were more than two times likely to develop subsequent breast cancer events, while women with triple negative tumors were 25% more likely, as compared with women with luminal A tumors. Further, within each biologic subtype, the racial/ethnic disparities in the adjusted risk of subsequent breast cancer attenuated in the multivariable models. Our results suggest that recommending appropriate (and reducing health care barriers to) adjuvant endocrine and chemotherapy based on the tumor's biologic characteristics could dramatically reduce any apparent disparities in breast cancer outcomes.

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This study was approved by the KPSC institutional review board, which waived written and verbal informed consent. All pro-

cedures followed were in accordance with the ethical standards of the IRB and the Helsinki Declaration of 1975, as revised in 2000.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Haque, Xu, Shi, Kwan; Acquisition of data: Haque, Shi; Data analysis and interpretation: Haque, Xu, Shi, Kwan, Chlebowski; Manuscript draft: Haque, Xu, Shi, Kwan, Chlebowski; Statistical expertise: Haque, Xu, Shi, Kwan, Chlebowski; Acquisition of funding: Haque; Administrative: Haque, Shi, Kwan, Chlebowski; Supervision: Haque

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