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ORIGINAL REPORT

Racial Disparities in Treatment and Survival Among Women With Early-Stage Breast Cancer

Dawn Hershman, Russell McBride, Judith S. Jacobson, Lois Lamerato, Kevin Roberts, Victor R. Grann, and Alfred I. Neugut

From the Department of Medicine and the Herbert Irving Comprehensive Cancer Center, College of Physicians and Surgeons, and the Departments of Epidemiology and Biostatistics, Mailman School of Public Health, Columbia University, New York, NY; and the Josephine Ford Cancer Center, Henry Ford Health System, Detroit, MI.

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Address reprint requests to Dawn Hershman, MD, MS, New York Presbyterian Hospital, 161 Ft Washington Ave, Rm 1068, New York, NY 10032; e-mail: dlh23@columbia.edu.

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ABSTRACT

Purpose
Black women with breast cancer are known to have poorer survival than white women. Suboptimal treatment may compromise the survival benefits of adjuvant chemotherapy. We analyzed the association of race and survival with duration of treatment and number of treatment cycles among women receiving chemotherapy for early-stage breast cancer.

Patients and Methods
Patients were women in the Henry Ford Health System tumor registry who were diagnosed with stage I/II breast cancer between January 1, 1996, and December 31, 2001, who received adjuvant chemotherapy. We calculated an observed/expected ratio of treatment duration and of completed chemotherapy cycles for each patient. Using Cox proportional hazards models, we analyzed the association of early treatment termination and treatment duration with all-cause mortality, controlling for age, race, stage, hormone receptor status, grade, comorbidity score, and doxorubicin use.

Results
Of 472 eligible patients, 28% (31% black, 23% white; $P = .03$) received fewer cycles of treatment than expected. Black race, receipt of $\leq 75\%$ of the expected number of cycles, increasing age, hormone receptor negativity, and a comorbidity score of more than 1 were associated with poorer survival. Among the 344 patients receiving the expected number of cycles, 60% experienced delays. These delays did not reduce survival.

Conclusion
This study is the first to find that a substantial fraction of women with early-stage breast cancer terminated their chemotherapy prematurely and that early termination was associated with both black race and poorer survival. A better understanding of the determinants of suboptimal treatment may lead to interventions that can reduce racial disparities and improve breast cancer outcomes for all women.

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INTRODUCTION

Despite lower breast cancer incidence, women of African ancestry (black women) have significantly worse survival from breast cancer than women of European ancestry (white women). Some of the disparity in survival is attributable to differences in stage distribution at diagnosis, but it persists even when the stage at diagnosis is equivalent.[1,2] Black women's breast cancers are also more likely than white women's to have unfavorable biologic parameters such as negative estrogen receptor (ER) status, high nuclear grade, and high S-phase fraction.[2,3] However, several studies indicate that significant differences in survival remain even after controlling for these biologic factors. For example, in five consecutive adjuvant breast cancer trials coordinated by the Southwest Oncology Group,[4] adjusted for age, receptor status, number of positive lymph nodes, and

tumor size, black patients fared worse than other patients with respect to disease-free, overall, and cause-specific survival.[4] Similarly, in a cohort of 205,736 breast cancer patients, entered into the Surveillance, Epidemiology, and End Results (SEER) database between 1990 and 2000, controlling for age, stage, histology, hormone receptor status, and metropolitan/statewide residence area, black women had significantly worse survival than white women.[5] However, in two cooperative-group analyses, black and white women had similar survival.[6,7]

What else may contribute to the racial disparity in breast cancer survival? One possibility is that racial differences exist in treatment. Studies in other malignancies have found differences by race in subspecialty referrals,[8-10] access to lung cancer surgery,[11] prostate cancer surgery,[12,13] the use[14-16] and aggressiveness of adjuvant colon and rectal cancer chemotherapy[17] and radiation therapy,[18,19] and the use of chemotherapy for metastatic lung cancer.[20] Major advances in the treatment of breast cancer have improved survival, and thus similar variations in the receipt of treatment could lead to survival differences.

Recently, large clinical trials have established that dose reductions, delays, or interruptions of chemotherapy for breast cancer can reduce its benefit.[21-23] Nonetheless, these types of undertreatment are common. In a nationwide retrospective study of dose-intensity among 20,799 patients in community oncology practices, Lyman et al[24] found that 36.5% of patients received less than 85% of their planned cumulative dose; 24.9% experienced treatment delays longer than 7 days; and an aggregate of 55% failed to receive the threshold 85% relative dose-intensity (RDI). Black race is associated with delays in initial breast cancer diagnosis and subsequent treatment.[25] Furthermore, studies by our group and others suggest that chemotherapy use and intensity may differ between the races and, in turn, contribute to differences in outcome.[26-28] However, these prior community and hospital-based studies did not evaluate the impact of either failure to receive all treatment cycles or delays in completing treatment on survival.

To our knowledge, ours is the first study to analyze the effects of incomplete treatment and treatment delays on all-cause mortality and to compare patterns of treatment between black and white women receiving adjuvant chemotherapy for early-stage breast cancer.

PATIENTS AND METHODS

Data Source

The Henry Ford Health System (HFHS) is a large, vertically integrated healthcare system serving the primary and specialty health care needs of patients in Detroit, Michigan, and its surrounding counties. The mixed-model health maintenance organization population includes a substantial number of both Medicare (N = 47,000) and Medicaid (N = 6,800) enrollees, as well as patients covered by other payment and reimbursement paradigms. Annually, the HFHS provides more than 2.5 million patient contacts, 20,000 ambulatory surgeries, and 40,000 hospital admissions. Approximately 200 HFHS patients are diagnosed with stage I or II breast cancer each year; more than 30% of these women are black.

Among female patients who were entered in the HFHS tumor registry with a diagnosis of stage I or II breast cancer from January 1, 1996, through December 31, 2001, we used administrative billing records to identify those who received chemotherapy, the type of chemotherapy they received, the number of cycles, and the duration of treatment relative to the date of pathologic diagnosis. Basic demographic information and tumor characteristics were obtained from the tumor registry, and comorbidity data were obtained from administrative databases. Before analysis, all patient identifiers were removed, and date information was transformed into numbers representing the number of days past the date of diagnosis.

We excluded from the analysis patients treated for recurrent disease only and patients for whom no chemotherapy could be identified, patients who received neoadjuvant chemotherapy, patients with an incomplete chemotherapy record, and patients whose treatment was not one of those described in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[29]

The study was approved by the institutional review board at the Henry Ford Health Center. Because only de-identified data were analyzed, no informed consent was required. The principal investigator had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Comorbid Disease

To assess the prevalence of comorbid disease in our cohort, we used the Deyo adaptation of the Charlson comorbidity index. All relevant International Classification of Diseases (ninth revision) diagnosis codes within the hospital discharge database and the physician-encounter outpatient administrative database were searched to identify individuals with a history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild to severe liver disease, diabetes with or without end-organ damage, hemiplegia, moderate or severe renal disease, or AIDS from 365 days before to 120 days after their diagnosis of cancer. Each category was weighted based on the Charlson index.[30]

Treatment Duration

For each combination of chemotherapeutic agents, an expected duration of treatment was calculated on the basis of the number of cycles and the cycle length. The expected number of chemotherapy cycles for each chemotherapy regimen was based on the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[29] Treatment duration was calculated as the number of days from first to last chemotherapy treatment that was administered in patients who received the expected number of cycles. To define incomplete treatment we calculated an observed/expected completed chemotherapy cycles ratio for each patient (Appendix 1). Many of the clinical trials discussed used an RDI of 85%. We therefore used 85% of cycles as our standard for

completeness of treatment. We also used a cut point of 75% to evaluate the possibility of dose response.

Among patients who received complete treatment, we analyzed treatment delay as treatment that took ≥ 7 days longer than expected. In the group that experienced delay, we analyzed the effects of 1 week's delay, 2 weeks' delay, and longer delay.

Outcome Assessment

All-cause mortality data were obtained from the HFHS tumor registry and the electronic medical record. Cancer-registry guidelines call for complete follow-up of all patients annually. Every month, the registry determined which patients had follow-up visits at the institution and which patients had in-hospital deaths. For patients who did not have follow-up visits when expected, registrars tried to contact physicians and families. If those efforts failed, death-certificate listings were checked.

Statistical Analysis

All statistical analyses were carried out by using SAS 9.0 (SAS Institute, Cary, NC). Pearson's χ^2 test was used to compare black and white women and those with complete and incomplete chemotherapy by age, American Joint Committee on Cancer stage,[31] hormone receptor status (a tumor stain ≥ 10% was classified as ER or progesterone receptor [PR] positive), tumor histologic grade, comorbidities, and use of doxorubicin. We did not control for the regimens because of the large number used. However, we included a variable for the presence or absence of doxorubicin because of the toxicity associated with its use. The Student's *t* test was used to compare the means of percentage differences in observed/expected treatment duration ratios.

Cox proportional hazards models were used to determine all-cause death-rate ratios while controlling for potential confounding variables. The Kaplan-Meier method was used to plot survival curves for patients with complete and incomplete chemotherapy.

RESULTS

Of the 1,130 women listed in the tumor registry as diagnosed with American Joint Committee on Cancer stage I[31] or II breast cancer between 1996 and 2001, 560 were treated with chemotherapy. Excluded from the analysis were 88 patients (65 white and 23 black): 42 who had been treated only for metastatic or recurrent disease and 46 who had received nonstandard chemotherapy regimens.

Of the 472 patients included in the analysis, 202 (43%) were black, 348 (74%) had stage II disease, and 130 (28%) received less than the optimal number of chemotherapy cycles. Of the patients who received the optimal number of chemotherapy cycles, only 41% received them without treatment delay (30% of the total sample). Age ≥ 50 years, black race, stage II (versus I), and comorbidity score ≥ 1 were associated with an increased likelihood of any early treatment termination. (The most common comorbid conditions were arthritis, diabetes, and chronic obstructive pulmonary disease. Diabetes was associated with incomplete treatment and with race.) All subjects had insurance: 25% were covered by a health maintenance organization or preferred provider organization, 74% were covered by the Henry Ford Health Plan, and 1% were covered by Medicaid alone. Insurance coverage was not associated with race/ethnicity, early termination of treatment, or survival. Patients who received doxorubicin were more likely than other patients to complete treatment (Table 1).

Black race was associated with stage II (rather than stage I) disease, hormone receptor–negative cancer, higher tumor grade, and incomplete treatment (Table 2). Only 68% of black patients, compared to 76% of white patients, completed all prescribed cycles of adjuvant chemotherapy ($P = .03$). However, among women who completed the expected number of chemotherapy cycles, race was not associated with treatment delays.

Among the 472 women diagnosed from 1996 to 2001, 57 deaths occurred by January 1, 2004, giving an unadjusted 5-year overall survival rate for the entire population of 88%. Kaplan-Meier survival curves were used to obtain unadjusted estimates of 5-year overall survival for patients who received at least 75% of the expected chemotherapy treatments compared to the rest of the patients (Fig 1). Of the 344 patients who completed 100% of the number of cycles, 89% were alive 5 years after diagnosis; of the 120 who did not complete treatment, only 74% survived for 5 years ($P = .03$). Of 270 white patients, 93% were alive 5 years after diagnosis, and of 202 black patients, 81% were alive 5 years after diagnosis.

In a Cox proportional-hazards model that included age, stage, ER/PR status, grade, and comorbidity score, all-cause mortality was associated with older age, black race, higher comorbidity score, ER/PR-negative status, and any incomplete treatment. The hazard ratio for all-cause mortality increased from 1.8 to 3.1 as the observed percentage of chemotherapy cycles diminished from 85% to 75% of expected. In this model, the all-cause mortality rate was twice as high among black women than among white women (Table 3).

In a model that did not include treatment, the all-cause mortality rate ratio for black versus white women was higher than that shown in Table 3. The difference between the two hazard ratios suggests that some of the effect of race on survival was a result of treatment. Removing ER/PR status, stage, and grade from the model also increased the hazard ratio for race (data not shown). However, even in a model that included all the above mentioned clinical factors, tumor-related factors, and treatment-related factors, black women with breast cancer had a higher all-cause mortality rate (Table 3).

A Cox proportional hazards model was also used to estimate the hazard ratios for all-cause mortality among 344 subjects who completed the expected number of chemotherapy cycles. Advanced age (≥ 50), black race, and a comorbidity score of ≥ 1 were positively associated with all-cause mortality. Treatment delays were not associated with all-cause mortality, but few deaths occurred in this subset of subjects, so the statistical power is limited (Table 4).

Table 1. Demographic and Clinical Characteristics of Patients Who Received Complete and Any Incomplete Treatment

	Treatment					
	Complete (N = 342)		Incomplete (N = 130)			
	No.	%	No.	%	Total (N = 472; No.)	*P*
Age, years						
≤ 50	176	78	50	22	226	.01
> 50	166	67	80	33	246	
51-64	111	70	48	30	159	
65-74	41	63	24	37	65	
≥ 74	14	64	8	36	22	
Race						
White	206	76	64	23	270	.03
Black	136	68	66	31	202	
Stage						
I	77	62	47	38	124	.003
II	265	76	83	26	348	
Hormone receptor status						
ER or PR positive	213	73	80	27	293	.88
ER and PR negative	129	72	50	29	179	
Histologic grade						
I						
I/II	149	71	60	29	209	.54
III	188	74	68	26	256	
Charlson-Deyo comorbidity score						
0	285	75	96	25	381	.05
1	37	65	20	35	57	
> 1	20	59	14	41	34	
Chemotherapy						
With doxorubicin	257	85	45	15	302	< .001
Without doxorubicin	85	50	85	50	170	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

DISCUSSION

In this cohort of patients with breast cancer, we found that discontinuation of treatment and treatment delays were common, that women who discontinued treatment before completion had poorer survival than those who completed the prescribed treatment, that black women were more likely than white women to terminate treatment prematurely, and that they were twice as likely to die as white women. To our knowledge, this study is the first to find an association between early termination of chemotherapy and racial disparities in breast cancer outcomes.

Suboptimal chemotherapy is a known predictor of suboptimal survival.[32] Dose-intensity (the amount of chemotherapy delivered in a specific time interval) can be diluted by either decreasing the total dose or extending the time interval. Lowering the dose-intensity of adjuvant therapy for breast cancer alters the effectiveness of the treatment.[33-37] RDI has been linked to disease-free survival among both premenopausal and postmenopausal women and among women with both less than and more than three involved lymph nodes.[31] Randomized trials have shown that increasing the dose density of chemotherapy improves both disease-free and overall survival.[36]

Many patients do not receive the full RDI of chemotherapy for breast cancer. A nationwide retrospective study of dose-intensity among 20,799 patients in community oncology practices reported results similar to our findings. Lyman et al[24] found that both dose reductions and treatment delays were common: 36.5% of patients received less than 85% of planned cumulative dose, 24.9% experienced treatment delays longer than 7 days, and 45% received at least the threshold 85% RDI. In our study, only 30% of patients received complete treatment without any delay.

Two analyses by cooperative groups suggest that black and white patients enrolled onto cooperative group trials do not differ in breast cancer mortality. However, patients enrolled onto clinical trials are more likely to get complete treatment without delays than other patients; these findings may therefore reflect a treatment effect.[6,7]

Like others,[3,38] we found that black race was associated with advanced stage, negative hormone receptor status, and higher-grade tumors (Table 2). Black women were also at

Table 2. Demographic and Clinical Characteristics of Patients According to Race

	Race					
	White (N = 270)		Black (N = 202)			
	No.	%	No.	%	Total (N = 472; No.)	*P*
Age, years						
≤ 50	121	53	105	47	226	.12
> 50	149	60	97	40	246	
51-64	97	61	62	39	159	
65-74	37	57	28	43	65	
≥ 74	15	68	7	32	22	
Stage						
I	81	65	43	35	124	.03
II	189	54	159	46	348	
Hormone receptor status						
ER or PR positive	185	63	108	37	293	.0009
ER and PR negative	85	47	94	53	179	
Histologic grade						
I/II	132	63	77	37	209	.009
III	131	51	125	49	256	
Charlson-Deyo comorbidity score						
0	226	59	157	41	381	.17
1	24	42	31	58	57	
> 1	20	59	14	41	34	
Chemotherapy						
With doxorubicin	175	58	127	42	302	.66
Without doxorubicin	95	56	75	44	170	
Treatment						
Incomplete	64	49	66	51	130	.03
Complete	206	60	138	40	344	
On time	85	60	56	40	141	
Any delay	121	60	82	40	203	.88
Delayed 1 week	45	62	28	38	73	
Delayed 2 weeks	29	57	22	43	51	
Delayed > 2 weeks	47	59	32	41	79	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

higher risk than white women for both delayed initial therapy and less dose-dense therapy in an analysis that controlled for access to care, poverty index, and method of detection.[25]

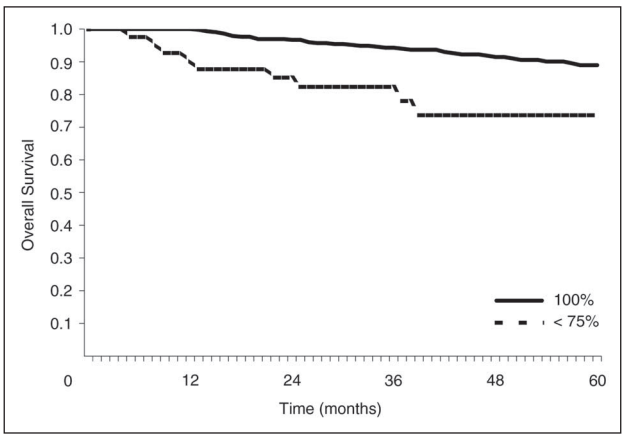

Fig 1. Unadjusted Kaplan-Meier curve of overall survival for women who received complete (100%) versus incomplete (≤ 75%) chemotherapy.

The relationship between race and dose-intensity in the treatment of breast cancer was assessed in a retrospective chart review.[26] Black subjects received less chemotherapy than white subjects ($P = .03$), and overweight seemed to modify the association of treatment with race. In a multivariable model, compared to normal- or low-weight white patients, normal- or low-weight black patients were nearly four times as likely but overweight black patients were nearly 20 times as likely to receive lower-dose treatment. Our study found similar associations of race with treatment, but it also was the first to find that undertreatment contributed to the association of race with survival.

Racial differences in baseline WBC may contribute to black patients' risk of receiving suboptimal treatment. Low baseline WBC is one of the strongest predictors of an RDI of less than 85%, and WBC may be 25% to 40% lower on average among blacks than among whites.[39] In our pilot study, black women had lower WBC than white women, both at baseline and after treatment, and took longer than white women to complete treatment for each of the common adjuvant

Table 3. Hazard Ratios for All-Cause Mortality Among Study Patients (n = 465)

	Hazard Ratios	95% CI	P
Age			
< 50 years	0.4	0.2 to 0.8	.01
50-65 years	1.0	Referent	
> 65 years	1.3	0.7 to 2.5	.4
Race			
White	1.0	Referent	
Black	2.2	1.2 to 3.8	.005
Stage			
I	1.0	Referent	
II	1.7	0.9 to 3.5	.1
Histologic grade			
I/II	1.0	Referent	
III	1.4	0.7 to 2.6	.3
Hormone receptor status			
ER and PR minus	1.0	Referent	
ER or PR positive	0.5	0.3 to 0.9	.04
Charlson-Deyo comorbidity score			
0	1.0	Referent	
1	1.4	0.7 to 3.0	.3
>1	2.2	1.1 to 5.3	.04
Chemotherapy			
Without doxorubicin	1.0	Referent	
With doxorubicin	1.6	0.9 to 3.1	.1
Treatment			
Complete	1.0	Referent	
Incomplete	1.8	1.0 to 3.2	.04
≤ 85% expected	1.8	0.97 to 3.3	.06
≤ 75% expected	3.1	1.6 to 6.1	.001

NOTE. Each variable in the model is adjusted for all other variables listed. Grade was missing for six patients.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

Table 4. Hazard Ratios for All-Cause Mortality Among Patients Who Completed All Cycles of Treatment (n = 344)

	Hazard Ratios	95% CI	P
Age, years			
< 50	0.4	0.2 to 1	.05
50-65	1.0	Referent	
> 65	1.3	0.6 to 3.3	.5
Race			
White	1.0	Referent	
Black	2.6	1.1 to 5.1	.01
Stage			
I	1.0	Referent	
II	2.3	0.8 to 6.6	.1
Hormone receptor status			
ER and PR negative	1.0	Referent	
ER or PR positive	0.5	0.2 to 1.1	.1
Histologic grade			
I/II	1.0	Referent	
III	1.2	0.5 to 2.8	.2
Charlson-Deyo comorbidity score			
0	1.0	Referent	
1	1.7	0.6 to 4.4	.2
> 1	2.1	1.2 to 8.9	.02
Chemotherapy			
Without doxorubicin	1.0	Referent	
With doxorubicin	1.7	0.7 to 4.3	.2
Treatment			
On time	1.0	Referent	
Delayed	0.8	0.4 to 1.6	.5

NOTE. Each variable in the model is adjusted for all other variables listed.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

chemotherapy regimens, although the differences were not statistically significant.[27]

In our study and others,[24] delays in treatment were common; however, we saw no association between race and dose delay or between dose delay and all-cause mortality. Only 17% of the patients in our sample had delays longer than 2 weeks. Cumulative dose delays longer than 30 days have been found to increase the risk of relapse. In our sample, the delays may not have been long enough to affect survival, our study may have been underpowered to detect their effects, or, under conditions that have resulted in delay in other studies, the patients in our sample may have been more likely to discontinue treatment entirely than to delay completing it.

Our study was observational, using cancer registry and billing data to assess the effects of treatment on breast cancer outcomes among unselected patients from an ethnically mixed urban community. From a public health perspective, our findings are similar to those of other studies using different methods, suggesting that improving the quality of care overall may improve breast cancer outcomes. Using a mathematical model of the natural history of breast cancer, Mandelblatt et al[40] demonstrated that ensuring that black women receive complete adjuvant therapy could reduce overall mortality and would be more cost effective than enhancing screening programs to improve the survival of black women. Our findings, based on the actual experience of the patients in the cancer registry, support this conclusion.

One limitation of our study was a lack of information about chemotherapy dosing. Data on dose reductions might have helped to explain why the observed outcomes of patients who received the expected number of cycles in the expected amount of time were not measurably different from those of patients whose completion of treatment was delayed but not why their outcomes were so different from those of patients who terminated treatment early.

Another limitation was a lack of data on other relevant factors such as performance status, socioeconomic status, and obesity. Those factors may be related to completeness of treatment and to survival. A third limitation was a maximum follow-up of 8 years. Although we could not evaluate factors that may affect survival in the longer term, a longer follow-up might have introduced unknown confounders such as changes in treatment for late recurrences or the

development of comorbid conditions related to aging. We did find an association of diabetes with incomplete treatment (44% of diabetic patients but only 26% of nondiabetic patients received incomplete treatment) and with race (60% of the diabetic patients were black). A fourth limitation was completeness of follow-up. Our study included only patients who received at least two cycles of chemotherapy at Henry Ford Health Center. It is possible that some patients who we classified as discontinuing treatment subsequently received care elsewhere. However, poor women are less likely than more affluent women to have done so because the HFHS accepts Medicaid, Medicare, and its own prepaid health plan.

Of the 472 women with breast cancer, only 57 died during the follow-up period. Few of these deaths were designated as breast cancer specific. In a larger sample, with breast cancer–specific mortality as the outcome of interest, our findings might have been different. However, the observed association of all-cause mortality with treatment was statistically significant.

In our data, receiving the expected number of chemotherapy cycles in the expected time interval seemed to achieve its purpose of prolonging life. The association we observed between early treatment discontinuation and race may help to account for the disparity in survival between black women and white women with breast cancer. Our analysis does not, however, explain why some white women and even more black women received suboptimal chemotherapy. The determinants of suboptimal treatment may include inadequate physician-patient communication, treatment toxicity, racial differences in drug metabolism, social-support networks, comorbidities, and other factors. A better understanding of these associations may lead to interventions that can improve breast cancer outcomes and reduce racial disparities in breast cancer survival.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Appendix 1. Chemotherapy Regimens Received by Study Participants

	Expected No. of Cycles	Expected Treatment Duration (days)	No. of Patients
Doxorubicin + cyclophosphamide (AC)	4	64	182
Doxorubicin + cyclophosphamide, followed by paclitaxel (AC → T)	8	148	103
Cyclophosphamide, methotrexate, 5-fluorouracil (CMF)			
Oral (28-day cycle)	6	126	80
Intravenous (21-day cycle)	8	148	90
Cyclophosphamide, doxorubicin, 5-fluorouracil (CAF)			
Oral (28-day cycle)	6	126	10
Intravenous (21-day cycle)	6	105	7

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