Published in final edited form as:

Cancer Causes Control. 2014 August ; 25(8): 959–968. doi:10.1007/s10552-014-0395-1.

Racial/ethnic differences in breast cancer survival by inflammatory histology and hormonal receptor status: An analysis of the Surveillance, Epidemiology, and End Results data

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Abstract

Background—Compared to non-inflammatory breast cancer (non-IBC), inflammatory breast cancer (IBC) has less favorable survival and is more likely to be estrogen receptor (ER) and progesterone receptor (PR) negative. ER+/PR+ tumors, regardless of histology, have less favorable survival. While black women are more likely to have IBC and ER+/PR+ tumors than white women, it is unclear whether the racial disparity in survival is explained by these factors. The objective of this study was to assess racial/ethnic differences in breast cancer survival by inflammatory histology and hormone receptor status.

Methods—This study examined breast cancer mortality among non-Hispanic white (NHW), Hispanic white (HW), black, and Asian/Pacific Islander (API) women diagnosed between 1990 and 2004. Kaplan-Meier survival curves and Cox proportional hazard ratios (HRs) assessed the relationship between race/ethnicity and survival.

Results—Black women had significantly poorer survival than NHW women regardless of inflammatory histology and hormone receptor status. Compared to NHWs, the HRs for black women were 1.32 (95% CI 1.21–1.44), 1.43 (95% CI 1.20–1.69) and 1.30 (95% CI 1.16–1.47) for IBC, IBC with ER+/PR+, and with ER–/PR–, respectively. Similar HRs were found for non-IBC, non-IBC with ER+/PR=, and non-IBC with ER–/PR–. API women had significantly better survival than NHW women regardless of inflammatory histology and hormone receptor status.

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Conflicts of interest: The authors declare that they have no conflict of interest.

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Conclusion—Compared to NHW women, black women had poorer survival regardless of inflammatory status and hormone receptor status and API women had better survival. These results suggest that factors other than histology and hormone receptor status may play a role in racial/ethnic disparities in breast cancer survival.

Keywords

Breast cancer; Hormone receptor; Inflammatory; Race; SEER; Survival

Background

It is well known that black patients have significantly shorter survival from breast cancer compared to white patients (1). Part of the racial disparity may be related to racial differences in inflammatory histology and hormone-receptor status of the disease. Inflammatory breast cancer (IBC) is an uncommon type of breast cancer that is notably more aggressive and has less favorable survival outcomes compared to non-inflammatory breast cancer (non-IBC). Patients with IBC have a 43% higher rate of death than those with non-IBC after adjusting for factors related to prognosis (2). While it is known that overall breast cancer mortality rates for black women are 39% greater than that for white women (1), studies showed that black women are more likely to be diagnosed with IBC compared to white women (3). Nevertheless, within IBC, black women had a shorter median survival time (20 months) than their white counterparts (32 months) (3, 4).

Hormone receptor status (estrogen receptor, ER, and progesterone receptor, PR) is well known to be an independent predictor of breast cancer survival (5–9): breast cancer patients with hormone receptor negative tumors have increased mortality and shorter survival compared to those with hormone receptor positive tumors. It is well known that black women are nearly twice as likely to have ER and PR negative tumors compared to white women (5, 10–12). While the higher rates of hormone receptor negative tumors among black women may account for some of the black-white disparity in survival (5), other factors must also be important because this disparity persists after accounting for hormone receptor status (13).

Inflammatory histology and hormone receptor status of breast cancer may be related. IBC patients are more likely to have ER/PR negative tumors (11, 14). In addition, IBC survival may be worse if tumors are also hormone-receptor negative (14). Because black patients are more likely to have both IBC and ER+/PR+ tumors than white patients, it would be important to know whether the black/white difference in IBC survival is explained at least partially by more ER+/PR+ tumors among blacks and whether the black/white disparity in IBC survival is greater among patients with tumors that are also ER- and PR-. To the best of our knowledge, there have been no studies that have assessed black/white differences in breast cancer survival by both inflammatory histology and hormone receptor status of the disease. Furthermore, no other racial/ethnic groups have been compared with non-Hispanic whites for breast cancer survival by both histology and hormone receptor status. The objective of this study was to assess if blacks, non-Hispanic whites (NHWs), Hispanic whites (HWs) and Asian/Pacific Islanders (APIs) differ in breast cancer survival by both

inflammatory histology and hormone receptor status using the National Cancer Institute's Surveillance Epidemiology, and End Results (SEER) data.

Methods

Data source and study subjects

This study was based on the National Cancer Institute's SEER database for public use that consists of eighteen population-based registries (SEER-18, November 2011 Submission) (15). The SEER program has collected cancer registry data since 1973 and had data available through 2009 at the time of this study. The eighteen registries included San Francisco-Oakland (1973–2009), Connecticut (1973–2009), Metropolitan Detroit (1973–2009), Hawaii (1973–2009), Iowa (1973–2009), New Mexico (1973–2009), Seattle-Puget Sound (1974–2009), Utah (1973–2009), Metropolitan Atlanta (1975–2009), San Jose-Monterey (1992–2009), Los Angeles (1992–2009), rural Georgia (1992–2009), greater California-excluding San Francisco Los Angeles & San Jose (2000–2009), Kentucky (2000–2009), Louisiana (2000–2009, except July – December 2005), New Jersey (2000–2009), greater Georgia-excluding Atlanta and Rural Georgia (2000–2009), and Alaska (1992–2009) (15), which represent approximately 28% of the United States population (16). Since the Alaska Native Registry only collects data on American Indian and Alaska Native populations, it was excluded from the study.

The subjects of this study were women aged 18 or older who were histologically diagnosed with breast cancer. Data on ER and PR became available in 1990; therefore, only patients diagnosed from 1990 to 2009 were included. Racial/ethnic groups included in the study were NHWs, HWs, blacks, and APIs. All black and API women were eligible for inclusion regardless of ethnicity. Other races were excluded due to insufficient sample size. As IBC is always diagnosed at least as stage IIIB breast cancer due to involvement of the dermal lymphatics (17), only women with American Joint Committee on Cancer (AJCC) stages IIIB, IIIC or IV were included.

Study variables

The study subjects were classified by whether their cancer was inflammatory or non-inflammatory, as well as by hormone receptor status. IBC cases were defined using the comprehensive case definition which includes: histologic type ICD-O-3 equaling to '8530' (18), historic extent of disease equaling to 70 for years 1990 to 2003, or derived AJCC extent of the tumor (T, 6th edition) equaling to 'T4d' and collaborative staging extension being between 71 and 73 for years 2004 and later (19–21). Hormone receptors included ER and PR. The positive and negative states of ER or PR were determined by tumor specimen assay results prior to receipt of neoadjuvant systemic therapy (if available) or after systemic treatment (otherwise). If any sample was recorded as receptor positive, then the receptor was documented as positive (22). Based on the states of ER and PR, there were three mutually exclusive hormone receptor groups. Tumors that were positive for both estrogen and progesterone receptors were categorized as hormone receptor positive (ER+/PR+), and tumors that were negative for both receptors were grouped as hormone receptor negative (ER-/PR-). If estrogen or progesterone receptor states did not coincide, hormonal status

was defined as being mixed (ER+/PR- or ER-/PR+). Cases not belonging to any of the three ER/PR groups were excluded from the analysis.

Vital status was determined as of December 31, 2009. Cause of death was obtained from the SEER cause-specific death classification, which is supplied by cancer registries based on the underlying cause of death from death certificates. The outcome for this study was death of breast cancer. Women who died of causes other than breast cancer were censored.

Statistical Analyses

We first described the distribution of demographic, pathologic, and tumor characteristics by race/ethnicity and inflammatory status. We then conducted survival analysis. Breast cancer-specific survival time in years was defined as time from diagnosis date until death date, last contact date, or study cutoff date (December 31, 2009) if still alive.

We used the Kaplan-Meier method to estimate breast cancer-specific survival time by race/ethnicity and the log-rank statistic to evaluate if there were statistical differences between racial/ethnic groups within each subgroup defined by inflammatory status or/and hormone receptor status.

For each of the subgroups stratified by inflammatory status or/and hormone receptor status, the Cox proportional hazard regression analysis was used to assess racial/ethnic differences while adjusting for potential confounders including age at diagnosis, marital status, stage, grade, surgery, and radiation. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. To evaluate if racial/ethnic differences might vary by menopausal status of the patients, we further conducted Cox analysis stratified by age (<50 vs. ≥50 years, a surrogate of menopausal status). The assumptions of the proportional hazards model were confirmed by visual assessment of the residuals. A two-sided p-value of 0.05 was used to determine statistical significance. SAS 9.3 (SAS Institute, Inc., Cary, NC) was utilized for all analyses.

Results

The study subjects were 30,258 NHW, 6,448 black, 4,183 HW, and 2,691 API female breast cancer patients, including 7,748 (18%) diagnosed with IBC and 35,832 (82%) with non-IBC (Table 1). For both IBC and non-IBC, HWs, APIs, and blacks tended to be younger compared to NHWs. Compared to other racial/ethnic groups, black patients were less likely to be married, undergo surgery and radiation treatment for both IBC and non-IBC. Inflammatory breast tumors were more likely to be ER+/PR+ for all racial/ethnic groups. Despite inflammatory status, blacks were more likely to have ER+/PR+ tumors than women in the other racial/ethnic groups. NHWs tended to be less likely to have stage IV IBC or grade III/IV non-IBC than minority groups.

The log-rank statistic showed that there were racial/ethnic differences for each of the Kaplan-Meier curves by hormone receptor and inflammatory status (see Figures 1–2). Specifically, for all of the subgroup comparisons, black women tended to have shorter survival than women in other racial/ethnic groups despite inflammatory status or hormone

receptor status. A similar racial difference was observed when data were stratified by both inflammatory status and hormone receptor status (data not shown). API women tended to have the longest survival, except for IBC as a whole or IBC with ER/PR both being negative or positive.

Table 2 shows the HRs of minority groups compared to NHWs adjusted for potential confounders. Blacks tended to have significantly increased hazard compared to NHWs despite inflammatory histology or/and hormone receptor status. The adjusted HRs were 1.32 (95% CI 1.21–1.44), 1.43 (95% CI 1.20–1.69), and 1.30 (95% CI 1.16–1.47) for IBC, IBC with ER+/PR+, and IBC with ER+/PR+, respectively. The HRs were similar for non-IBC, non-IBC with ER+/PR+, and non-IBC with ER+/PR+. When ER/PR states were mixed, the results remain similar (data not shown). API women tended to have a lower hazard than NHWs for all ER/PR states and most combinations of ER/PR and inflammatory states. While the HRs tended to be slightly lower than one for HWs compared to NHWs, the differences were never statistically significant.

Table 3 shows the adjusted HRs stratified by age at diagnosis. The results among patients aged 50 or older were similar to those in Table 2 except that the HR became no longer significant for APIs with IBC as a whole. Among patients aged younger than 50 years, the HRs for blacks compared to NHWs were higher than the corresponding estimates in the older group for ER+/PR+ or non-IBC with ER+/PR+. The same tendency was observed for non-IBC, and IBC with ER+/PR+. For APIs, the HRs were no longer significantly lower in the younger group. The HRs for younger HWs compared to NHWs were similar to those from the older group. Racial differences in the strata with mixed ER/PR states tended to be similar (data not shown).

Discussion

Black women had significantly worse survival compared to NHW women regardless of inflammatory status, hormone receptor status, and age group in our study of stage III and IV breast cancer. Conversely, API women tended to have the better breast cancer survival compared to NHW women, despite inflammatory histology or ER/PR status. The better survival among API women was observed for most groups defined by a combination of inflammatory and ER/PR states. HW and NHW women tended to have similar survival regardless of inflammatory and ER/PR states. In general, we found that racial/ethnic differences in breast cancer survival might be similar despite inflammatory histology and hormone receptor status.

Racial/ethnic differences in survival may relate to various factors such as accessibility to medical care, use of medical care, and tumor pathologic and biological features. Our study found similar racial/ethnic differences regardless of tumor characteristics (hormone receptor status and inflammatory histology). This is consistent with some previous studies, which also suggested similar racial/ethnic difference for breast cancer with various pathologic features (23, 24). These research results imply that factors other than these tumor features may play a large role in racial/ethnic disparities in breast cancer survival.

Use of medical care may be a major factor explaining the identified racial/ethnic disparities. It has been documented that, on average, blacks have a lower level of access to health care compared to whites (25). Therefore, they are less likely to have timely diagnosis and treatment, receive standard treatment, and complete follow-up surveillance and care than white patients (26–29). It is also well demonstrated that black patients were more likely to present with clinically-detected cancers rather than screen-detected cancer, and have delayed diagnoses compared to white patients (26). Many, but not all (30–32), studies found that black patients are more likely to have delayed treatment (26, 29, 33, 34) and are less likely to receive definitive primary therapy and adjuvant chemotherapy (34–38), hormonal therapy (30), radiation after lumpectomy (29, 39, 40) or mastectomy (41) than their white counterparts. While research on racial disparity in follow-up care has been sparse, it has been suggested that black patients may receive less medical monitoring or follow-up care (28). As a result of the racial disparities in diagnosis, treatment, and follow-up care, black patients may have worse survival than whites across different breast cancer types including inflammatory histology and ER/PR status. Our study also showed that the racial difference in survival appeared larger for patients younger than 50 years than those older among the patients with ER+/PR+. A similar result was observed previously in a study that suggested that Medicare availability for older women might help reduce racial differences in cancer care (42).

We do not exclude the possibility that biological features other than inflammatory histology and hormone receptor status may be related to the racial/ethnic differences in survival. For example, black patients may be more likely to have tumors with negative status of human epidermal growth factor-like receptor 2 (HER2) (43, 44) or *P53* mutation (45), which are related to survival (43, 46–48). Although inconsistent (43, 47, 48), some studies on triple negative breast cancer, which included HER2- in addition to ER+/PR+, have found no racial differences in survival (49–51), suggesting a minimal potential impact of HER2 on racial differences. Therefore, there is a possibility that biomarkers of breast cancer other than inflammatory histology and ER/PR status may be associated with racial/ethnic disparities in survival in addition to the access to and use of medical care. Our finding of better survival among API women than whites is consistent with previous studies (52, 53). Similar to our study, an earlier SEER-based study found that, after adjusting for potential confounding variables, Asians experience significantly better survival compared to NHWs regardless of ER/PR status (13). It is largely unclear what factors may account for the survival differences between APIs and other racial/ethnic groups because data on Asians have been limited and research results have been inconsistent. Some studies have shown that Asian women were more likely to adhere to adjuvant hormonal therapy (54) or have follow-up mammography (55) than white women. However, other studies found no differences between Asian and white women in the receipt of adjuvant radiation treatment after breast conserving surgery (BCS) (56) but Asian women were less likely to undergo BCS than whites (57). Therefore, research is warranted on the role of medical care and other factors on survival differences between Asians and other racial/ethnic groups.

While the large dataset from the SEER registries makes it possible to assess racial/ethnic differences in survival by both inflammatory histology and ER/PR status, the limitations of this study should be kept in mind. The study was based on the existing data from the cancer

registries; therefore, the effects of confounding factors that are not contained in the dataset cannot be excluded. For example, information on cancer treatment is not complete and detailed in the SEER data, precluding us from having solid assessment of and control for its potential effects on the results. Lack of individual-level information on socioeconomic status, which is related to breast cancer survival and correlated with racial/ethnic background (58), prevented us from controlling for its impacts in the analyses. This analysis was limited to cancer stages III and IV based on the definition of IBC. Thus, the results on ER/PR reflect only those for these tumor stages rather than all stages including stages I and II.

In conclusion, our study found that racial/ethnic disparities in breast cancer survival persist despite inflammatory histology and hormone receptor status. These results imply that factors other than inflammatory histology and hormone receptor status, such as access to or use of medical care, and/or other biomarkers, may play a role in racial/ethnic disparities in breast cancer survival.

Acknowledgments

This project was supported by John P. Murtha Cancer Center, Walter Reed National Military Medical Center via the Uniformed Services University of the Health Sciences under the auspices of the Henry M. Jackson Foundation for the Advancement of Military Medicine.

The authors thank Dr. Lindsey Enewold at the National Cancer Institute for her comments on the manuscript. This project was supported by John P. Murtha Cancer Center, Walter Reed National Military Medical Center via the Uniformed Services University of the Health Sciences under the auspices of the Henry M. Jackson Foundation for the Advancement of Military Medicine.

Abbreviations

IBC	Inflammatory breast cancer
ER	Estrogen receptor
PR	progesterone receptor
NHW	non-Hispanic white
HW	Hispanic white
API	Asian/Pacific Islander
SEER	Surveillance Epidemiology, and End Results
HR	hazard ratios
CI	confidence intervals

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Figure 1.
Kaplan-Meier survival curves by race/ethnicity for non-inflammatory and inflammatory breast cancers, SEER 18, 1990–2009.

Figure 2. Kaplan-Meier survival curves by race/ethnicity for ER+/PR+ or ER-/PR- hormone receptor states, SEER 18, 1990–2009.

Characteristic	Non-inflammatory breast cancer								Inflammatory breast cancer							
	NH White	No. of patients %	Black	No. of patients %	Hispanic White	No. of patients %	API	No. of patients %	NH White	No. of patients %	Black	No. of patients %	Hispanic White	No. of patients %	API	No. of patients %
No	13,242	53.1%	2,936	55.5%	1,768	53.4%	1,140	49.4%	2,155	40.4%	565	48.7%	392	44.9%	166	43.5%
Unknown	772	3.1%	183	3.5%	105	3.2%	61	2.6%	219	4.1%	48	4.1%	48	5.5%	16	4.2%
Hormone receptor status																
ER and PR+	14,270	57.2%	2,234	42.2%	1,753	53.0%	1,213	52.5%	2,101	39.4%	341	29.4%	322	36.8%	140	36.6%
ER and PR–	6,207	24.9%	2,105	39.8%	1,001	30.3%	702	30.4%	2,284	42.8%	609	52.5%	389	44.5%	181	47.4%
ER+/PR– or ER–/PR+	4,449	17.8%	949	17.9%	555	16.8%	394	17.1%	947	17.8%	210	18.1%	163	18.6%	61	16.0%

NH=Non-Hispanic, API=Asian/Pacific Islander

Cox proportional hazard ratios by inflammatory status and ER/PR states among breast cancer patients, SEER 18, 1990–2009

Table 2

Strata	Race	No. of patients	No. of deaths	Adjusted HR ^a	95% Confidence intervals	
1. Non-IBC						
2. IBC	NH White	24,926	11,510	1.00	Reference	
	Black	5,288	2,716	1.21	1.16	1.27
	Hispanic White	3,309	1,313	0.97	0.92	1.03
	API	2,309	873	0.87	0.81	0.93
3. ER+/PR+	NH White	5,332	2,623	1.00	Reference	
	Black	1,160	684	1.32	1.21	1.44
	Hispanic White	874	404	0.99	0.89	1.11
	API	382	171	0.84	0.72	0.98
4. ER-/PR-	NH White	16,371	6,638	1.00	Reference	
	Black	2,575	1,193	1.32	1.24	1.41
	Hispanic White	2,075	717	0.98	0.91	1.06
	API	1,353	432	0.88	0.79	0.97
5. Non-IBC and ER+/PR+	NH White	8,491	4,757	1.00	Reference	
	Black	2,714	1,591	1.17	1.11	1.24
	Hispanic White	1,390	688	0.97	0.90	1.06
	API	883	413	0.85	0.77	0.94
6. IBC and ER+/PR+	NH White	14,270	5,807	1.00	Reference	
	Black	2,234	1,023	1.32	1.23	1.41
	Hispanic White	1,753	595	0.97	0.89	1.06
	API	1,213	372	0.84	0.76	0.94
	NH White	2,101	831	1.00	Reference	
	Black	341	170	1.43	1.20	1.69

Strata	Race	No. of patients	No. of deaths	Adjusted HR ^a	95% Confidence intervals
7. Non-IBC and ER-/PR-	Hispanic White	322	122	1.07	0.88 1.30
	API	140	60	1.24	0.95 1.61
	NH White	6,207	3,445	1.00	Reference
	Black	2,105	1,197	1.14	1.07 1.23
8. IBC and ER-/PR-	Hispanic White	1,001	481	0.98	0.89 1.08
	API	702	320	0.87	0.77 0.97
	NH White	2,284	1,312	1.00	Reference
	Black	609	394	1.30	1.16 1.47
	Hispanic White	389	207	0.96	0.83 1.12
	API	181	93	0.82	0.66 1.01

^aHR Hazard ratio, adjusted for: age at diagnosis, marital status, stage, grade, surgery, radiation, ER/PR status, and IBC status. The stratified variables were not included in stratified models.

IBC=Inflammatory breast cancer, NH=Non-Hispanic, API=Asian/Pacific Islander

Table 3

Cox proportional hazard ratios by inflammatory status, ER/PR states, and age at diagnosis among breast cancer patients, SEER 18, 1990–2009

Age at diagnosis < 50										Age at diagnosis ≥ 50	
Strata	Race	No. of patients	No. of deaths	Adjusted HR ^a	95% Confidence intervals		No. of patients	No. of deaths	Adjusted HR ^a	95% Confidence intervals	
1. Non-IBC											
2. IBC	NH White	4,875	1,962	1.00	Reference		20,051	9,548	1.00	Reference	
	Black	1,561	776	1.33	1.21	1.45	3,727	1,940	1.18	1.12	1.24
	Hispanic White	1,211	420	1.00	0.90	1.11	2,098	893	0.96	0.90	1.03
	API	711	262	1.03	0.91	1.18	1,598	611	0.83	0.76	0.90
3. ER+/PR+	NH White	1,455	702	1.00	Reference		3,877	1,921	1.00	Reference	
	Black	455	270	1.38	1.19	1.59	705	414	1.28	1.14	1.42
	Hispanic White	392	182	0.98	0.83	1.15	482	222	0.99	0.86	1.14
	API	139	59	0.86	0.66	1.12	243	112	0.85	0.70	1.02
4. ER-/PR-	NH White	3,195	1,077	1.00	Reference		13,176	5,561	1.00	Reference	
	Black	728	323	1.60	1.41	1.82	1,847	870	1.25	1.16	1.34
	Hispanic White	787	234	1.00	0.87	1.15	1,288	483	0.97	0.89	1.07
	API	444	131	0.98	0.82	1.17	909	301	0.85	0.76	0.95
5. Non-IBC and ER+/PR+	NH White	2,187	1,142	1.00	Reference		6,304	3,615	1.00	Reference	
	Black	983	565	1.22	1.10	1.35	1,731	1,026	1.15	1.07	1.24
	Hispanic White	592	278	0.96	0.84	1.09	798	410	0.98	0.88	1.08
	API	280	134	1.03	0.86	1.24	603	279	0.79	0.70	0.89
6. IBC and ER+/PR+	NH White	2,647	870	1.00	Reference		11,623	4,937	1.00	Reference	
	Black	601	257	1.60	1.39	1.85	1,633	766	1.25	1.16	1.35
	Hispanic White	635	178	1.03	0.87	1.21	1,118	417	0.96	0.87	1.07
	API	388	109	0.94	0.77	1.15	825	263	0.82	0.72	0.93
		548	207	1.00	Reference		1,553	624	1.00	Reference	

Age at diagnosis < 50										Age at diagnosis ≥ 50			
Strata	Race	No. of patients	No. of deaths	Adjusted HR ^a	95% Confidence intervals	No. of patients	No. of deaths	Adjusted HR ^a	95% Confidence intervals				
7. Non-IBC and ER−/PR−	Black	127	66	1.80	1.35	214	104	1.28	1.03	1.59			
	Hispanic White	152	56	0.96	0.71	170	66	1.13	0.87	1.46			
	API	56	22	1.30	0.83	84	38	1.22	0.88	1.70			
	NH White	1,497	748	1.00	Reference	4,710	2,697	1.00	Reference				
	Black	722	396	1.21	1.07	1,383	801	1.12	1.04	1.22			
8. IBC and ER−/PR−	Hispanic White	408	180	0.97	0.82	593	301	0.98	0.87	1.11			
	API	217	102	1.09	0.89	485	218	0.80	0.70	0.92			
	NH White	690	394	1.00	Reference	1,594	918	1.00	Reference				
	Black	261	169	1.26	1.05	348	225	1.32	1.14	1.53			
	Hispanic White	184	98	0.93	0.74	205	109	0.98	0.80	1.20			
	API	63	32	0.88	0.61	118	61	0.80	0.61	1.04			

^aHR Hazard ratio, adjusted for: age at diagnosis, marital status, stage, grade, surgery, radiation, ER/PR status, and IBC status. The stratified variables were not included in stratified models.

IBC=Inflammatory breast cancer, NH=Non-Hispanic, API=Asian/Pacific Islander