African-American Race Is Associated With a Poorer Overall Survival Rate for Breast Cancer Patients Treated With Mastectomy and Doxorubicin-Based Chemotherapy

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BACKGROUND. African-American (AA) race has been associated with a worse outcome in breast cancer. It is unclear whether this is due to biological factors, socioeconomic factors, or both.

METHODS. The records from 2 independent cohorts of breast cancer patients treated on institutional protocols with mastectomy and adjuvant (n = 1456) or neoadjuvant (n = 684) doxorubicin-based chemotherapy were retrospectively reviewed.

RESULTS. The adjuvant (Adj) chemotherapy cohort included 1142 Caucasian (CA), 186 Hispanic (HI), and 128 (AA) patients. The neoadjuvant (Neo) chemotherapy protocols included 448 CA, 114 HI, and 122 AA patients. In both groups, AA patients had later-stage tumors (Adj $P = .017$; Neo $P = .051$), a higher rate of estrogen receptor (ER)-negative disease (Adj $P = .054$; Neo $P = .039$), and a worse 10-year actuarial overall survival rate than CA or HI patients (Adj, 52%, 62%, and 62%, respectively, $P = .009$; Neo, 40%, 50%, and 56%, respectively, $P = .015$). In multivariate analyses, AA race remained independently associated with a poorer overall survival rate in both cohorts (Adj, hazard ratio = 1.39, $P = .018$; Neo, hazard ratio = 1.37, $P = .02$).

CONCLUSIONS. The data suggest that AA race is associated with less favorable biological tumor features, such as an increased likelihood of ER-negative disease, than those found in CA and HI patients. Such differences in tumor biology, as well as previously described socioeconomic factors, likely contribute to the lower rate of survival in the AA breast cancer population. ***Cancer*** **2006;107:2662–8.**

KEYWORDS: race, African-American, Hispanic, breast cancer, mastectomy.

Population-based epidemiology studies have demonstrated that African-American (AA) women with breast cancer have lower overall survival (OS) and cancer-specific survival rates than Caucasian (CA) women with breast cancer.[1,2] Many factors have been implicated in this disparity, including differences in access to healthcare, screening, use of adjuvant therapy, body mass index, comorbidities, socioeconomic status, and side effects from adjuvant therapies that lead to lower doses, as well as biases among physicians and patients.[3–9] In addition, some data suggest that AA patients more commonly have high-grade and estrogen receptor (ER)-negative disease.[10–14] However, the validity of such data has been questioned, and in a consensus statement concerning race and breast cancer, Middleton et al.[15] concluded that the aggressive tumor histology reported in AA women needs to be studied further. Newman et al.[8] compared pooled outcome

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data of 14,013 AA women and 76,111 CA patients and concluded that AA ethnicity was associated with excess risk of overall mortality and breast cancer-specific mortality even after adjusting for socioeconomic factors and tumor characteristics.

In this study, we examined the tumor characteristics and outcomes of women with breast cancer treated with mastectomy and doxorubicin-based chemotherapy on prospective clinical trials. We analyzed the effect of race on outcome in 2 independent cohorts: women treated with neoadjuvant chemotherapy and women treated with adjuvant chemotherapy. Limiting the study to patients treated on prospective institutional trials minimized biases related to access to treatment and differences in treatment type, although this cannot affect biases present before enrollment on protocol or registration at our institution. Regional demographics allow for comparisons between AA patients, CA patients, and Hispanic (HI) patients. Herein, we report that AA race was an independent predictor of poorer overall survival rates.

MATERIALS AND METHODS

Patient, Tumor, and Treatment Characteristics

Between 1975 and 2000, 2140 patients were treated with doxorubicin-based adjuvant or neoadjuvant systemic therapy, with or without tamoxifen and mastectomy, on sequential, prospective clinical trials at the University of Texas M. D. Anderson Cancer Center. We retrospectively analyzed the outcomes of 2 independent cohorts of patients: the 1456 patients who were treated on adjuvant systemic therapy protocols and the 684 patients treated with neoadjuvant chemotherapy protocols. The Institutional Review Board (IRB) approved each protocol, and all patients provided written informed consent for study participation. IRB approval was obtained for the current study. Forty-seven patients whose self-reported race was other than CA, HI, or AA were excluded from this analysis because the number was too small for adequate analysis. Although HI race was self-reported, it is important to note that HI reflects individuals from a variety of racial backgrounds, which should be considered in comparing this population to other races as reported here.

Patients over the age of 75, those with evidence of distant metastasis at diagnosis, and those with a prior or concurrent malignancy were not eligible for inclusion in these trials. All patients underwent either a radical mastectomy or a modified radical mastectomy and adjuvant or neoadjuvant systemic therapy that consisted of combination chemotherapy that included doxorubicin. Details of each regimen have been published previously.[16–25] Table 1 shows the racial distribution of patients in each protocol. In addition to chemotherapy, 575 (27%) patients who had ER+ and/or progesterone receptor-positive tumors received tamoxifen. Although fewer AA patients had ER+ tumors, the percentage of ER+ patients treated with tamoxifen was not different by race (AA 53% vs CA 51% $P = .364$). Postmastectomy radiation therapy was used in 53% of cases. The clinical, biologic, treatment, pathologic, and outcome data for all patients were retrospectively recorded from the medical records. All patients had pathology results reviewed at our institution before treatment. All patients were clinically staged according to the 1988 American Joint Committee on Cancer Staging and End Results Reporting guidelines.

TABLE 1
Breast Cancer Chemotherapy Protocol Enrollment by Race

	No. of patients		
Protocol	AA	HI	CA
75–23	10	9	136
77–30	16	20	157
80–26	17	38	220
82–79	28	26	180
85–01	21	36	111
86–12	55	91	440
89–005	0	0	1
89–007	31	17	73
91–015	18	23	76
94–002	7	12	69
97–099	12	9	43
Advanced primary	33	17	75

AA indicates African American; HI, Hispanic; CA, Caucasian.

Follow-up, Endpoints, and Statistical Analysis

Patient follow-up was done according to protocol guidelines and consisted of physical examination, routine laboratory studies, chest X-rays, and bone scans. Median follow-up from the date of initial diagnosis for all patients was 9.9 years (range, 0.5–24 years).

The comparison of tumor and patient characteristics between races was performed using the chi-square test. Actuarial rates of OS and distant metastasis-free survival (DMFS) were calculated using the Kaplan-Meier method, with comparisons among groups performed using 2-sided log rank tests.[26,27] Multivariate analysis was performed using the Cox proportional hazards model. Histologic grade was not included in the multivariate analysis because of the large number of unknown values. All P values were 2-tailed, with a value of ≤ 0.05 considered significant.

TABLE 2
Adjuvant Cohort: Patient and Tumor Characteristics

Characteristic	No. of patients (%) N = 1456			P*
	AA	HI	CA	
Stage				.017
I	5 (4)	4 (2)	31 (3)	
IIA	27 (23)	48 (27)	361 (36)	
IIB	58 (49)	93 (53)	460 (46)	
IIIA	28 (24)	26 (15)	139 (14)	
IIIB	0 (0)	3 (2)	7 (1)	
IV	0 (0)	2 (1)	7 (1)†	
Histologic grade				NS
Well differentiated	5 (6)	15 (11)	67 (9)	
Moderately differentiated	41 (46)	70 (52)	369 (49)	
Poorly differentiated	43 (48)	50 (37)	310 (42)	
No. involved nodes				NS
0	17 (13)	20 (11)	108 (10)	
1–3	54 (43)	75 (41)	456 (40)	
4–9	36 (28)	58 (32)	336 (30)	
≥10	20 (16)	29 (16)	230 (20)	
Pathologic size of primary tumor, cm				.002
0–2	23 (19)	45 (26)	343 (34)	
2.1–5	70 (59)	105 (61)	527 (53)	
>5	25 (22)	22 (13)	129 (13)	
ER status				.054‡
Positive	36 (28)	71 (39)	441 (39)	
Negative	52 (41)	58 (32)	373 (33)	
Unknown	40 (31)	55 (30)	326 (29)	

AA indicates African American; HI, Hispanic; CA, Caucasian; NS, not significant; ER, estrogen receptor.
* Chi-square test.
† Because of small differences in rounding numbers, percentages do not always equal 100%.
‡ Comparison excluding unknowns.

RESULTS

Patients Treated with Adjuvant Chemotherapy

Table 2 shows the demographic and tumor characteristics for the CA, HI, and AA patients treated in the adjuvant chemotherapy protocols (n = 1456). This cohort included 1142 CA, 186 HI, and 128 AA patients. There was no statistically significant difference in age of diagnosis between AA and CA women. AA women were diagnosed at a median age of 50 (range, 15–79), and CA women were diagnosed at a median age of 49 (range, 22–78). HI women were younger at diagnosis (median age, 47; range, 18–74) than either AA or CA women ($P = .001$ and .0001, respectively).

On univariate analysis, AA patients had larger primary tumors, later-stage tumors, and a higher rate of ER-negative disease than did the other 2 groups ($P = .002$, .017, and .054, respectively). Twenty-four percent of AA women presented with Stage III or had supraclavicular nodal disease, compared with 16% of CA women. Twenty-two percent of AA women presented with >5 cm primary tumors compared with 13% of CA women. In addition, 41% of AA women had ER-negative tumors compared with 33% of CA women. Although a higher percentage of AA women had higher-grade disease than CA or HI women (48% vs 42% and 37%, respectively), this difference did not reach statistical significance ($P = .432$). There was no difference in the total number of chemotherapy cycles between AA and non-AA women, with both groups receiving a median of 8 cycles ($P = .241$).

The Kaplan-Meier curves for DMFS and OS according to race for the patients treated on adjuvant chemotherapy trials are shown in Figure 1A, B, respectively. AA patients had lower 10-year actuarial DMFS rates than did CA and HI patients (11% vs 31% and 35%, respectively; $P = .001$ for all race groups). AA patients also had lower 10-year actuarial OS rates (52% vs 62% and 62%, respectively; $P = .009$, for all 3 race categories).

Patients Treated with Neoadjuvant Chemotherapy

Table 3 shows the demographic and tumor characteristics for the CA, HI, and AA patients treated on the neoadjuvant chemotherapy trials (n = 684). This population included 448 CA, 114 HI, and 122 AA patients. There was no statistically significant difference in the age of diagnosis between AA, HI, and CA women ($P = .305$). As in the adjuvant chemotherapy cohort, the AA patients who received neoadjuvant chemotherapy had more advanced clinical stage disease, larger primary tumors, and higher rates of ER-negative disease than did the CA and HI patients ($P = .051$, .005, and .039, respectively). AA women also had a lower rate of response (complete response [CR] or partial response [PR]) to neoadjuvant chemotherapy, although this did not reach statistical significance (73%, 85%, and 78% for AA, HI, and CA women, respectively; $P = .076$). This difference was marginally significant when the rates of clinical CR only were compared (6%, 12%, and 14% for AA, HI, and CA women, respectively; $P = .051$). The respective rates of pathologic CR in the 3 groups were 11%, 17%, and 15% ($P = .452$). AA women received more total cycles of chemotherapy than did non-AA women, a median of 9.5 cycles vs 8 cycles ($P = .004$).

Figure 1C,D displays the DMFS and OS curves according to race for the patients treated with neoadjuvant chemotherapy. The 10-year DMFS rate was lower for AA women than for HI or CA women (46% vs 54% and 49%, respectively), although this was not statistically significant ($P = .200$). However, the 10-year actuarial OS rate was worse for AA patients than for CA or HI patients (40% vs 50% and 56%, respectively; $P = .015$). The difference in OS between CA and HI patients was not statistically significant ($P = .715$).

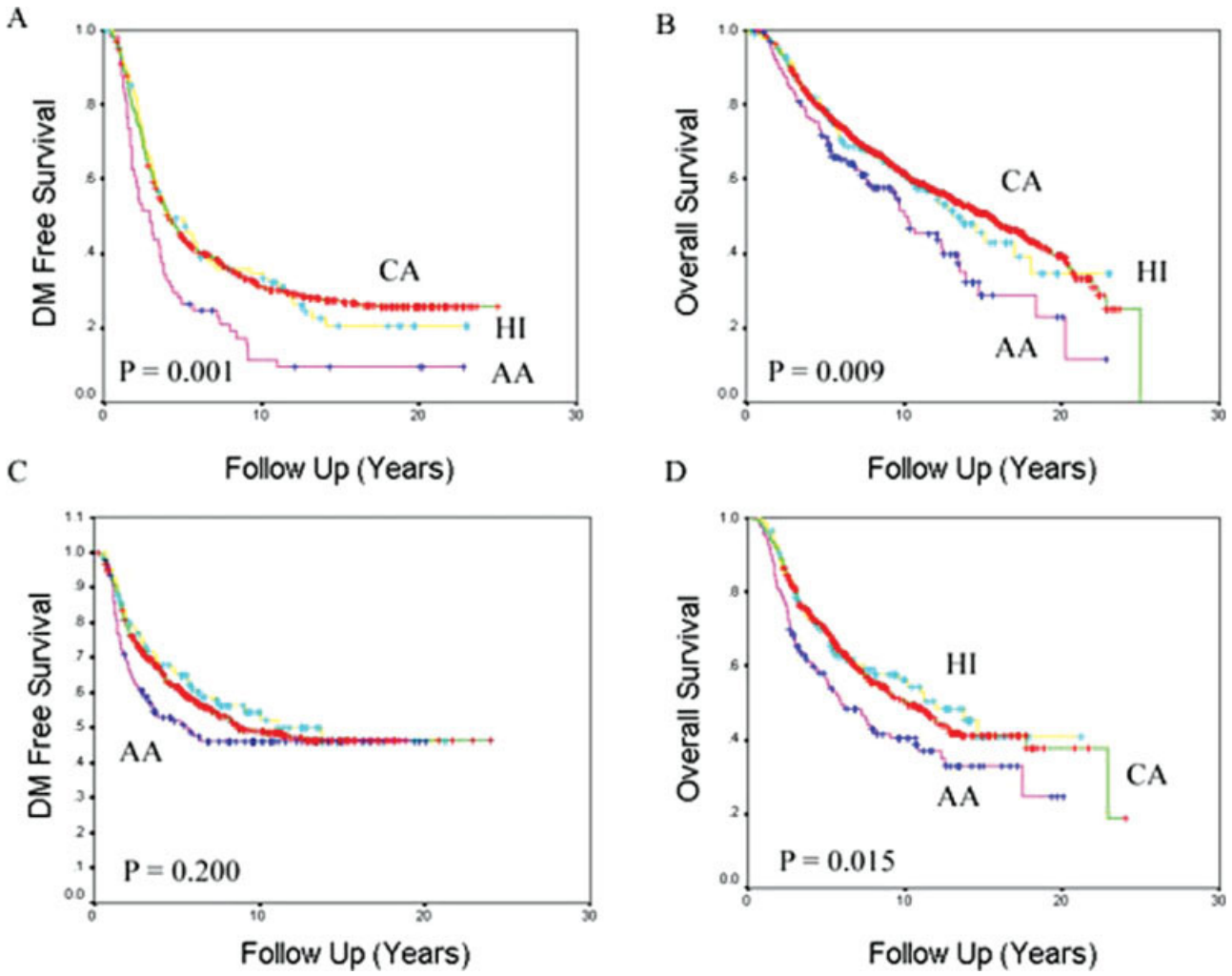

FIGURE 1. (A) Adjuvant cohort: African-American patients have a lower distant metastasis-free survival rate than that of Caucasian and Hispanic patients (11%, 31%, and 35%, respectively). (B) Adjuvant cohort: African-American patients have a lower overall survival rate than Caucasian patients (52% vs 62%). Caucasian and Hispanic patients have equal 10-year distant metastasis-free survival (DMFS) rates (62%). (C) Neoadjuvant cohort: African-American patients have a lower DMFS rate compared with Caucasian and Hispanic patients, although this difference is not statistically significant (46%, 49%, and 54%, respectively). (D) Neoadjuvant cohort: African-American patients have a lower overall survival rate than Hispanic and Caucasian patients (40%, 56%, and 50%, respectively).

Multivariate Analyses

Table 4 demonstrates the results of multivariate analyses adjusted for differences in clinical stage. Histologic grade was excluded from these analyses because of the large number of patients with missing values. The neoadjuvant multivariate analysis was run using clinical stage instead of pathologic factors as well as with pathologic factors instead of clinical stage, as pathologic variables may be confounded by the response to chemotherapy. As shown, AA race remained an independent predictor of lower OS rates in both cohorts (adjuvant, hazard ratio = 1.39, $P = .018$; neoadjuvant [clinical stage], hazard ratio = 1.37, $P = .020$; neoadjuvant [pathologic factors], hazard ratio = 1.44, $P = .008$) in both forward and backward regression analyses. AA race also remained an independent predictor for distant metastasis in the adjuvant dataset (adjuvant, hazard ratio = 1.54, $P = .005$).

DISCUSSION

In this study, we report that AA race was independently associated with a lower OS rate than that in both CA and HI races in women with locally advanced, nonmetastatic breast cancer treated with mastectomy and doxorubicin-based chemotherapy. We confirmed this finding in 2 independent datasets of patients treated on prospective protocols.

This study has several advantages over previous retrospective studies that have evaluated race and

TABLE 3
Neoadjuvant Cohort Patient and Tumor Characteristics

Characteristic	No. (%) N = 684 AA	HI	CA	*P**
Stage				.051
IIA	0 (0)	5 (4)	20 (4)	
IIB	14 (11)	18 (16)	83 (19)	
IIIA	34 (29)	32 (28)	130 (29)	
IIIB	65 (53)	46 (40)	168 (38)	
IV	9 (7)	13 (10)†	47 (10)	
Histologic grade				NS
Well differentiated	7 (7)	7 (7)	39 (10)	
Moderately differentiated	38 (38)	40 (40)	165 (43)	
Poorly differentiated	56 (55)	52 (52)	183 (47)	
No. involved nodes				NS
0	39 (34)	30 (27)	128 (29)	
1–3	15 (13)	13 (12)	53 (12)	
4–9	41 (34)	44 (40)	138 (31)	
≥10	25 (21)	23 (21)	124 (28)	
Pathologic size of primary tumor, cm				.005‡
0–2	46 (38)	57 (51)	220 (50)	
2.1–5	55 (45)	40 (37)	168 (38)	
>5	21 (17)	14 (13)	54 (12)	
ER status				.039
Positive	43 (35)	55 (48)	204 (46)	
Negative	63 (52)	44 (39)	165 (37)	
Unknown	16 (13)	15 (13)	79 (18)	
Clinical CR/PR				.076
No	33 (27)	17 (15)	97 (22)	
Yes	89 (73)	97 (85)	350 (78)	
Pathologic CR				NS
No	108 (89)	92 (83)	374 (85)	
Yes	14 (11)	19 (17)	68 (15)	

AA indicates African American; HI, Hispanic; CA, Caucasian; NS, not significant; ER, estrogen receptor; CR, complete response; PR, partial response.

* Chi-square test.

† Because of small differences in rounding numbers, percentages do not always equal 100%.

‡ *P* from comparison as continuous variable between AA and CA.

TABLE 4
Multivariate Analysis of Overall Survival for Adjuvant and Neoadjuvant Cohorts*

Adjuvant cohort	HR	95% CI	Neoadjuvant cohort	HR	95% CI
Positive LN >0	1.95	1.18–3.22	Positive LN >0	1.69	1.22–2.34
Pathologic primary >2 cm	1.64	1.33–2.00	Pathologic primary >2 cm	1.58	1.25–2.00
Age >50 y	1.28	1.08–1.52	Age >60 y	1.51	1.15–1.99
ER-negative/unknown	1.41	1.17–1.69	ER-negative disease	1.42	1.13–1.79
AA race	1.39	1.05–1.83	AA race	1.44	1.12–2.19

LN indicates lymph nodes; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; AA, African American.

* Histologic grade excluded from analysis because of missing data.

breast cancer outcome including an older report of unselected patients treated at this institution before the adjuvant chemotherapy era[28] and a more recent report on a smaller cohort of patients treated on 2 neoadjuvant chemotherapy protocols that was expanded herein.[29] All patients included in this report were treated according to protocol guidelines. In general, patients were enrolled in these studies only if they were able to undergo chemotherapy and had the resources to be compliant with treatment. Indeed, we found that AA women received at least as many chemotherapy cycles than did non-AA women, making it highly unlikely that noncompliance with treatment led to the poorer OS rates. Also, our study population included a significant number of HI patients. In the greater Houston area, HI and AA women have similar socioeconomic status (discussed in greater detail below). Therefore, HI patients served as an important comparison group for the AA patients in this study. For these reasons, we interpret these data as suggesting that intrinsic biologic differences in the disease and response to treatment among racial groups contributed to the poorer OS rates seen in the AA cohorts.

It is clear that, as with any cohort grouped by self-reported race, those who self-report their race as AA or black represent a genetically and culturally diverse group. Therefore, explaining how AA race is associated with biologically more aggressive breast cancer will likely be difficult. One avenue for future study would be to investigate whether some cohorts of AA women have genetic polymorphisms involved in estrogen regulation than other racial groups. It is possible that epigenetic phenomena, such as an increased likelihood of being exposed to a carcinogen, contribute to the formation of more virulent breast cancer; however, it is important to note that racial disparity in survival outcomes from breast cancer did not emerge in the Surveillance, Epidemiology, and End Results (SEER) data until 1980.[30] In the era of targeted therapy it is possible that it is not inherent baseline differences in biology that drive disparate outcomes but rather imbalances in the biological factors that determine response to new therapy and to which newer therapies are targeted. The findings of this study suggest that additional work aimed at elucidating biological mechanisms for this phenomenological relation is warranted.

Our findings support some previously reported studies. Data from the National Surgical Adjuvant Breast Project (NSABP) B-06 trial indicated that AA women more frequently had ER-negative disease and high-grade tumors and that AA race was associated with a poorer survival rate.[31] More recently, investigators from the Southwestern Oncology Group (SWOG) studied the relation between race and outcome for

patients treated on clinical trials. This study also found AA race to be associated with a lower OS rate (hazard ratio of 1.41 [$P = .007$] among premenopausal women and 1.49 [$P < .0001$] among postmenopausal women).[32] The SWOG study included an analysis of socioeconomic status and body mass index and found that the correlation of race with outcome was independent from these factors.[32] In contrast, Cross et al.[6] and data from NSABP B-04[31] found that race was not an independent predictor of outcome after adjusting for low socioeconomic status.

National statistics show that poorer survival rates in AA breast cancer patients than in CA breast cancer patients[1,7,33,34] are also in part due to socioeconomic variables, including less frequent screening, less aggressive treatment, and failure to seek medical care. As our study investigated only patients treated on clinical trials, some of these potentially confounding socioeconomic variables were minimized (bias or delay impacting referral patterns to our center are not minimized by protocol enrollment; however, there is no obvious reason to suggest this would disparately impact AA over HI patients at outside referral centers). Although we did not directly study whether socioeconomic status affected outcome, we feel it is unlikely that it completely explains the lower OS rate found in the AA population in our study. In our patient referral area the socioeconomic status of HI and AA women is roughly similar. For example, cumulative results of a survey of Harris Country residents showed that 55% of AA residents, 58% of US-born HI residents, and 70% of HI immigrants make <$25,000 annually. The survey also reported that, whereas only 12.8% of AA residents do not have a high school diploma, 20.9% of US-born HI residents and 34.4% of HI immigrants have not completed high school or a high school equivalency exam.[35,36] Another important finding of this study is that HI and CA women had similar breast cancer outcomes. Although there have been numerous previous reports of breast cancer outcomes in AA women, many fewer studies have focused on HI women. Our results are consistent with those of a recently published report that used the National Cancer Institute's SEER Program database and found that self-reported HI race was associated with a lower breast cancer incidence and death rate than that in non-HI whites.[29] In our study, HI women had equal or higher OS and DMFS rates than non-HI whites, although these differences were not statistically significant.

It is important to recognize the limitations of our report. As previously mentioned, we were unable to measure socioeconomic status directly in this study. This limitation is shared by many recent studies, as this information is difficult to obtain retrospectively. Therefore, it is possible that unidentified socioeconomic factors contributed to the differences noted in this study. In addition, AA patients had more advanced disease at the time of treatment. We were not able to determine whether this was due to less access to healthcare, neglect in seeking healthcare, or intrinsic differences in tumor biology. Although we demonstrated that AA women did not receive fewer cycles of chemotherapy, we were not able to critically evaluate the dose intensity. Hershman et al.[4] reported that lower baseline white blood counts led to lower dose intensity among AA women. Although treatment on protocol may reduce bias of this type, it cannot be completely eliminated. Tumor grade, which has a well-recognized association with outcome, was not included in our multivariate analysis due to missing data. Lastly, demographics from the SEER database indicate that a greater proportion of AA women are <50 years old at the time of diagnosis compared to CA women.[3] Our finding that there was no significant difference in age between the AA and CA patients may demonstrate variation between the demographics of our study population and the general US population.

Appropriately, there have been significant efforts to increase breast cancer awareness and screening within the AA population over the past decade. We think that it is equally important to further elucidate whether differences in tumor biology between races also contribute to the noted disparity in outcome. Ideally, the differences in tumor biology according to race would be best studied in randomized clinical trials that prospectively stratify patients according to socioeconomic factors that also may affect breast cancer outcome.

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