Population-Based Study on Cancer Subtypes, Guideline-Concordant Adjuvant Therapy, and Survival Among Women With Stage I–III Breast Cancer

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ABSTRACT

Background: Breast cancer subtype is a key determinant in treatment decision-making, and also effects survival outcome. In this population-based study, in-depth analyses were performed to examine the impact that breast cancer subtype and receipt of guideline-concordant adjuvant systemic therapy (AST) have on survival using a population-based cancer registry's data. **Methods:** Women aged ≥20 years with microscopically confirmed stage I–III breast cancer diagnosed in 2011 were identified from the Louisiana Tumor Registry. Breast cancer subtypes were categorized based on hormone receptor (HR) and HER2 status. Guideline-concordant treatment was defined using the NCCN Guidelines for Breast Cancer. Logistic regression was applied to identify factors associated with guideline-concordant AST receipt. Kaplan-Meier survival curves were generated to compare survival among subtypes by AST receipt status, and a semiparametric additive hazard model was used to verify the factors impacting survival outcome. **Results:** Of 2,214 eligible patients, most (70.8%) were HR+/HER2– followed by HR–/HER2– (14.4%), and 78.6% received guideline-concordant AST. Compared with patients with the HR+/HER2+ subtype, women with other subtypes were more likely to be guideline-concordant after adjusting for sociodemographic and clinical variables. Women with the HR–/HER2+ or HR–/HER2– subtype had a higher risk of any-cause and breast cancer–specific death than those with the HR+/HER2+ subtype. Those who did not receive AST had an additional adjusted hazard of 0.0191 (P=.0001) in overall survival and 0.0126 (P=.0011) in cause-specific survival compared with those who received AST. **Conclusions:** Most patients received guideline-concordant AST, except for those with the HR+/HER2+ subtype. Patients receiving guideline-adherent adjuvant therapy had better survival outcomes across all breast cancer subtypes.

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Background

Since the molecular phenotypes of breast carcinomas were distinguished by gene expression patterns in 2000, breast cancer is no longer considered a single disease but rather a group of molecularly distinct neoplastic disorders.[1–4] Based on hormone receptor (HR) status, including estrogen receptor (ER) and progesterone receptor (PR), HER2 status, and proliferation markers or histologic grade, 4 distinct intrinsic molecular subtypes of breast cancer have been identified: luminal A, luminal B, basal-like (triple-negative: ER–/PR–/HER2–), and HER2+/ER–.[1,4] These subtypes vary by race and influence survival rate.[5]

When physicians prescribe appropriate adjuvant systemic therapies (ASTs) for patients with breast cancer, molecular subtypes are a key determinant. Clinical trials have demonstrated that patients with HR+ (ER+ and/or PR+) breast cancer benefit from tamoxifen, those with HR– (ER– and PR–) benefit from adjuvant chemotherapy, and those with HER2+ disease benefit from trastuzumab by decreasing recurrence and increasing survival.[6–9] The significance of these tumor markers led ASCO in 2007 to recommend measuring ER/PR and HER2 expression and/or amplification in every primary invasive breast cancer.[10] In addition, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer have taken ER/PR and HER2 status into account in guiding clinical care.[11]

Few population-based studies have examined the association of breast cancer subtypes with guideline-concordant AST and survival. Studies on guideline-concordant AST have mainly focused on adjuvant hormone therapy and chemotherapy, which was based on HR (ER and PR) status,[12,13] or examined the use of trastuzumab only.[14] No studies have examined AST with hormone therapy, chemotherapy, and trastuzumab together by breast cancer subtype. The goal of the present study was to investigate whether receipt of guideline-concordant AST varied by breast cancer

subtype after adjusting for patients' sociodemographic and tumor characteristics, and to examine the impact of guideline-concordant treatment status and cancer subtype on survival outcome.

Methods

Data Source and Study Cohort

Data on female breast cancer were obtained from the Louisiana Tumor Registry (LTR), a population-based specialized cancer registry funded by the Centers for Disease Control and Prevention's (CDC's) National Program of Cancer Registries that participates in the CDC-funded project Enhancing Cancer Registry Data for Comparative Effectiveness Research (CER) and the SEER registry. The CDC-CER registries reabstracted medical records and collected detailed and complete first-course treatment information, including type of surgery, radiation, and all systemic treatments, from all sources for patients diagnosed with breast cancer in 2011.[15] Because gene expression profiling is not performed routinely in many healthcare facilities or collected by population-based cancer registries, ER, PR, and HER2 status based on immunohistochemistry and/or fluorescence in situ hybridization (FISH) results are commonly used as surrogates to categorize breast cancer into 4 subtypes: HR+/HER2+, HR+/HER2–, HR–/HER2+, and HR–/HER2–.[16]

Eligible patients were women with breast cancer aged ≥20 years with microscopically confirmed stage I–III disease diagnosed in 2011 and who had undergone total mastectomy or breast-conserving surgery plus radiation. Eligibility was restricted to patients with histologic codes 8050, 8140, 8201, 8211, 8401, 8480, 8481, and 8500–8575 and with breast cancer as the only, first, or second primary cancer. Women who died within 30 days after surgery were excluded. A total of 32 patients were diagnosed with either bilateral breast cancers or 2 ipsilateral primary tumors in 2011; only the first primary was included. Selection of eligible patients is detailed in Figure 1.

Definition of Guideline-Concordant AST

Systemic therapies included in this study were hormonal, chemotherapy, and trastuzumab. Receipt of guideline-concordant AST was defined as treatment based on the NCCN Guidelines for Breast Cancer,[11] which takes into account cancer stage, histology, and subtype; tumor size; lymph node status; and risk score of recurrence (Table 1) for pathologically staged breast cancer. Patients who underwent total mastectomy or breast-conserving surgery plus radiation and received NCCN-recommended systemic therapy were categorized as guideline-concordant.

The multigene signature results or 21-gene recurrence score was used to determine whether chemotherapy was required for patients with HR+, node-negative, early-stage breast cancer.[11,17,18] Patients with early-stage HR+/HER2– breast cancer with tumor size >0.5 cm and negative lymph nodes were required to have chemotherapy if the recurrence score was ≥31 or there was a high risk of recurrence. In addition to routinely collected recurrence scores for breast cancer cases, LTR linked its breast cancer cases with the Oncotype DX (Genomic Health) database to obtain the recurrence risk score that was not captured in the routine data collection. In patients with node-negative, HR+/HER2– disease and tumor size >0.5 cm for whom the recurrence score assay was not performed, the NCCN Guidelines recommend chemotherapy be considered.[11] For patients aged >70 years with a subtype and tumor condition in whom adjuvant chemotherapy was an option, the guidelines suggest that chemotherapy be individualized based on the patient's comorbid conditions.[11] Hence, we used Deyo's enhanced Charlson comorbidity score (CCS)[19] to determine whether chemotherapy should be

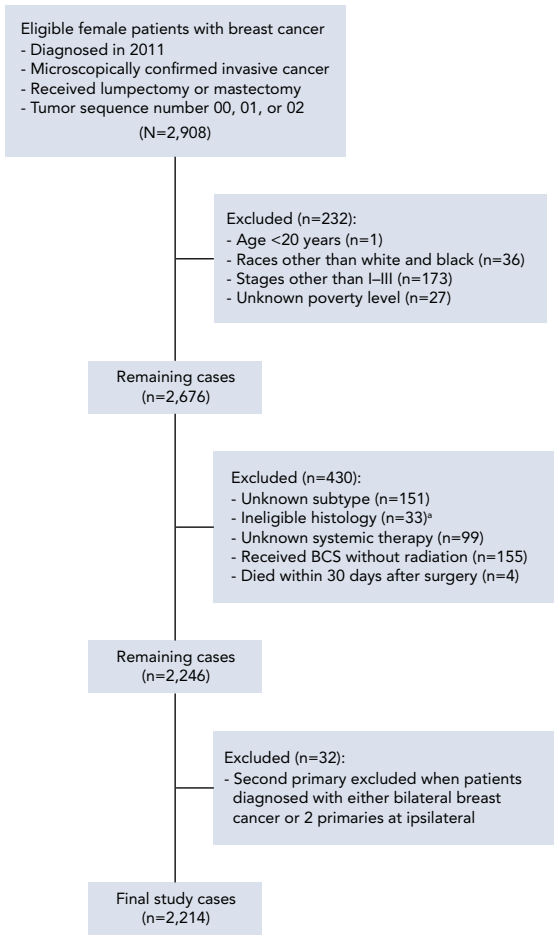

Figure 1. Flow chart of eligible study cohort selection.
[a]Histologies other than those with codes 8050, 8140, 8201, 8211, 8401, 8480, 8481, and 8500–8575 were ineligible.
Abbreviation: BCS, breast-conserving surgery.

Table 1. Recommended AST for Stage I–III Breast Cancer With Mastectomy or BCS Plus Radiation

Subtype	Lymph Node	Tumor Size	Hormone	Chemotherapy	Trastuzumab
Stage I, IIA, IIB, IIIA with N1; histology not tubular and colloid					
HR+/HER2+	pN0; pN1mi (≤2 mm)	≤0.5 cm or MI	pN0: Yes-c; pN1mi: Yes	pN1mi: Yes-c	pN1mi: Yes
		0.6–1.0 cm	Yes	Yes-c	Yes
		>1.0 cm	Yes	Yes	Yes
	Node-positive		Yes	Yes	Yes
HR+/HER2–	pN0	≤0.5 cm or MI	Yes-c		
	pN1mi (≤2 mm)	≤0.5 cm or MI	Yes		
	pN0; pN1mi (≤2 mm)	>0.5 cm	Yes	Yes[a]	
	Node-positive		Yes	Yes	
HR–/HER2+	pN0	≤0.5 cm or MI			
	pN1mi (≤2 mm)	≤0.5 cm or MI		Yes-c	Yes-c
	pN0; pN1mi (≤2 mm)	0.6–1.0 cm		Yes-c	Yes-c
		>1.0 cm		Yes	Yes
	Node-positive			Yes	Yes
HR–/HER2–	pN0	≤0.5 cm or MI			
	pN1mi (≤2 mm)	≤0.5 cm or MI		Yes-c	
	pN0; pN1mi (≤2 mm)	0.6–1.0 cm		Yes-c	
		>1.0 cm		Yes	
	Node-positive			Yes	
Stage I, IIA, IIB, IIIA with N1; histology tubular or colloid					
HR+	pN0; pN1mi (≤2 mm)	<1.0 cm			
		1.0–2.9 cm	Yes-c		
		≥3.0 cm	Yes		
	Node-positive		Yes	Yes-c	
HR–	Treat as HR– for histology not tubular and colloid				
Stage IIIA with N2+, IIIB, IIIC					
HR+/HER2+	NA	NA	Yes	Yes	Yes
HR+/HER2–	NA	NA	Yes	Yes	
HR–/HER2+	NA	NA		Yes	Yes
HR–/HER2–	NA	NA		Yes	

Data per the NCCN Guidelines for Breast Cancer.[11]
Abbreviations: AST, adjuvant systemic therapy; BCS, breast-conserving surgery; HR, hormone receptor; MI, microinvasive; NA, not applicable; Yes-c, considered adjuvant.
[a]Chemotherapy is considered if the 21-gene recurrence score is 18–30. Chemotherapy is required if the recurrence score is ≥31.

recommended for these patients. If the patients had any type of Charlson comorbidity, we assumed that adjuvant chemotherapy was not recommended.

Survival

This study assessed overall and breast cancer–specific survival. Eligible patients were followed up to December 31, 2017, if alive. Survival duration was the time between date of initial diagnosis until date of death, date of last contact, or closing follow-up if alive. The underlying cause of death for deceased patients was obtained from the state or the national death file. The event for overall survival was death from any cause. The definition of cause-specific survival for cases with tumor sequences 00 and 01 was based on the SEER cause-specific death classification using ICD-10,[20] whereas for sequence 02 cases, only patients with breast cancer as a cause of death were selected. Patients who died of other causes were censored.

Covariates

Patient demographic variables included race (white, black), age at diagnosis (<50, 50–59, 60–69, 70–79, ≥80 years), insurance status at diagnosis, marital status, and neighborhood poverty level (<10%, 10%–19.9%, ≥20%) at the census tract address at diagnosis. Clinical variables included AJCC stage (I, II, III) using the 7th edition of the AJCC Cancer Staging Manual, tumor sequence (00: 1 primary; 01 or 02: >1 primary), Bloom-Richardson grade (low, intermediate, high, unknown grade), and Deyo's enhanced CCS (no comorbidity documented, no Charlson comorbidity, CCS 1, CCS ≥2). Deyo's enhanced CCS was calculated based on comorbid conditions coded in medical records using ICD-9-CM diagnosis codes. Coding instructions and valid ICD-9-CM diagnosis codes for pre-existing comorbidity were based on the Facility Oncology Registry Data Standards (FORDS) manual.[21] The category "comorbidity not documented" included patients without a comorbid condition found in medical records or with an ICD-9-CM diagnosis code not included in the FORDS list.

Statistical Analysis

Descriptive statistics on breast cancer subtype, patient sociodemographic factors, and tumor characteristics by receipt of guideline-concordant AST were assembled, and the Pearson's chi-square test was used to assess the association. We used logistic regression to examine the association between cancer subtype and receipt of guideline-concordant AST for both unadjusted and adjusted models. The Kaplan-Meier method was used to estimate survival time by breast cancer subtype and AST receipt status, and statistically significant difference was based on the log-rank test. Although the Cox proportional hazards regression model, which estimates relative change, is the most popular model to estimate the hazard of an event occurring, it is a challenge to meet the proportional hazard assumption for a model that involves many covariates and assesses 2 different survival outcomes. Instead, we used the semiparametric additive hazard regression (SAHR) model[22,23] to estimate the regression parameter; this model can estimate the absolute change in risk rather than the relative change. Cox-Snell residuals were used to evaluate the overall fit of the SAHR model. If the model fits the data well, then the Cox-Snell residuals should follow a unit exponential distribution.[24,25] All analyses were performed using SAS 9.4 (SAS Institute Inc.), and statistical tests of significance were based on a 2-sided test with significance levels of 0.05.

Results

A total of 2,214 eligible female patients with breast cancer were included in the study: 1,582 (71.5%) were white and 632 (28.5%) were black, and 496 (22.4%) of them had either tumor sequence number 01 (192 cases) or 02 (304 cases) (Table 2). Most patients were HR+/HER2– (70.8%), followed by HR–/HER2– (14.4%), HR+/HER2+ (10.0%), and HR–/HER2+ (4.8%). The mean age was 60.0 years for HR+/HER2+, 61.9 years for HR+/HER2–, 56.6 years for HR–/HER2+, and 57.1 years for HR–/HER2–. Of 1,568 patients with HR+/HER2–, 35.6% had a recurrence score available and 3.4% were at high risk of recurrence.

Guideline-Concordant AST

An average of 78.6% of the study cohort received guideline-concordant AST. Women with the HR+/HER2+ subtype had the lowest percentage of receipt of adjuvant chemotherapy, hormone treatment, and trastuzumab (Figure 2) among the subtypes and >50% of patients with the HR+/HER2– subtype either were considered for chemotherapy or did not require chemotherapy. Compared with patients with the HR+/HER2+ subtype, patients with other subtypes were more likely to receive guideline-concordant AST with an adjusted odds ratio (aOR) of 4.08 (95% CI, 2.94–5.67) for HR+/HER2–, 3.68 (95% CI, 2.06–6.57) for HR–/HER2+, and 3.46 (95% CI, 2.29–5.23) for HR–/HER2– after controlling for other factors (Table 2). Among patients' sociodemographic factors, only age at diagnosis and poverty level were significantly associated with receipt of guideline-concordant AST (Table 2). Compared with patients aged <50 years, those aged 70–79 and ≥80 years had a 49% (aOR, 0.51; 95% CI, 0.34–0.75) and 78% (aOR, 0.22; 95% CI, 0.14–0.35) lower likelihood of receiving AST after adjusting for other covariants. Patients residing in a census tract ≥20% below poverty were more likely to be guideline-concordant (aOR, 1.47; 95% CI, 1.09–1.98) than those residing in a census tract <10% below poverty.

The percentage of patients receiving AST decreased in more advanced stages of disease. Women with stage IIA disease (T0N1M0/T1N1M0/T2N0M0) had a lower likelihood of receiving AST than those with stage IA (T1N0M0), with aOR 0.51 (95% CI, 0.38–0.67), whereas in women with stage IIIB disease (tumor directly extends to chest wall and/or skin), the aOR decreased to 0.11 (95% CI, 0.05–0.22). We also observed that women with a CCS of 1 were more likely to receive AST than those without a CCS (aOR, 1.82; 95% CI, 1.28–2.58), whereas other comorbid groups showed no statistically significant difference.

Survival Outcomes

Median follow-up was 74.8 months (range, 1.1–84.0 months). During the study period, 380 any-cause and 198 cause-specific deaths occurred. Overall, the SAHR models fitted the data well, with the Cox-Snell residuals following a unit-exponential distribution. In the unadjusted model, only women with the HR–/HER2– cancer subtype had an increased hazard of dying

Table 2. Study Cohort Characteristics and ORs of Receiving Guideline-Concordant AST

Variable	Case Count (N=2,214)	% Received AST	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Cancer subtype	*P*<.0001			
HR+/HER2+	221	56.11	Ref	Ref
HR+/HER2–	1,568	81.70	3.492 (2.600–4.689)	4.081 (2.940–5.665)
HR–/HER2+	107	80.37	3.204 (1.856–5.531)	3.679 (2.060–6.571)
HR–/HER2–	318	78.30	2.823 (1.937–4.113)	3.461 (2.290–5.229)
Sociodemographic variables				
Race	*P*=.9720			
White	1,582	78.57	Ref	Ref
Black	632	78.64	1.004 (0.802–1.257)	0.912 (0.69–1.204)
Age, y	*P*<.0001			
<50	457	79.43	Ref	Ref
50–59	567	81.31	1.126 (0.826–1.535)	1.003 (0.721–1.397)
60–69	601	83.53	1.313 (0.960–1.795)	0.961 (0.678–1.362)
70–79	398	76.38	0.837 (0.606–1.158)	0.508 (0.343–0.754)
≥80	191	57.59	0.352 (0.244–0.507)	0.221 (0.140–0.350)
Marital status	*P*=.0006			
Married[a]	1,139	81.83	Ref	Ref
Single/Separated[b]	1,001	75.32	0.678 (0.551–0.835)	0.819 (0.642–1.044)
Unknown	74	72.97	0.600 (0.351–1.023)	0.750 (0.407–1.384)
Insurance	*P*=.0384			
Private	1,160	80.34	Ref	Ref
Medicare/Other public	621	76.97	0.818 (0.646–1.036)	1.249 (0.929–1.680)
Medicaid	355	78.03	0.869 (0.650–1.161)	1.185 (0.851–1.649)
None/Unknown	78	67.95	0.519 (0.315–0.853)	0.670 (0.387–1.160)
% Poverty census tract	*P*=.3643			
<10%	575	77.04	Ref	Ref
10%–19.9%	815	78.16	1.066 (0.826–1.377)	1.165 (0.882–1.538)
≥20%	824	80.10	1.199 (0.926–1.553)	1.469 (1.089–1.982)
Clinical variables				
Tumor sequence	*P*=.3318			
00[c]	1,718	79.05	Ref	Ref
01[d] or 02	496	77.02	0.888 (0.699–1.128)	0.87 (0.669–1.132)
AJCC stage	*P*<.0001			
IA	1,062	86.06	Ref	Ref
IB	85	84.71	0.897 (0.485–1.660)	0.942 (0.485–1.828)
IIA	527	76.66	0.532 (0.408–0.694)	0.505 (0.381–0.671)
IIB	259	68.34	0.350 (0.255–0.479)	0.313 (0.222–0.439)
IIIA	158	64.56	0.295 (0.204–0.427)	0.248 (0.166–0.371)
IIIB	40	45.00	0.132 (0.069–0.253)	0.108 (0.054–0.216)
IIIC	83	63.86	0.286 (0.177–0.462)	0.233 (0.140–0.387)
Bloom-Richardson grade	*P*=.2826			
Low	478	81.17	Ref	Ref
Intermediate	929	78.26	0.835 (0.633–1.102)	1.047 (0.774–1.417)
High	642	76.64	0.761 (0.567–1.020)	1.189 (0.833–1.698)
Unknown	165	80.61	0.964 (0.615–1.510)	1.268 (0.778–2.067)

(continued on next page)

Variables included in the adjusted model were subtype, sociodemographic, and clinical.
Abbreviations: AST, adjuvant systemic therapy; CC, Charlson comorbidity; HR, hormone receptor; OR, odds ratio.
[a]Married or living with partner.
[b]Single, divorced, widowed, or separated.
[c]Breast cancer is the only primary cancer.
[d]Breast cancer is either the first or the second primary cancer.

Table 2. Study Cohort Characteristics and ORs of Receiving Guideline-Concordant AST (cont.)

Variable	Case Count (N=2,214)	% Received AST	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Clinical variables (cont.)				
Comorbidity		P=.0151		
Not documented	862	77.38	0.993 (0.794–1.242)	0.930 (0.728–1.187)
No CC	889	77.50	Ref	Ref
CC score 1	368	84.24	1.551 (1.125–2.140)	1.817 (1.281–2.578)
CC score ≥2	95	77.89	1.023 (0.615–1.703)	1.483 (0.841–2.615)

Variables included in the adjusted model were subtype, sociodemographic, and clinical.
Abbreviations: AST, adjuvant systemic therapy; CC, Charlson comorbidity; HR, hormone receptor; OR, odds ratio.
[a]Married or living with partner.
[b]Single, divorced, widowed, or separated.
[c]Breast cancer is the only primary cancer.
[d]Breast cancer is either the first or the second primary cancer.

of 0.0266 (*P*=.0001) compared with those with the HR+/HER2+ subtype (Table 3), which implies that on average an additional 27 per 1,000 women with the HR–/HER2– subtype died of any-cause death per year compared with those with the HR+/HER2+ subtype. However, for cause-specific survival, women with the HR–/HER2+ or the HR–/HER2– subtype had an increased hazard of dying of 0.0199 (*P*=.0113) and 0.0283 (*P*<.0001), respectively, compared with those with the HR+/HER2+ subtype. After adjusting for guideline-concordant AST and other factors, women with the HR–/HER2+ or the HR–/HER2– subtype had a significantly increased hazard of dying of any cause (0.0216 and 0.0266, respectively) or cause-specific death (0.0196 and 0.0262, respectively) compared with those with the HR+/HER2+ subtype.

The survival probability for women who were guideline-discordant translated to a significantly increased hazard of dying of any cause and cause-specific death compared with those adhering to guidelines in both the unadjusted and the adjusted models (Table 3). However, the impact of treatment effect on survival reduced after adjustment with a hazard of 0.0322 to 0.0191 for overall survival and 0.0182 to 0.0126 for cause-specific survival. Other covariates, such as patients with Medicaid as the primary insurance, >1 tumor, and advanced cancer stage, showed an increased hazard of death for both overall and cause–specific survival outcomes, and an older age group, a high Bloom-Richardson grade, and Charlson comorbidity were associated with risk of dying of any cause only when compared with their counterparts after adjustment.

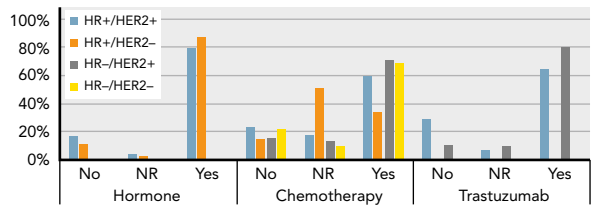

Figure 2. Percentage of patients with stage I–III breast cancer receiving adjuvant systemic therapy by treatment type and cancer subtype.
Abbreviations: HR, hormone receptor; NR, treatment not required or was considered but not received.

When comparing survival among cancer subtypes stratified by guideline-concordant AST status (Figure 3), we found that among women who received recommended AST, those with the HR–/HER2– subtype had the worst survival in both survival outcomes (Figure 3A, C). Yet among guideline-discordant women, those with the HR–/HER2– subtype had worse survival than those with other subtypes observed before year 5 after cancer diagnosis for both any-cause and cause-specific death, whereas at the fifth year after cancer diagnosis, women with the HR–/HER2+ subtype had the worst survival (Figure 3B, D). Furthermore, we compared survival between patients who were guideline-concordant and guideline-discordant receiving AST stratified by cancer subtype (Figure 4). Overall, for both survival outcomes, those receiving AST had significantly better survival across all subtypes except cause-specific survival for patients with the HR+/HER2+ subtype, which was not a significant difference (*P*=.2350; Figure 4E).

Discussion

Clinical decisions for AST for patients with breast cancer profoundly depend on their ER/PR and HER2 status. Although population-based cancer registries have been collecting ER and PR biomarkers from pathology reports and medical charts for >2 decades, it was not until the implementation of the second version of the Collaborative Stage Data Collection System, version 2,[26] on January 1, 2010, that the collection of HER2 test results was required. This is the first population-based study comprehensively evaluating the administration of complete NCCN-recommended AST by breast cancer subtype. In this study, breast cancer subtype was significantly associated with receiving guideline-concordant AST. Women with the HR+/HER2+ subtype had the lowest adherence rate (56%) for recommended AST, which may be

Table 3. Effect Estimate and SE From SAHR Model Fitting for Overall and Cause-Specific Survival

Variable	Overall Survival				Cause-Specific Survival			
	Unadjusted Model Estimate (SE)	*P* Value	Adjusted Model Estimate (SE)	*P* Value	Unadjusted Model Estimate (SE)	*P* Value	Adjusted Model Estimate (SE)	*P* Value
Cancer subtype								
HR+/HER2+	Ref		Ref		Ref		Ref	
HR+/HER2–	0.0031 (0.0046)	.5029	0.0095 (0.0050)	.0559	0.00004 (0.0031)	.9945	0.0063 (0.0035)	.0685
HR–/HER2+	0.0178 (0.0095)	.0608	0.0216 (0.0096)	.0248	0.0199 (0.0079)	.0113	0.0196 (0.0080)	.0146
HR–/HER2–	0.0266 (0.0069)	.0001	0.0266 (0.0071)	.0002	0.0283 (0.0056)	<.0001	0.0262 (0.0058)	<.0001
Guideline-concordant								
No	0.0322 (0.0050)	<.0001	0.0191 (0.0050)	.0001	0.0182 (0.0037)	<.0001	0.0126 (0.0039)	.0011
Yes	Ref		Ref		Ref		Ref	
Sociodemographic								
Race								
White	Ref		Ref		Ref		Ref	
Black	0.0088 (0.0036)	.0157	0.0006 (0.0040)	.8747	0.0135 (0.0029)	<.0001	0.0060 (0.0030)	.0484
Age, y								
<50	Ref		Ref		Ref		Ref	
50–59	−0.0059 (0.0037)	.1127	−0.0018 (0.0038)	.6291	−0.0061 (0.0034)	.0741	−0.0014 (0.0034)	.6758
60–69	−0.0017 (0.0038)	.6540	0.0049 (0.0042)	.2397	−0.0083 (0.0032)	.0110	−0.0005 (0.0035)	.8944
70–79	0.0191 (0.0052)	.0003	0.0228 (0.0061)	.0002	−0.0040 (0.0038)	.2975	0.0021 (0.0045)	.6477
≥80	0.0895 (0.0117)	<.0001	0.0863 (0.0124)	<.0001	0.0102 (0.0065)	.1148	0.0131 (0.0072)	.0701
Marital status								
Married[a]	Ref		Ref		Ref		Ref	
Single/Separated[b]	0.0222 (0.0033)	<.0001	0.0047 (0.0033)	.1570	0.0095 (0.0024)	.0001	0.0016 (0.0024)	.4999
Unknown	−0.0021 (0.0069)	.7548	−0.0101 (0.0071)	.1569	0.00003 (0.0054)	.996	−0.0046 (0.0057)	.4229
Insurance								
Private	Ref		Ref		Ref		Ref	
Medicare/Other public	0.0212 (0.0039)	<.0001	−0.0004 (0.0046)	.9333	0.0048 (0.0026)	.0601	0.0023 (0.0030)	.4430
Medicaid	0.0289 (0.0053)	<.0001	0.0178 (0.0055)	.0012	0.0178 (0.0041)	<.0001	0.0096 (0.0042)	.0222
None/Unknown	0.0005 (0.0070)	.9435	−0.0026 (0.0072)	.7169	−0.0003 (0.0052)	.9471	−0.0049 (0.0055)	.3695
% Poverty census tract								
<10%	Ref		Ref		Ref		Ref	
10%–19.9%	0.0050 (0.0029)	.0828	−0.0007 (0.0037)	.8621	0.0047 (0.0026)	.0673	0.0023 (0.0026)	.3840
≥20%	0.0096 (0.0031)	.0018	0.0004 (0.0041)	.9157	0.0085 (0.0027)	.0018	0.0019 (0.0029)	.5134
Tumor sequence								
00[c]	Ref		Ref		Ref		Ref	
01[d] or 02	0.0248 (0.0046)	<.0001	0.0228 (0.0046)	<.0001	0.0052 (0.003)	.0808	0.0075 (0.0031)	.0155
AJCC stage								
I	Ref		Ref		Ref		Ref	
II	0.0157 (0.0032)	<.0001	0.0136 (0.0033)	<.0001	0.0121 (0.0022)	<.0001	0.0079 (0.0022)	.0004
III	0.0632 (0.0079)	<.0001	0.0581 (0.0080)	<.0001	0.0535 (0.0067)	<.0001	0.0472 (0.0067)	<.0001
Bloom-Richardson grade								
Low	Ref		Ref		Ref		Ref	
Intermediate	0.0046 (0.0036)	.2029	0.0006 (0.0037)	.8736	0.0020 (0.0023)	.3840	−0.0031 (0.0023)	.1901
High	0.0211 (0.0045)	<.0001	0.0130 (0.0052)	.0126	0.0212 (0.0034)	<.0001	0.0074 (0.0038)	.0544
Unknown	−0.0030 (0.0053)	.5750	−0.0075 (0.0056)	.1769	0.0026 (0.0039)	.5041	−0.0068 (0.0040)	.0946

(continued on next page)

Variables included in the adjusted model were subtype, guideline-concordant adjuvant systemic therapy, sociodemographic, and clinical.
Abbreviations: CC, Charlson comorbidity; HR, hormone receptor; SAHR, semiparametric additive hazard regression model; SE, standard error.
[a]Married or living with partner.
[b]Single, divorced, widowed, or separated.
[c]Breast cancer is the only primary cancer.
[d]Breast cancer is either the first or the second primary cancer.

Table 3. Effect Estimate and SE From SAHR Model Fitting for Overall and Cause-Specific Survival (cont.)

Variable	Overall Survival				Cause-Specific Survival			
	Unadjusted Model Estimate (SE)	*P* Value	Adjusted Model Estimate (SE)	*P* Value	Unadjusted Model Estimate (SE)	*P* Value	Adjusted Model Estimate (SE)	*P* Value
Sociodemographic (cont.)								
Comorbidity								
Not documented	−0.0037 (0.0031)	.2358	−0.0002 (0.0032)	.9576	−0.0027 (0.0024)	.2593	−0.0014 (0.0025)	.5812
No CC	Ref		Ref		Ref		Ref	
CC score 1	0.0174 (0.0052)	.0009	0.0117 (0.0053)	.0269	0.0027 (0.0035)	.4338	0.0016 (0.0035)	.6466
CC score ≥2	0.0564 (0.0135)	<.0001	0.0437 (0.0134)	.0011	0.0161 (0.0084)	.0559	0.0117 (0.0084)	.1635

Variables included in the adjusted model were subtype, guideline-concordant adjuvant systemic therapy, sociodemographic, and clinical.
Abbreviations: CC, Charlson comorbidity; HR, hormone receptor; SAHR, semiparametric additive hazard regression model; SE, standard error.
[a]Married or living with partner.
[b]Single, divorced, widowed, or separated.
[c]Breast cancer is the only primary cancer.
[d]Breast cancer is either the first or the second primary cancer.

attributed to all 3 regimens of systemic therapy (hormone, chemotherapy, trastuzumab) being recommended for early-stage disease (stage I, II, and IIIA with N1), except for stage I disease with tumor size ≤1 cm or favorable histologies (tubular and colloid). Compliance rates for other subtypes were similar, at approximately 80%.

Among sociodemographic variables, age was inversely associated with receipt of AST and remained highly significant after adjusting for cancer subtype and other variables, consistent with previous studies.[12,13,27] We observed no differences in guideline concordance for women aged <70 years, whereas adherence to AST decreased significantly for those aged ≥70 years. In addition, women living in a census tract ≥20% below poverty had a higher adherence rate for AST, which could be attributed to Louisiana's unique public hospital system that provides free standard care to patients who are underserved. Regarding the association between receipt of AST and clinical variables, our results indicate that the likelihood of guideline concordance decreases with advanced disease stages and that women with mild comorbidity (CCS 1) are more likely to be guideline-concordant than those without comorbidity, which contradicts findings of other studies.[12] One possible explanation is that previous studies excluded cases for which adjuvant therapy was "considered," whereas our study categorized "considered" systemic therapy as guideline-concordant despite whether the treatment was received.

Numerous clinical trials have demonstrated the benefit of specific systemic therapy for HR+ or HER2+ breast cancer. By jointly considering all AST, we found that women who were guideline-concordant significantly improved in both survival outcomes across the 4 subtypes. The study revealed that women with HR+ disease regardless of HER2 status had almost identical cause-specific survival among those receiving guideline-recommended AST. Most studies have found that patients with the HR+/HER2– subtype had the best survival rate among subtypes[28–31]; nevertheless, our data showed that women with HR+/HER2+ tumors had the best survival outcomes except for cause-specific survival in the guideline-concordant cohort. Another key finding from this study is that among patients with HR–, those with HER2+ had better overall and cause-specific survival than those with HER2– when they received NCCN-recommended chemotherapy and trastuzumab. Survival differences in these patients were amplified with longer observation. This result confirmed the effect of trastuzumab after chemotherapy for HER2+ tumors, demonstrated in several clinical trials,[8,9] particularly in HR– cohorts. Although 80% of patients with HR–/HER2– were guideline-concordant, their survival rate was worst among the 4 subtypes in both overall and cause-specific death, primarily because there are no effective biomarker-targeted therapies to prolong patient survival and maintain a high relapse rate,[32,33] and the only option for treatment in these patients is conventional chemotherapy.

We found that women aged ≥70 years were less likely to be guideline-concordant and had an increased hazard in overall survival, but not in cause-specific survival, compared with their counterparts. After stratifying by age group, we found that women aged ≥70 years who were guideline-concordant had a significantly improved overall survival (*P*=.0009). Treating elderly patients with breast cancer is a complex process, and several factors such as life expectancy, existing comorbidity, treatment complications, benefit, and quality of life are usually considered in treatment decision-making. However, elderly patients with breast cancer should be informed of the standard adjuvant treatment and available options that would benefit them.[34]

This study has several strengths. First, it is a population-based study, using high-quality data from a statewide cancer registry. Second, complete treatment information was collected from all sources, including

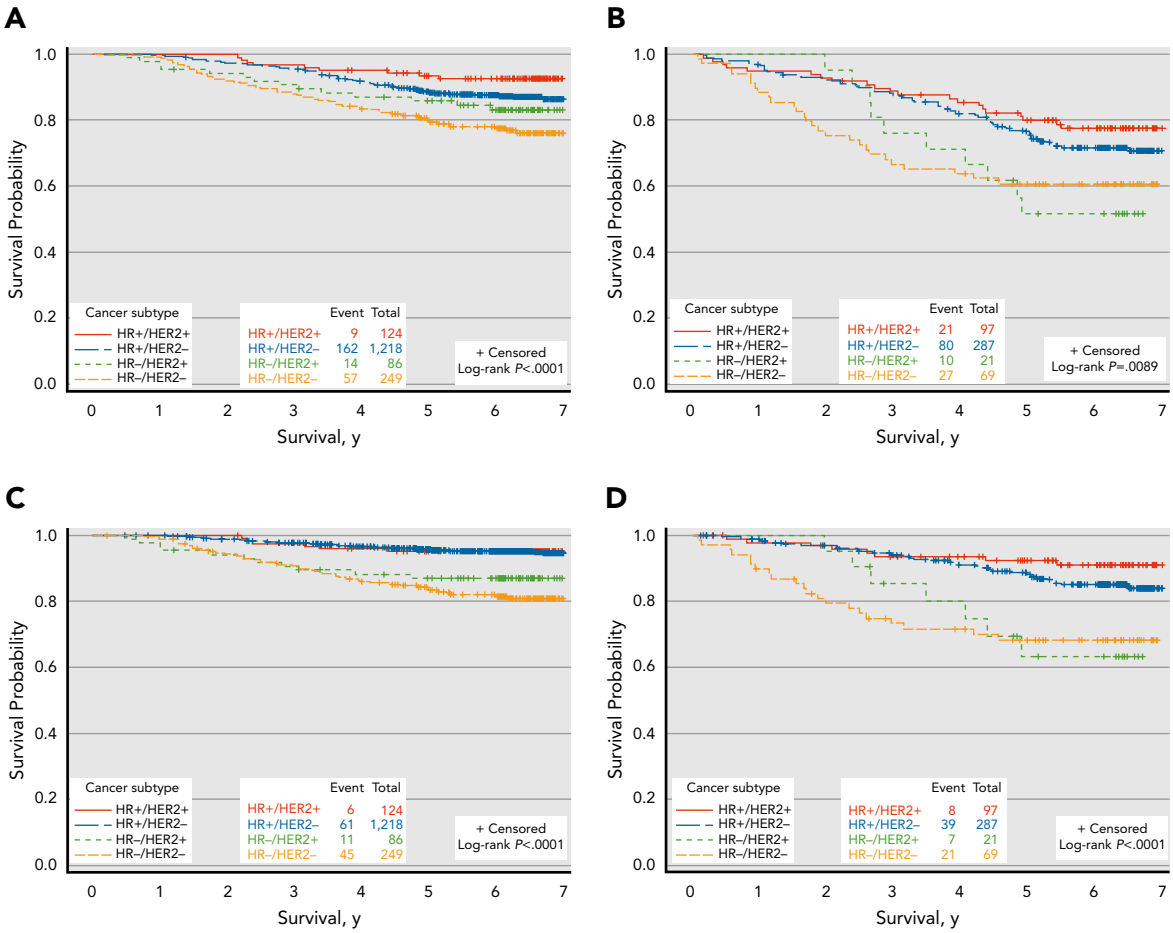

Figure 3. Kaplan-Meier survival curves by subtype for (A) overall survival for guideline-concordant AST, (B) overall survival for guideline-discordant AST, (C) cause-specific survival for guideline-concordant AST, and (D) cause-specific survival for guideline-discordant AST.
Abbreviations: AST, adjuvant systemic therapy; HR, hormone receptor.

physicians' offices, for all types of systemic therapy, including the Cancer Chemotherapy National Service Center (NSC) number on systemic therapy drugs and the completion status of chemotherapy. This comprehensive process enabled us to separate trastuzumab (NSC number: 688097), which is specifically recommended for patients with HER2+, from chemotherapy drugs due to the classification. Third, the linkage of LTR data with the Oncotype DX database allowed us to capture recurrence risk score from multigene signature tests and supplement this site-specific factor in the registry data. The recurrence risk score is an important determinant in chemotherapy administration for patients with node-negative, HR+/HER2–, early-stage breast cancer per the NCCN Guidelines.[11]

A few limitations should be noted. First, information was lacking on the rationale behind a physician's decision whether to give AST to patients with disease for which the NCCN Guidelines recommend adjuvant therapy be "considered" with certain systemic therapy. In addition, administering recommended adjuvant chemotherapy to patients aged ≥70 years may vary by physician based on the approach to this age group when taking into consideration patients' existing comorbid conditions, life expectancy, or preference. Another limitation was using the immunohistochemical-based (and/or FISH-based) surrogate cancer subtype to estimate survival, which may not be comparable to gene-expression profile cancer subtype. However, this study demonstrated that the benefits of adhering to guideline-concordant AST among subtypes are the same as in clinical trials based on gene-expression profiling. Finally, the follow-up time may not have been long enough to capture adequate events for subtypes that had a longer survival time, such as HR+, to ensure estimated statistical tests with sufficient power,[35] particularly in cause-specific survival.

Conclusions

This study showed that in a community setting, women with breast cancer had better survival outcomes if they

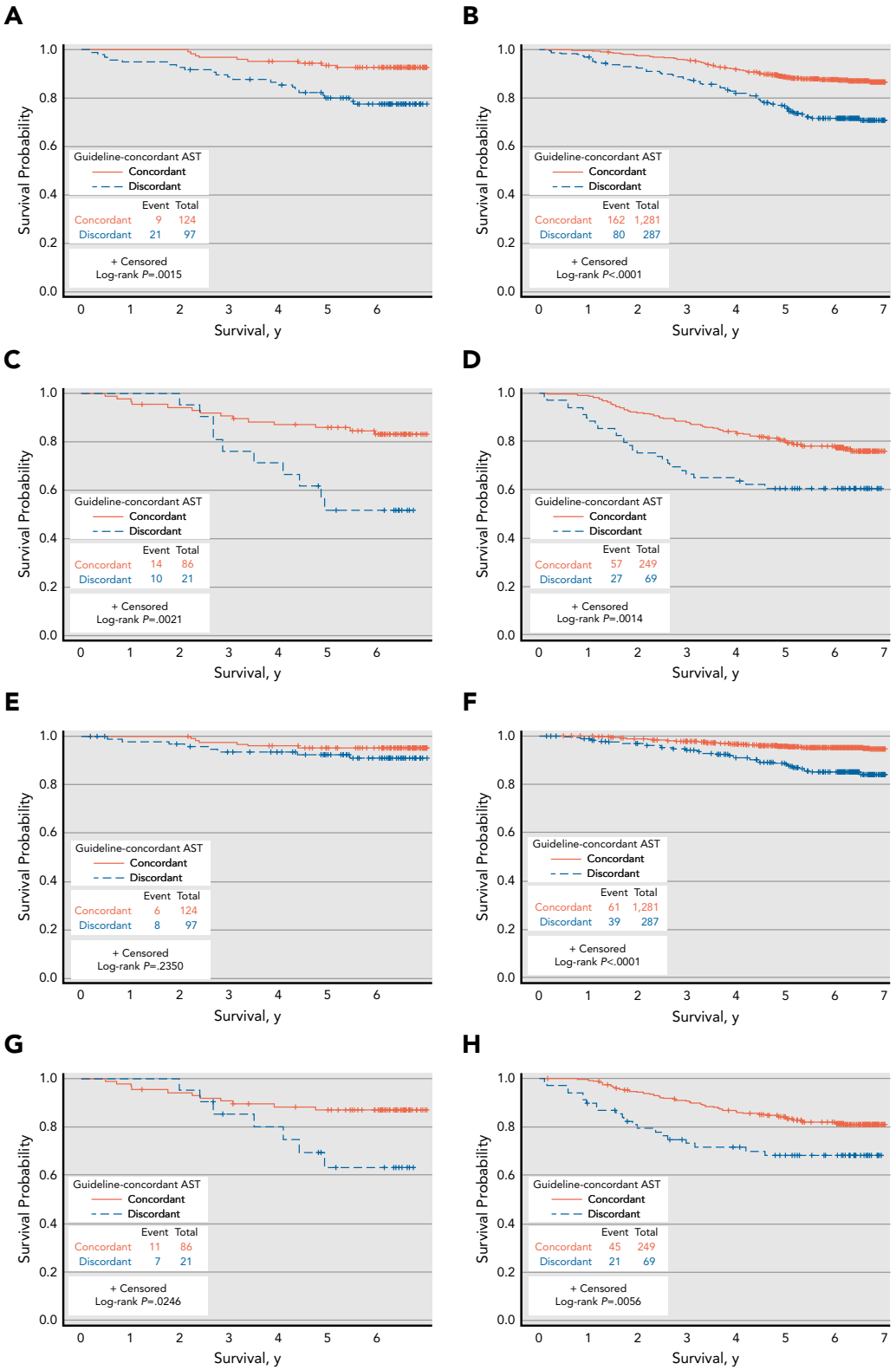

Figure 4. Kaplan-Meier survival curves by guideline-concordant AST status stratified by cancer subtype among women with stage I–III breast cancer. Overall survival for (A) HR+/HER2+, (B) HR+/HER2–, (C) HR–/HER2+, and (D) HR–/HER2–. Cause-specific survival for (E) HR+/HER2+, (F) HR+/HER2–, (G) HR–/HER2+, and (H) HR–/HER2–.

Abbreviations: AST, adjuvant systemic therapy; HR, hormone receptor.

adhered to guideline-concordant AST. Although women with the HR+/HER2+ subtype had the lowest rate of receiving guideline-concordant treatment, their overall and cause-specific survival rates were the best among the 4 subtypes. In contrast, patients with HR–/HER2– had the worst survival outcomes even with a high rate of guideline-adherent treatment. Advances in treatment options other than chemotherapy are urgently needed to improve survival for women with HR–/HER2– breast cancer.

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