Clinical Cancer Research

Impact of Breast Cancer Subtypes on Prognosis of Women with Operable Invasive Breast Cancer: A Population-based Study Using SEER Database

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Abstract

Purpose: To determine the prognostic roles of breast cancer subtypes in females with operable invasive breast cancer.

Experimental Design: Data of 321,958 patients from Surveillance, Epidemiology, and End Results (SEER) database were analyzed. Breast cancer subtypes were classified into four categories according to the status of hormone receptor (HRc) and HER2: HRc(+)/HER2(−), HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−).

Results: Proportions of HRc(+)/HER2(−), HRc(+)/HER2(+), HRc(−)/HER2(+), HRc(−)/HER2(−), and unknown subtype were 70.3%, 9.4%, 3.9%, 10.4%, and 6.0%, respectively. HRc(+)/HER2(−) showed the highest 5-year breast cancer–specific survival (BCSS) rate (95.5%), followed by HRc(+)/HER2(+) (94.1%), HRc(−)/HER2(+) (89.3%), and HRc(−)/HER2(−) (83.1%). HRc(+)/HER2(−) and HRc(+)/HER2(+) showed higher 5-year overall survival (OS) rates (88.4% and 88.2%, respectively) than HRc(−)/HER2(+) and HRc(−)/HER2(−) (83.9% and 76.5%, respectively). HRc(−)/HER2(−) showed the worst BCSS irrespective of race, age, or stage. Although proportions of HRc(−)/HER2(−) in the subgroup with negative event regarding BCSS and OS were 10.4% and 10.2%, respectively, they were 34.2% and 22.7%, respectively, in the subgroup with positive event. Subtype was a significant factor in both univariable and multivariable analyses regarding both BCSS and OS (all $P < 0.001$).

Conclusions: Breast cancer subtype was a significant independent prognostic factor regarding both BCSS and OS in multivariable analyses. HRc(+) subtypes showed better prognosis compared with HRc(−) subtypes regarding both BCSS and OS. HRc(−)/HER2(+) showed better prognosis than HRc(−)/HER2(−) but worse prognosis than HRc(+) subtypes regarding both BCSS and OS. The triple-negative subtype showed the worst BCSS compared with the other subtypes irrespective of race, age, or stage.

Introduction

Breast cancer is the most common female cancer and the leading cause of female cancer-related deaths. In 2016, the estimated incidence cases of female breast cancer were 1.68 million (95% uncertainty intervals, 1.61–1.78 million) and 535,000 (95% uncertainty intervals, 506,000–573,000) deaths were caused by female breast cancer (1). The TNM staging system developed by the American Joint Committee on Cancer (AJCC) has become the global standard in prognosis prediction of various cancers including breast cancer. Since Perou and colleagues shed light on the existence of intrinsic subtypes in breast cancer according to the expression microarray patterns in 1999 and 2000 (2, 3), subsequent studies have reported the clinical importance of breast cancer subtypes (4–6). The St. Gallen guideline partially incorporated the concept of intrinsic subtypes into clinical guidelines (7–9). The National Comprehensive Cancer Network guideline (https://www.nccn.org/) classifies breast cancer subtypes into the following four categories according to the status of hormone receptor (HRc) and HER2: HRc(+)/HER2(−), HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−). This four-subtype classification is practically crucial to decide systemic treatment plans for patients with breast cancer. The proportion of each breast cancer subtype has been reported in previous studies. We reviewed five main previous studies, and the proportion of each subtype in subtype-known breast cancer was 66.3% (range, 54.8%–72.9%), 12.6% (range, 5.9%–16.6%), 6.2% (range, 4.7%–7.2%), and 15.0% (range, 11.4%–21.5%) for HRc(+)/HER2(−), HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−), respectively (10–14). Although various factors could cause variation in the proportion rate of each subtype, main causality might be explained by methodologic

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Translational Relevance

This population-based study aimed to determine prognostic roles of breast cancer subtypes in women with operable invasive breast cancer. This study analyzed data of 321,958 patients with breast cancer from Surveillance, Epidemiology, and End Results (SEER) database and found that breast cancer subtype was a significant independent prognostic factor in breast cancer. Hormone receptor (HRc)-positive subtypes showed better prognosis compared with HRc -negative subtypes. HRc -positive and HER2-negative subtype showed better prognosis than HRc -negative and HER2-negative subtype but worse prognosis than HRc-positive subtypes. The triple-negative subtype showed the worst prognosis compared with other subtypes irrespective of race, age, or stage. Breast cancer subtypes are important prognostic factors in women with operable breast cancer, and triple-negative breast cancer shows the worst prognosis of all subtypes. Clinicians should consider breast cancer subtypes carefully in clinical setting and further studies are needed to identify long term prognostic impact of each subtype on breast cancer.

variation for the diagnosis of HR and HER2, demographic variation of enrolled subjects, and chronologic changes regarding breast cancer screening, diagnosis, and treatment.

The prognostic influence of these four subtypes on breast cancer has been occasionally reported by researchers, showing that HRc(+)/HER2(−) subtype has the best prognosis, whereas HRc(−)/HER2(+) and HRc(−)/HER2(−) subtypes has adverse prognoses compared with other subtypes (10–14). Previous studies have also reported that HRc(+)/HER2(−) subtype represents the majority of breast cancer cases, and HRc(−)/HER2(−) subtype, also known as triple-negative breast cancer, has unfavorable clinicopathologic features and poor prognosis (10, 15–18). Regarding breast cancer, the prognostic roles of HRc and HER2 have been widely acknowledged. As a result, HRc and HER2 were finally incorporated into main factors to determine prognostic stage groups as well as TNM classification and histologic grade in eighth edition of the AJCC Cancer Staging Manual (19). Although prognostic roles of these four breast cancer subtypes have been partly unveiled in previous studies, most previous studies enrolled relatively small numbers of subjects from a single institute, making it difficult to extrapolate their results to the general population. Although there have been significant chronologic changes in standard treatment modalities for patients with breast cancer, results of some previous studies could not reflect recent changes of treatment modalities. For example, adjuvant HER2-targeted therapy was introduced in practice since the second half of the period between 2001 and 2010. Some studies that enrolled subjects before that period could not adequately reflect treatment impact of HER2-targeted therapy. Some previous studies had relatively short follow-up periods with only short-term results of survival analyses (14).

Recently, the Surveillance, Epidemiology, and End Results (SEER) program released SEER incidence data (1973–2015) including data of more than 1.6 million breast cancer cases (https://seer.cancer.gov/). As SEER program has provided information for HER2 status and breast cancer subtype since 2010, the maximal follow-up period could reach almost 6 years. Thus, the objective of this study was to perform holistic analyses on prognostic roles of four breast cancer subtypes in females with operable invasive breast cancer using population-based SEER database. We also analyzed survivals and proportions of each subtype in various subgroups according to race, age, stage, and more.

Materials and Methods

Study subjects

The total number of subjects who had been diagnosed as breast cancer and registered in SEER incidence data (1973–2015) was 1,631,572. Of these subjects, females with operable invasive breast cancer who had information of breast cancer subtype were target subjects of this study. Male patients with breast cancer ($N = 10,848$) were excluded. Patients without information of subtype ($N = 1,151,840$), patients with carcinoma *in situ* ($N = 94,209$) or initial stage IV ($N = 20,691$), and patients with unknown stage ($N = 15,591$) were also excluded in sequence. After further exclusion of patients without surgery or unknown about surgery status ($N = 16,435$), the final number of subjects was 321,958 (Supplementary Fig. S1). As SEER database has provided information of breast cancer subtype since 2010, all subjects were enrolled between 2010 and 2015.

SEER collects cancer incidence data from population-based cancer registries covering approximately 34.6% of the U.S. population. The SEER registries collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, and first course of treatment, and they follow up with patients for vital status. This database collects data from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, Utah, San Jose–Monterey, Los Angeles, Rural Georgia, Alaska Natives, Greater California, Kentucky, Louisiana, New Jersey, and greater Georgia (https://seer.cancer.gov/).

Clinicopathologic parameters

T category, N category, and anatomic stage group were described according to the seventh edition of the AJCC. Status of estrogen receptor (ER) or progesterone receptor (PR) was defined based on result of IHC test (20). HRc status was defined as positive when IHC test for either ER or PR was positive. HRc was defined as negative when both ER and PR were negative. HER2 status was defined as positive or negative according to the algorithm used for deriving HER2 summary variable based on the results of IHC test and *in situ* hybridization tests (21). Race was classified into three groups: Caucasian, African-American, and other races including American Indian/Alaska Native and Asian/Pacific Islander. Age was classified into three groups: age $\leq$50 years, 50 < age $\leq$ 65 years, and age >65 years. Breast cancer subtypes were classified into four groups: HRc(+)/HER2(−), HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(+).

All data and parameters were utilized from SEER Program Research Data (1973–2015), NCI, Division of Cancer Control and Population Sciences, Surveillance Research Program, released April 2018, based on the November 2017 submission.

Statistical analyses

Pearson χ^2 test was used to determine statistical differences in clinicopathologic parameters between groups. Survival

analyses were carried out with respect to breast cancer–specific survival (BCSS) and overall survival (OS). Time duration of BCSS was calculated as the time from initial diagnosis of primary breast cancer to death from breast cancer. Time duration of OS was calculated as the time from initial diagnosis of primary breast cancer to death from any cause. The event of each subject regarding both BCSS and OS was defined as yes, when the subject was dead or no, when the subject was alive at the time of the last follow-up. Kaplan–Meier estimator was used to analyze survival rates whereas log-rank test was used to determine the significance of differences between two or more survival curves. Cox proportional hazards model was used for univariable and multivariable analyses. HR and 95% confidence interval (CI) were calculated. All statistical analyses were carried out using IBM SPSS Statistics, version 20.0 (IBM Corp.). All tests were two-sided. Statistical significance was considered when P value was less than 0.05.

Results

Clinicopathologic characteristics of study subjects

The total number of subjects was 321,958. Their mean age was 61.4 ± 13.3 years (median, 62.0 years). The mean follow-up period was 32.0 ± 20.5 months (median, 31.0 months; range, 0–71 months). Total numbers of deaths from breast cancer and any cause during this period were 8,320 (2.6%) and 22,100 (6.9%), respectively. Clinicopathologic characteristics of study subjects are summarized in Table 1. Numbers of subjects with HRc(+)/HER2(−), HRc(+)/HER2(+), HRc(−)/HER2(+), HRc(−)/HER2(−), and unknown subtype were 226,326 (70.3%),

Table 1. Clinicopathologic characteristics of subjects according to breast cancer subtypes

	Subtypes						
Characteristics	**HRc(+)/HER2(−) No. (%)**	**HRc(+)/HER2(+) No. (%)**	**HRc(−)/HER2(+) No. (%)**	**HRc(−)/HER2(−) No. (%)**	**Unknown No. (%)**	***P***	**Total No. (%)**
All	226,326 (70.3%)	30,295 (9.4%)	12,592 (3.9%)	33,497 (10.4%)	19,248 (6.0%)		321,958 (100%)
Mean age (years)	62.4 ± 13.0	58.0 ± 13.5	58.2 ± 13.1	59.0 ± 13.9	62.2 ± 13.6		61.4 ± 13.3
T category						<0.001	
T1	152,442 (67.4%)	16,263 (53.7%)	6,124 (48.7%)	15,779 (47.2%)	12,936 (67.4%)		203,544 (63.3%)
T2	59,760 (26.4%)	10,915 (36.1%)	4,604 (36.6%)	13,735 (41.1%)	4,727 (24.6%)		93,741 (29.1%)
T3	10,557 (4.7%)	2,023 (6.7%)	1,078 (8.6%)	2,559 (7.7%)	1,046 (5.4%)		17,263 (5.4%)
T4	3,437 (1.5%)	1,071 (3.5%)	767 (6.1%)	1,374 (4.1%)	490 (2.6%)		7,139 (2.2%)
N category						<0.001	
N0	165,465 (73.1%)	19,144 (63.2%)	7,523 (59.8%)	23,016 (68.7%)	14,950 (77.8%)		230,098 (71.5%)
N1	45,790 (20.2%)	8,035 (26.5%)	3,452 (27.4%)	7,274 (21.7%)	3,175 (16.5%)		67,726 (21.0%)
N2	9,974 (4.4%)	2,017 (6.7%)	922 (7.3%)	1,917 (5.7%)	738 (3.8%)		15,568 (4.8%)
N3	5,031 (2.2%)	1,090 (3.6%)	692 (5.5%)	1,271 (3.8%)	354 (1.8%)		8,438 (2.6%)
Anatomic stage group						<0.001	
Stage I	134,608 (59.5%)	13,513 (44.6%)	4,991 (39.6%)	13,505 (40.3%)	11,791 (61.3%)		178,408 (55.4%)
Stage II	70,592 (31.2%)	12,132 (40.0%)	5,032 (40.0%)	15,039 (44.9%)	5,746 (29.9%)		108,541 (33.7%)
Stage IIII	21,126 (9.3%)	4,650 (15.3%)	2,569 (20.4%)	4,953 (14.8%)	1,711 (8.9%)		35,009 (10.9%)
ER						<0.001	
Negative	2,126 (0.9%)	831 (2.7%)	12,592 (100.0%)	33,497 (100.0%)	2,068 (15.8%)		51,114 (16.2%)
Positive	224,102 (99.1%)	29,423 (97.3%)	0 (0.0%)	0 (0.0%)	11,054 (84.2%)		264,579 (83.8%)
PR						<0.001	
Negative	26,298 (11.7%)	7,901 (26.2%)	12,592 (100.0%)	33,497 (100.0%)	3,493 (27.4%)		83,781 (26.6%)
Positive	199,225 (88.3%)	22,272 (73.8%)	0 (0.0%)	0 (0.0%)	9,275 (72.6%)		230,772 (73.4%)
HER2						<0.001	
Negative	226,326 (100.0%)	0 (0.0%)	0 (0.0%)	33,497 (100.0%)	337 (81.0%)		260,160 (85.8%)
Positive	0 (0.0%)	30,295 (100.0%)	12,592 (100.0%)	0 (0.0%)	79 (19.0%)		42,966 (14.2%)
Histologic grade						<0.001	
Well differentiated	68,178 (31.0%)	2,091 (7.2%)	206 (1.7%)	747 (2.3%)	3,871 (23.7%)		75,093 (24.2%)
Moderately differentiated	110,056 (50.0%)	12,225 (41.9%)	2,846 (23.9%)	5,826 (18.0%)	7,114 (43.5%)		138,067 (44.5%)
Poorly differentiated	41,652 (18.9%)	14,721 (50.5%)	8,737 (73.5%)	25,556 (78.9%)	5,148 (31.5%)		95,814 (30.9%)
Undifferentiated	315 (0.1%)	108 (0.4%)	99 (0.8%)	245 (0.8%)	214 (1.3%)		981 (0.3%)
Race						<0.001	
Caucasian	184,857 (82.2%)	23,475 (78.0%)	9,167 (73.2%)	24,237 (72.7%)	15,150 (79.5%)		256,886 (80.3%)
African-American	19,997 (8.9%)	3,403 (11.3%)	1,716 (13.7%)	6,628 (19.9%)	2,089 (11.0%)		33,833 (10.6%)
Other races	20,163 (9.0%)	3,233 (10.7%)	1,635 (13.1%)	2,472 (7.4%)	1,810 (9.5%)		29,313 (9.2%)
Age group (years)						<0.001	
≤50	45,767 (20.2%)	9,265 (30.6%)	3,520 (28.0%)	9,594 (28.6%)	4,023 (20.9%)		72,169 (22.4%)
>50, ≤65	86,641 (38.3%)	12,291 (40.6%)	5,581 (44.3%)	13,149 (39.3%)	7,385 (38.4%)		125,047 (38.8%)
>65	93,915 (41.5%)	8,737 (28.8%)	3,490 (27.7%)	10,754 (32.1%)	7,839 (40.7%)		124,735 (38.7%)
Year of diagnosis						<0.001	
2010	34,393 (15.2%)	4,605 (15.2%)	1,995 (15.8%)	5,590 (16.7%)	4,143 (21.5%)		50,726 (15.8%)
2011	36,584 (16.2%)	4,613 (15.2%)	2,053 (16.3%)	5,840 (17.4%)	3,580 (18.6%)		52,670 (16.4%)
2012	37,791 (16.7%)	4,894 (16.2%)	2,062 (16.4%)	5,628 (16.8%)	3,027 (15.7%)		53,402 (16.6%)
2013	38,833 (17.2%)	5,050 (16.7%)	2,038 (16.2%)	5,462 (16.3%)	2,879 (15.0%)		54,262 (16.9%)
2014	38,897 (17.2%)	5,491 (18.1%)	2,179 (17.3%)	5,490 (16.4%)	2,894 (15.0%)		54,951 (17.1%)
2015	39,828 (17.6%)	5,642 (18.6%)	2,265 (18.0%)	5,487 (16.4%)	2,725 (14.2%)		55,947 (17.4%)

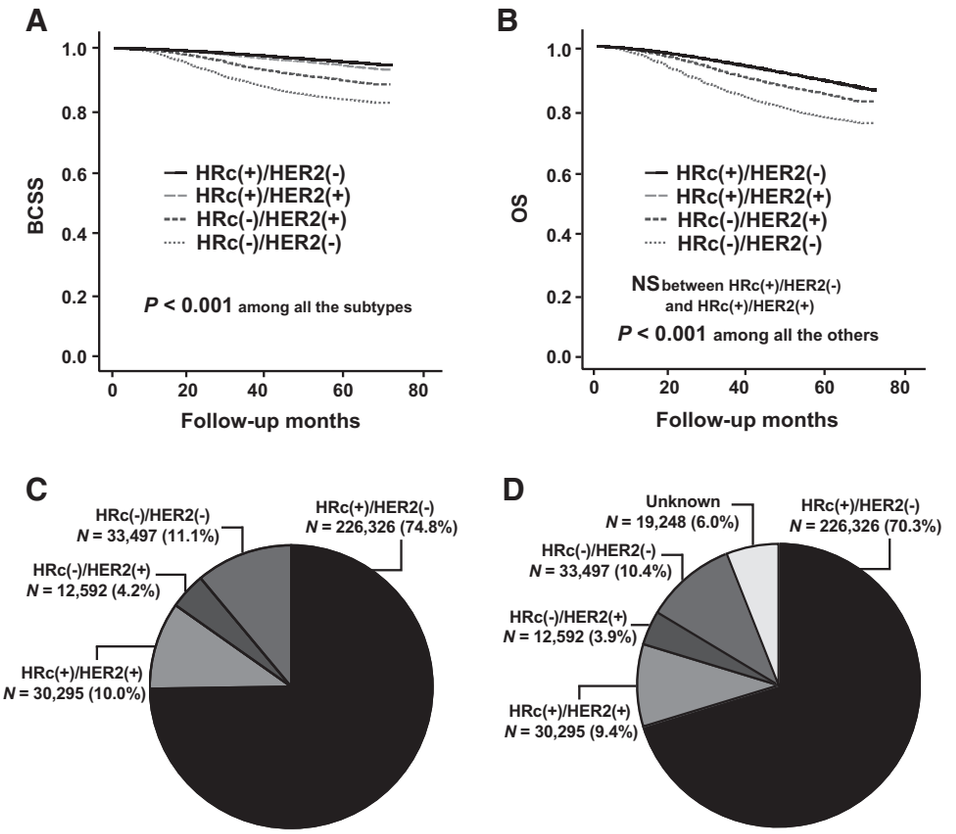

Figure 1.
Survival curves and subject proportions according to breast cancer subtypes. BCSS (**A**) and OS (**B**) according to breast cancer subtypes were depicted. Subject proportions according to breast cancer subtypes without the unknown subtype (**C**) and with the unknown subtype (**D**) were also depicted.

30,295 (9.4%), 12,592 (3.9%), 33,497 (10.4%), and 19,248 (6.0%), respectively.

Survival analysis of all subjects according to breast cancer subtypes

Among the four breast cancer subtypes, HRc(+)/HER2(−) subtype showed the highest five-year BCSS rate (95.5%). HRc(+)/HER2(+) subtype showed a higher 5-year BCSS (94.1%) than HRc(−)/HER2(+) (89.3%) and HRc(−)/HER2(−) (83.1%). HRc(−)/HER2(−) subtype showed the lowest BCSS (Fig. 1A). Regarding OS, HRc(+)/HER2(−) and HRc(+)/HER2(+) subtypes showed higher five-year OS rates (88.4% and 88.2%, respectively) than HRc(−)/HER2(+) and HRc(−)/HER2(−) subtypes (83.9% and 76.5%, respectively). There was no significant difference in OS between the two HRc(+) subtypes. The triple-negative subtype showed the lowest OS (Fig. 1B). Detailed BCSS and OS rates of each subtype for every 1-year interval are summarized in Supplementary Table S1.

Survival analysis for subgroups according to race, age, and stage

In this study, race was classified into three groups: Caucasian, African-American, and other races. Other races showed the highest BCSS rate, whereas African-American showed the lowest BCSS (Fig. 2). In Caucasian women, HRc(+)/HER2(−) subtype showed the highest BCSS rate, followed by HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−) in order. In African-American women and other races, HRc(+)/HER2(−) and HRc(+)/HER2(+) subtypes showed the highest BCSS rates and there was no significant difference in BCSS rate between these two subtypes. HRc(−)/HER2(−) subtype showed the worst BCSS in these subgroups.

The subgroup of age between 50 and 65 years showed the highest BCSS rate among all three age groups (Fig. 3). In subgroup analysis for those with age $\leq$ 50 years, HRc(+)/HER2(−) and HRc(+)/HER2(+) subtypes showed the highest BCSS rates, followed by HRc(−)/HER2(+) and HRc(−)/HER2(−) subtypes in order. In subgroup analysis for those with age between 50 and 65 years and those with age > 65 years, HRc(+)/HER2(−) subtype showed the highest BCSS rate, followed by HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−) subtypes in order.

Stage I showed the highest BCSS rate, followed by stage II and stage III in order (Fig. 4). In stage I, HRc(+)/HER2(−) showed the highest BCSS rate, followed by HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−) subtypes in order. In stage II and stage III, HRc(+)/HER2(−) and HRc(+)/HER2(+) subtypes showed higher BCSS rates than HRc(−)/HER2(+) and HRc(−)/HER2(−) subtypes. HRc(−)/HER2(−) subtype showed the worst BCSS in stage II and III.

Survival analysis for subgroups according to other factors including ER, PR, HER2, T category, N category, and histologic grade

Subgroups with ER(+), PR(+), and HER2(−) showed better BCSS rates than subgroups with ER(−), PR(−), and HER2(+), respectively (Supplementary Fig. S2). The proportion of HRc(+)/HER2(−) was 4.3% in the subgroup with ER(−), whereas it was 32.8% in the subgroup with PR(−). Proportions of

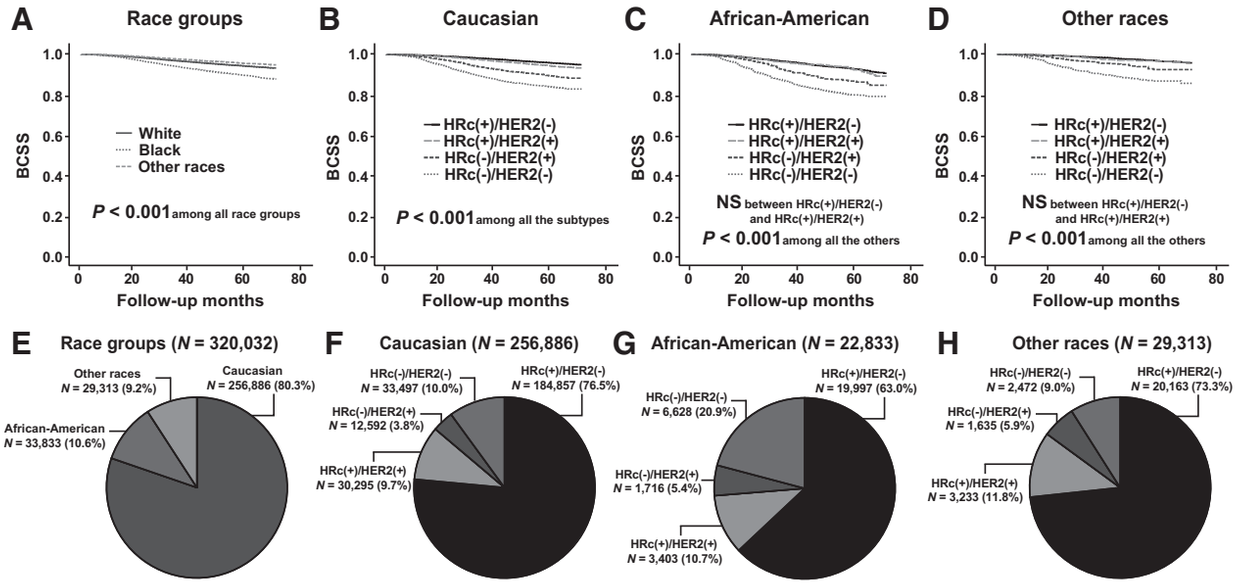

Figure 2.

BCSS curves according to the race groups (**A**) and subject proportions of the race groups (**E**). Survival curves of each subtype for Caucasian (**B**), African-American (**C**), and other races (**D**) and subject proportions of each subtype for Caucasian (**F**), African-American (**G**), and other races (**H**) were depicted.

HRc(−)/HER2(−) subtype in the subgroup with ER(−) and PR(−) were 68.3% and 41.7%, respectively. BCSS curves and subtype proportions in each subgroup according to T category, N category, and histologic grade are depicted in Supplementary Fig. S3. The proportions of HRc(−)/HER2(−) in the subgroup with negative event regarding BCSS and OS were 10.4% and 10.2%, respectively, but they were 34.2% and 22.7%, respectively, in the subgroup with positive event (Supplementary Fig. S4).

Univariable and multivariable analyses

Regarding BCSS, all eleven clinicopathologic factors including subtype, T category, N category, anatomic stage group, ER, PR,

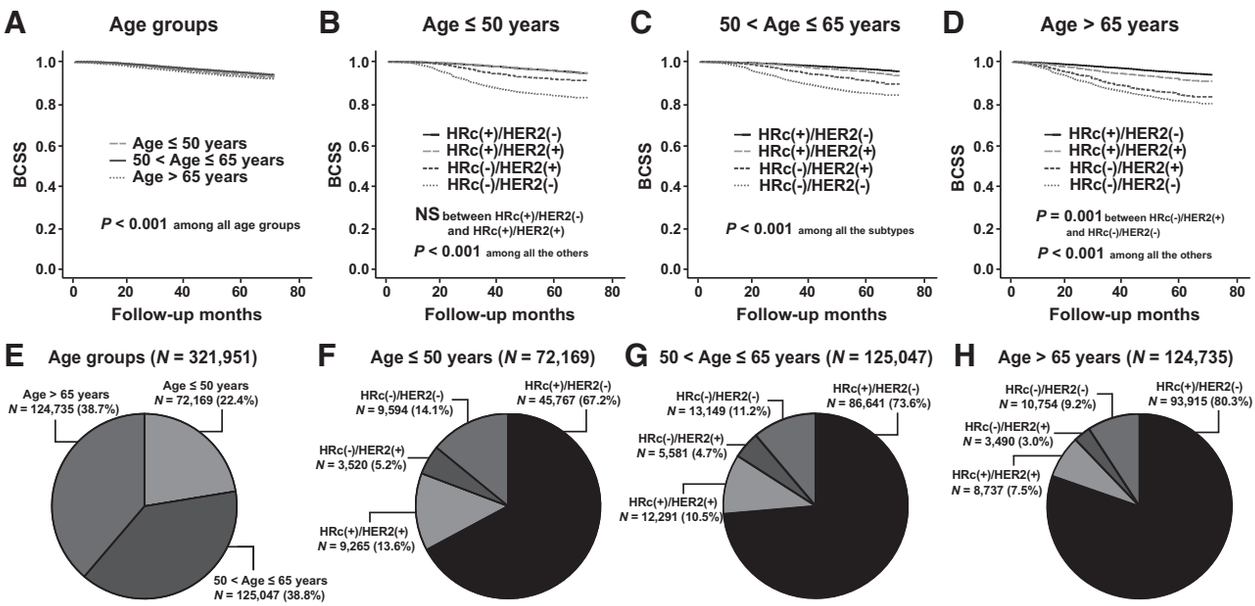

Figure 3.

BCSS curves according to the age groups (**A**) and subject proportions of the age groups (**E**). Survival curves of each subtype for age ≤50 years (**B**), 50 < age ≤ 65 years (**C**), and age >65 years (**D**) and subject proportions of each subtype for age ≤50 years (**F**), 50 < age ≤ 65 years (**G**), and age >65 years (**H**) were depicted.

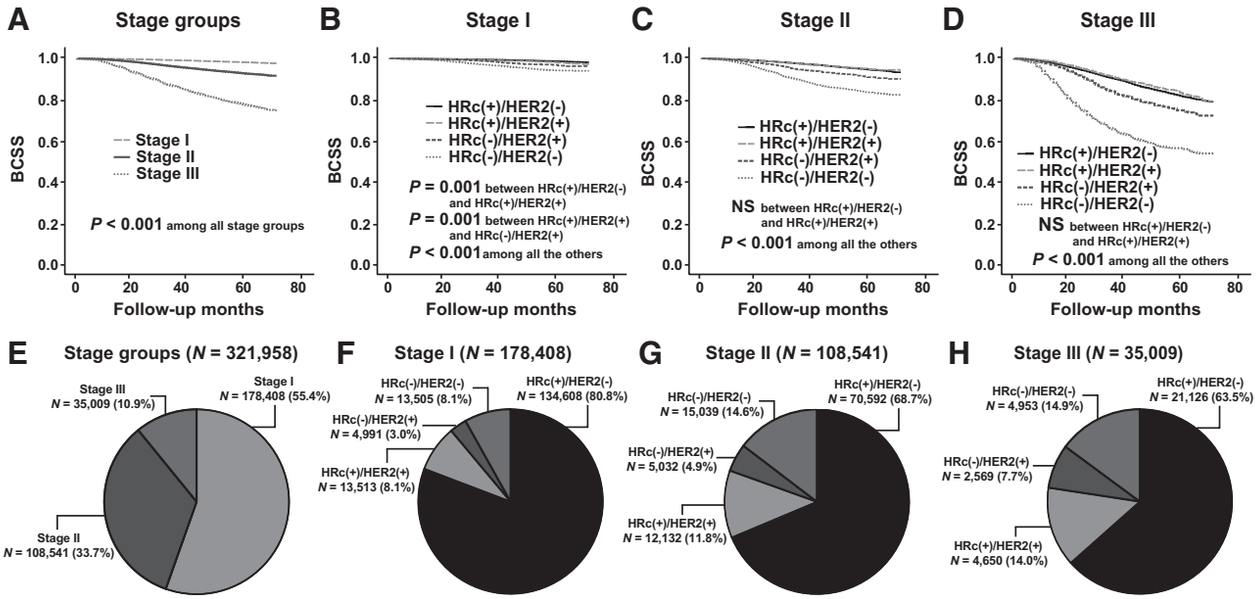

Figure 4.

BCSS curves according to the stage groups (**A**) and subject proportions of the stage groups (**E**). Survival curves of each subtype for stage I (**B**), stage II (**C**), and stage III (**D**) and subject proportions of each subtype for stage I (**F**), stage II (**G**), and stage III (**H**) were depicted.

HER2, histologic grade, race, age group, and year of diagnosis were significant in univariable analyses (Table 2). HRs for HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−) were 1.305 (95% CI: 1.203–1.415; $P < 0.001$), 2.652 (95% CI: 2.431–2.894; $P < 0.001$), and 4.755 (95% CI: 4.527–4.995; $P < 0.001$), respectively, with HRc(+)/HER2(−) as reference. Subtype was a significant independent prognostic factor in multivariable analysis after adjusting for six basic clinicopathologic factors including T category, N category, histologic grade, race, age group, and year of diagnosis. HRs for HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−) were 0.810 (95% CI: 0.745–0.881; $P < 0.001$), 1.212 (95% CI: 1.105–1.330; $P < 0.001$), and 2.528 (95% CI: 2.390–2.674; $P < 0.001$), respectively, with HRc(+)/HER2(−) as reference. Regarding OS, ten clinicopathologic factors except for HER2 were significant in univariable analyses. Subtype was also a significant independent prognostic factor in multivariable analysis after adjustment ($P < 0.001$).

Discussion

This study investigated the prognostic roles of four breast cancer subtypes based on the status of HRc and HER2 in female patients with operable invasive breast cancer by analyzing the data of 321,958 subjects from population-based SEER database. This study revealed that HRc(+) subtypes had better prognosis than HRc(−) subtypes. Although there was a minor difference in both BCSS and OS rates between HRc(+)/HER2(−) and HRc(+)/HER2(+) subtypes, HRc(−)/HER2(+) subtype showed superior prognosis than HRc(−)/HER2(−) subtype. Breast cancer subtype was a significant prognostic factor in univariable analysis and it still remained a significant independent factor in multivariable analyses regarding both BCSS and OS.

Some previous studies have reported the prognostic roles of breast cancer subtypes (Supplementary Table S2 shows review summary of current and previous studies for prognostic influence of breast cancer subtypes). The British Columbia Cancer Agency (BCCA) study analyzed data of 4,046 female patients with invasive breast cancer who had been referred to the BCCA between 1986 and 1992. With a median follow-up time of 12.5 years, it reported that 5-year BCSS rates of HRc(+)/HER2(−), HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−) were 91%, 75%, 60%, and 73%, respectively (10, 15). The Carolina Breast Cancer Study (CBCS) analyzed the data of 496 breast cancer cases diagnosed between 1993 and 1996 with a maximal follow-up period of 11.2 years. It reported that HRc(−)/HER2(+) subtype showed worse 10-year BCSS rate (52%) compared with other subtypes [84% for HRc(+)/HER2(−), 87% for HRc(+)/HER2(+), and 75% for triple-negative subtype] (11). The California Cancer Registry study analyzed data of 61,309 patients with invasive breast cancer who were registered between 1999 and 2004. It reported that HRc(−)/HER2(+) and HRc(−)/HER2(−) subtypes showed the worst and essentially identical 5-year relative cumulative survival rates of 75.9% and 76.2%, respectively (12). The authors of that study mentioned that their results could reflect the natural history of HER2(+) breast cancers as the subject enrollment period was prior to the era of routine trastuzumab therapy (12). Another study analyzed data of 12,052 patients with primary nonmetastatic invasive breast cancer who had been registered in the regional cancer registry of Saxony-Anhalt from Germany between 2000 and 2016. With a median follow-up time of 80.8 months, it reported that 10-year OSs for HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−) subtypes were 79.6%, 74.4%, and 75.8%, respectively (13). Another study analyzed data of 196,094 patients with invasive breast cancer from SEER database (2010–2013) with a maximum follow-up time of 59 months. It reported that 4-year BCSS rates of HRc(+)/HER2(−), HRc(+)/HER2(+), HRc(−)/HER2(+), and HRc(−)/HER2(−) subtypes were 92.5%, 90.3%, 82.7%, and 77.0%, respectively (14).

Table 2. Univariable and multivariable analyses regarding BCSS and OS

	BCSS						OS					
	Univariable analysis			Multivariable analysis[a]			Univariable analysis			Multivariable analysis[a]		
Characteristics	**HR**	**CI (95%)**	***P***	**HR**	**CI (95%)**	***P***	**HR**	**CI (95%)**	***P***	**HR**	**CI (95%)**	***P***
Subtype			<0.001			<0.001			<0.001			<0.001
HRc(+)/HER2(−)	Reference			Reference			Reference			Reference		
HRc(+)/HER2(+)	1.305	1.203 (1.415)	<0.001	0.810	0.745 (0.881)	<0.001	1.036	0.986 (1.089)	0.161	0.911	0.865 (0.960)	<0.001
HRc(−)/HER2(+)	2.652	2.431 (2.894)	<0.001	1.212	1.105 (1.330)	<0.001	1.511	1.419 (1.608)	<0.001	1.103	1.032 (1.179)	0.004
HRc(−)/HER2(−)	4.755	4.527 (4.995)	<0.001	2.528	2.390 (2.674)	<0.001	2.488	2.406 (2.573)	<0.001	1.882	1.811 (1.956)	<0.001
Unknown	1.445	1.316 (1.586)	<0.001	1.316	1.191 (1.454)	<0.001	1.324	1.257 (1.394)	<0.001	1.270	1.202 (1.343)	<0.001
T category			<0.001			<0.001			<0.001			<0.001
T1	Reference			Reference			Reference			Reference		
T2	4.162	3.939 (4.397)	<0.001	2.281	2.150 (2.421)	<0.001	2.140	2.078 (2.204)	<0.001	1.761	1.705 (1.820)	<0.001
T3	9.015	8.421 (9.652)	<0.001	4.060	3.763 (4.380)	<0.001	3.426	3.276 (3.584)	<0.001	2.655	2.525 (2.791)	<0.001
T4	19.828	18.433 (21.329)	<0.001	6.115	5.625 (6.649)	<0.001	7.227	6.881 (7.592)	<0.001	4.152	3.923 (4.394)	<0.001
N category			<0.001			<0.001			<0.001			<0.001
N0	Reference			Reference			Reference			Reference		
N1	2.919	2.770 (3.076)	<0.001	1.946	1.840 (2.060)	<0.001	1.482	1.436 (1.530)	<0.001	1.273	1.229 (1.317)	<0.001
N2	6.579	6.172 (7.012)	<0.001	3.372	3.144 (3.616)	<0.001	2.721	2.602 (2.845)	<0.001	1.895	1.804 (1.990)	<0.001
N3	12.045	11.284 (12.857)	<0.001	5.149	4.784 (5.542)	<0.001	4.549	4.337 (4.771)	<0.001	2.747	2.605 (2.898)	<0.001
Anatomic stage group			<0.001						<0.001			
Stage I	Reference						Reference					
Stage II	4.300	4.027 (4.591)	<0.001				1.935	1.876 (1.996)	<0.001			
Stage IIII	15.285	14.329 (16.304)	<0.001				4.363	4.218 (4.513)	<0.001			
ER												
Negative	Reference						Reference					
Positive	0.242	0.232 (0.253)	<0.001				0.453	0.440 (0.466)	<0.001			
PR												
Negative	Reference						Reference					
Positive	0.258	0.246 (0.269)	<0.001				0.481	0.468 (0.494)	<0.001			
HER2												
Negative	Reference						Reference					
Positive	1.149	1.082 (1.220)	<0.001				0.989	0.950 (1.029)	0.584			
Histologic grade			<0.001			<0.001			<0.001			<0.001
Well differentiated	Reference			Reference			Reference			Reference		
Moderately differentiated	2.731	2.462 (3.029)	<0.001	1.793	1.613 (1.992)	<0.001	1.310	1.257 (1.364)	<0.001	1.084	1.040 (1.131)	<0.001
Poorly differentiated	9.462	8.575 (10.440)	<0.001	3.822	3.440 (4.247)	<0.001	2.434	2.339 (2.532)	<0.001	1.613	1.542 (1.687)	<0.001
Undifferentiated	10.343	8.082 (13.237)	<0.001	4.207	3.262 (5.424)	<0.001	2.915	2.475 (3.433)	<0.001	1.934	1.637 (2.285)	<0.001
Race			<0.001			<0.001			<0.001			<0.001
Caucasian	Reference			Reference			Reference			Reference		
African-American	1.886	1.784 (1.994)	<0.001	1.305	1.232 (1.384)	<0.001	1.402	1.350 (1.457)	<0.001	1.254	1.205 (1.305)	<0.001
Other races	0.736	0.674 (0.804)	<0.001	0.734	0.669 (0.804)	<0.001	0.633	0.597 (0.671)	<0.001	0.702	0.661 (0.745)	<0.001
Age group (years)			<0.001			<0.001			<0.001			<0.001
≤50	Reference			Reference			Reference			Reference		
>50, ≤65	0.823	0.778 (0.871)	<0.001	1.102	1.039 (1.168)	0.001	1.055	1.009 (1.104)	0.019	1.260	1.203 (1.319)	<0.001
>65	1.238	1.173 (1.307)	<0.001	2.106	1.989 (2.229)	<0.001	2.888	2.776 (3.005)	<0.001	3.922	3.762 (4.088)	<0.001
Year of diagnosis				0.016			0.379			0.001		0.040
2010	Reference			Reference			Reference			Reference		
2011	0.948	0.895 (1.004)	0.068	0.968	0.912 (1.027)	0.276	0.981	0.947 (1.017)	0.304	0.997	0.962 (1.034)	0.884
2012	0.930	0.872 (0.992)	0.027	0.961	0.900 (1.026)	0.238	0.978	0.939 (1.017)	0.264	0.993	0.953 (1.035)	0.738
2013	0.901	0.835 (0.972)	0.007	0.967	0.895 (1.045)	0.402	0.938	0.895 (0.983)	0.008	0.964	0.918 (1.011)	0.134
2014	0.890	0.803 (0.986)	0.025	0.950	0.855 (1.055)	0.336	0.918	0.862 (0.976)	0.007	0.945	0.887 (1.007)	0.082
2015	0.756	0.602 (0.951)	0.017	0.784	0.618 (0.993)	0.044	0.805	0.711 (0.911)	0.001	0.830	0.731 (0.942)	0.004

[a]The subtype factor was adjusted with six basic clinicopathologic factors including T category, N category, histologic grade, race, age, and year of diagnosis.

Although our study revealed that both HRc(+) subtypes showed favorable BCSS with minor prognostic difference between them, the BCCA study reported a prominently worse BCSS of the HRc(+)/HER2(+) subtype compared with HRc(+)/HER2(−). Although our results showed superior BCSS and OS rates of the HRc(−)/HER2(+) subtype compared with the triple-negative subtype, both the BCCA study and the CBCS study reported completely reversed results. Both the California Cancer Registry study and the Saxony-Anhalt study reported that HRc(−)/HER2(+) and HRc(−)/HER2(−) subtypes showed worse survival rates without survival difference between them. Considering that clinical application of adjuvant HER2-targeted therapy has been introduced since the second half of the period between 2000 and 2010, the prognosis of HER2(+) subtypes could be significantly improved by HER2-targeted therapy accordingly. This hypothesis could partially explain the worse prognoses of HER2(+) subtypes in the era before routine HER2-targeted therapy and the improved prognoses of them in the era after that. Further studies are needed to prove this plausible hypothesis.

In this study, although the proportions of HRc(+)/HER2(+) and HRc(−)/HER2(+) subtypes showed little variance across the race groups, HRc(+)/HER2(−) and HRc(−)/HER2(−) subtypes showed prominent variance; HRc(+)/HER2(−) and HRc(−)/HER2(−) subtypes were 76.5% and 10.0% in Caucasian women, but 63.0% and 20.9% in African-American women. African-American women showed worse BCSS rate than Caucasian women, and proportions of triple-negative breast cancers could be closely linked with this causality. The adverse prognosis of African-American women in breast cancer has been repeatedly reported (22–24). It might be associated with many factors such as early age of onset, unfavorable histologic features, lower socio-economic status, genetic predisposition, and so forth (16, 24). Some studies have stressed the association between higher proportion of triple-negative subtype and worse prognosis in African-American women (11, 16, 25–27).

In this study, although the proportion of HRc(+)/HER2(−) subtype increased as age increased, the proportion of the triple-negative subtype increased as age decreased. The proportion of triple-negative subtype was larger in the age group with age $\leq$50 years than that in the other two age groups with age >50 years. The CBCS reported that the proportion of the triple-negative subtype in premenopausal women (26.8%) was larger than that in postmenopausal women (15.9%) with known subtypes (11). Triple-negative breast cancer was known to be more prevalent in younger patients. This has been suggested as a factor to explain the adverse prognosis of young patients with breast cancer, especially that in African-American women (11, 15, 16). With our dataset, proportions of triple-negative breast cancer in age groups of $\leq$40 years, 40 < age $\leq$ 60 years, and age >60 years were 18.8% (N = 3,179), 12.1 % (N = 15,185), 9.4% (N = 15,133), respectively (data not shown). Especially, triple-negative subtype represented 27.0% in African-American women with age <40 years compared with 18.1% and 14.1% in Caucasian and other races with same ages, respectively.

This study showed that the proportion of HRc(+)/HER2(−) subtype decreased as anatomic stage advanced and the proportion of triple-negative subtype increased as the stage advanced. These association patterns were also observed regarding T category, N category, and histologic grade. T category showed a more prominent association pattern than N category. Histologic grade showed the most prominent association pattern. Previous studies have reported similar association between the proportion of subtypes and pathologic findings (13, 14, 17, 28). Weak correlation between T category and N category in triple negative or BRCA-associated breast cancers has been reported in previous studies (18, 29).

As breast cancer subtypes were classified according to the expression of ER, PR, and HER2, the prognosis of each subtype was also closely associated with the expression of those receptors. Subjects with ER(+), PR(+), and HER2(−) had higher BCSS rates than those with ER(−), PR(−), and HER2(+), respectively. These findings could partially explain the basic relationship between each subtype and prognosis. Previous studies have reported favorable prognosis of HRc(+) breast cancers (11, 12, 14) and adverse prognosis of HER2(+) breast cancers (11, 12, 14, 30, 31). The proportion of the HRc(−)/HER2(−) subtype in subjects with positive events of BCSS (34.2%) was three times larger than that in subjects with negative events of BCSS (10.4%). Regarding OS, the proportion of triple-negative breast cancer in subjects with positive events (22.7%) was about twice larger than subjects with negative events (10.2%). Improving the prognosis of the triple-negative subtype is crucial to improve the prognosis of unselected patients with breast cancer.

Although this study performed holistic analyses on the prognosis of breast cancer subtypes based on the largest database available in the world regarding this issue, it had also several limitations. First, the follow-up period was still relatively short. Although information of ER and PR has been available since 1990, SEER database has presented information of HER2 and breast cancer subtype since 2010. The mean follow-up period was 32 months (range, 0–71 months). Further studies are needed to validate long term follow-up results of this issue. Second, this study could not analyze effects of adjuvant treatments on the prognosis of each breast cancer subtype because no data regarding adjuvant treatments was available from the SEER database. Especially, we could not analyze the impact of endocrine therapy or HER2-targeted therapy, although they are crucial factors for the analysis of the prognostic role of breast cancer subtypes. The prognostic effect of chemotherapy or radiation therapy could not be analyzed either because of data unavailability.

In conclusion, breast cancer subtype was a significant independent prognostic factor in operable female invasive breast cancer regarding both BCSS and OS. HRc(+) subtypes such as HRc(+)/HER2(−) and HRc(+)/HER2(+) showed more favorable BCSS and OS rates than HRc(−) subtypes such as HRc(−)/HER2(+) and HRc(−)/HER2(−). HRc(−)/HER2(+) subtype showed better prognosis than HRc(−)/HER2(−) but worse prognosis than HRc(+) subtypes regarding both BCSS and OS. The triple-negative subtype showed the worst prognosis among all subtypes irrespective of race, age, or anatomic stage regarding BCSS. Further studies are needed to identify long term prognostic impact of each subtype on breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.-T. Hwang, S.W. Oh

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.-T. Hwang, S. Oh, J. Kim, J. Jung, Y.J. Chai, J.H. Chang, K.R. Hwang
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