Original Study

The Impact of Age and Adjuvant Chemotherapy Modifications on Survival Among Black Women With Breast Cancer

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Abstract

This study explored age as a moderator for the association between treatment modifications and survival in Black women with early stage breast cancer. The sample consisted of 115 Black women treated with adjuvant chemotherapy. Results indicate that older Black women with chemotherapy doses held experienced worse disease-free survival than those who did not.

Background: Black women receive less relative dose intensity with more dose reductions and early chemotherapy cessation compared with White women. Adding further risk, older patients with breast cancer are most at risk for treatment modifications; however, it is unclear if this remains true for Black patients. Furthermore, the clinical implications of treatment modifications and delays on survival is uncertain, particularly in Black patients. **Patients and Methods:** The purpose was to investigate whether age was a moderator for the association between treatment modifications (dose held, dose delayed, and early cessation) and overall survival and disease-free survival (DFS) in Black women with breast cancer using a retrospective cohort study of patients with early stage breast cancer treated with adjuvant chemotherapy. **Results:** Across the entire sample (n = 115), 37.4% (n = 43) of patients experienced a treatment modification. There was a significant interaction between age group and held dose for DFS ($P = .026$). Specifically, those diagnosed at 55 years of age and older, who had doses of chemotherapy held, experienced worse DFS compared with those who did not (hazard ratio, 4.185; 95% confidence interval, 1.187-14.75). In contrast, there was no difference in DFS between those who did and did not have doses held in patients diagnosed below 55 years of age (hazard ratio, 0.626; 95% confidence interval, 0.177-2.218). **Conclusion:** In this study, Black women receiving adjuvant chemotherapy for treatment of early stage breast cancer had roughly equal treatment modifications across age groups. However, held doses of chemotherapy in older Black patients were associated with worse DFS. Age may impact clinical outcomes seen with adjuvant chemotherapy treatment modifications.

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Introduction

Breast cancer is the most common cancer diagnosis in Black women.[1] In post-menopausal women, there is a lower prevalence of breast cancer in Black women than in White women; yet, breast cancer mortality rates in Black women are significantly higher than in their White counterparts.[1] The reasons for the survival disparity are not well understood and are likely of multiple origins. During chemotherapy for breast cancer, Black women are at greater risk for not receiving the full dose of prescribed adjuvant chemotherapy than are White women.[2,3] Furthermore, the clinical implications of chemotherapy modifications (dose held, dose delayed, and early cessation) on survival are uncertain, particularly in Black patients. In general, older women with breast cancer are at greater risk than younger women for chemotherapy modifications[4-6]; however, it is unclear if this remains true for Black women.

Treatment modifications among women with breast cancer are relatively common, with studies reporting modifications in 30% to 65% of patients.[5,7,8] Studies have found that Black women with breast cancer are at greater risk for experiencing treatment modifications than White women. Specifically, Black women with breast cancer receive less relative chemotherapy dose intensity and experience more held doses and early cessation compared with White

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women.[2,3,8] Some have found an association between adjuvant chemotherapy modifications and poorer clinical outcomes, including worse disease-free survival (DFS) and overall survival (OS),[9-11] whereas others have found no association,[12] suggesting that there may be potential modifiers of this relationship deserving further exploration.

Previous research has found that older women experience more treatment modifications than younger women.[4-6] However, 2 of these studies[4,5] did not report on race at all and are presumably largely comprised primarily of White patients. The third study[6] did report on race; however, more than 60% of patients identified as White. The purpose of this study was to investigate whether age (diagnosis < 55 years vs. diagnosis ≥ 55 years) was a moderator for the association between treatment modifications (dose held, dose delayed, and early cessation), DFS, and OS in Black women with breast cancer.

Patients and Methods

A retrospective cohort study of Black women with early-stage breast cancer treated with adjuvant chemotherapy was employed. The current study is a secondary, exploratory aim of the Attitudes, Communication, Treatment, and Support (ACTS) Intervention to Reduce Breast Cancer Treatment Disparity study. The ACTS study is a randomized controlled trial of a psychoeducational intervention to encourage acceptance and adherence to chemotherapy compared with usual care for Black women with breast cancer.[13] Participants for this secondary analysis were enrolled in a pilot project of the ACTS study or the larger study; both were randomized controlled trials with identical measures and timepoints. The pilot study was conducted from 2006 through 2008 and the larger trial was conducted from 2011 through 2015.

The inclusion criteria for participants in this secondary analysis study were: self-reported Black race, having non-metastatic breast cancer, recommended for chemotherapy, and having no history of previous chemotherapy. Recommended adjuvant therapy followed algorithms of best practice chemotherapy according to national and institutional guidelines for breast cancer subtype.[14] For each patient, medical record data extraction was utilized to identify whether they had dose held, dose delayed, and early cessation throughout the typical course of prescribed chemotherapy (6 months or less). Each of these variables was coded dichotomously. Dose held refers to a missed dose of prescribed chemotherapy. Dose delayed refers to a delay of ≥ 7 days in the administration of the next dose of chemotherapy. Early cessation refers to chemotherapy treatment that is not completed as originally prescribed. These modifications (dose held, dose delayed, and early cessation) are typically related to side effects or toxicity from treatment.[15,16] The sample was divided into 2 groups: those diagnosed at < 55 years of age and those diagnosed at ≥ 55 years of age.

Outcomes of Interest

The primary outcomes were DFS and OS. DFS is the period of time from 6 months after diagnosis (the approximate time when cancer therapy would be completed) to either metastatic diagnosis or death, whichever came first. The follow-up period was from the date of early-stage breast cancer diagnosis (2006-2008) to April 30, 2018. OS was the time from 6 months after early-stage breast cancer diagnosis to death from any cause.

Table 1 Sample Characteristics by Age Group

Characteristic	Age Group, n (%)		*P* Value[b]
	< 55 Years (n = 58)[a]	≥ 55 Years (n = 57)[a]	
Age, y	44.4 ± 6.94	61.3 ± 4.88	
Stage			
I	10 (17.24)	13 (23.21)	.585
II	28 (48.28)	28 (50.00)	
III	20 (34.48)	15 (26.79)	
Dose held			
Yes	13 (22.81)	14 (25.00)	.785
No	44 (77.19)	42 (75.00)	
Dose reduced			
Yes	8 (14.04)	9 (16.07)	.762
No	49 (85.96)	47 (83.93)	
Early cessation			
Yes	10 (17.24)	8 (14.04)	.636
No	48 (82.76)	49 (85.96)	

[a]Five subjects who progressed within 6 months after diagnosis were removed from the DFS cohort.
[b]*P* value is for the comparison between the age groups.

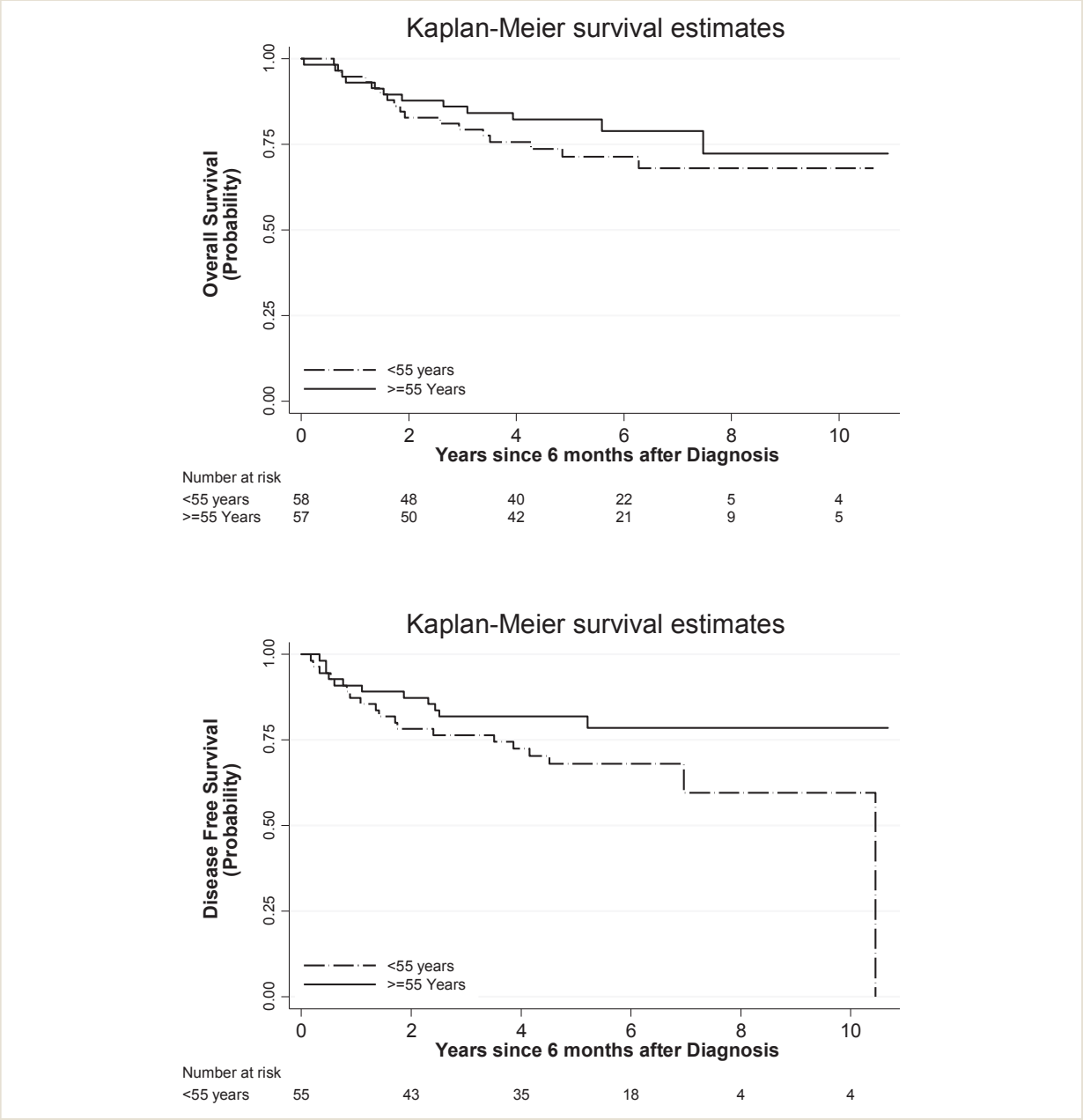
Covariates

Stage and hormone receptor status were controlled in the analysis. Cancer stage was derived from the American Joint Committee on Cancer (sixth edition) breast cancer criteria and was categorized as I, II, or III.[17] Participants' estrogen receptor (ER) and human epidermal growth factor receptor (HER2) status were gathered from medical records that are determined as part of routine clinical care. Patients were considered to have positive HER2 status ($HER2^+$) if they tested positive on immunohistochemistry and fluorescence in situ hybridization testing. Estrogen receptor (ER) status was determined via immunohistochemistry assay. As recommended by the guidelines put forth by the American Society of Clinical Oncology/College of American Pathologists, the cutoff to distinguish "positive" cases from "negative" cases is ≥ 1% ER-positive (ER^+) tumor cells.[18]

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics in each of the 2 age groups as well as in the entire sample. χ^2 tests were used to compare for differences in treatment modifications (dose held, dose reduced, and early cessation) between the 2 age groupings. Survival curves by age grouping were created using Kaplan-Meier analyses. The difference between these generated curves was analyzed using log-rank test. A landmark analysis was used to examine the interaction between age group and treatment modifications for OS and DFS, while controlling for stage and ER and HER2 status. The landmark time of 6 months after diagnosis was chosen as this is a typical length of prescribed chemotherapy for this patient population. If participants had disease progression within 6 months of diagnosis, they were removed from the DFS

Figure 1 Kaplan-Meier Survival Curves. A, Overall Survival ($P = .323$ Using Log-Rank Test); B, Disease-Free Survival ($P = .087$ Using Log-Rank Test)



analysis. If any participants died within 6 months of diagnosis, they were removed from the OS analysis. A P-value $< .05$ was considered significant. All P-values were 2-sided. All the analyses were conducted using SAS software (Cary, NC), version 9.4.

Results

Patients' Characteristics

A summary of patient characteristics can be seen in Table 1. There were different cohort sizes for the OS (n = 115) and DFS (n = 110) outcomes because 5 participants progressed within 6 months of diagnosis. In the study of 115 participants, 58 (50.4%) were diagnosed before the age of 55, and 57 (49.6%) were diagnosed at age 55 or older. There were no differences in stage or hormone receptor status among the 2 age groups. Across the entire sample, 43 (37.4%) patients experienced a treatment modification. In both the younger and older age groups, the most common modification was a held dose (22.81%; n = 13 and 25.00%; n = 14, respectively). There were no significant differences in the proportions of treatment modifications between the age groups (dose held, $P = .785$; dose reduced, $P = .762$; and early cessation, $P = .636$).

Table 2 Cox Proportional Hazards Regression Model for Predictors of DFS and OS

Treatment Modification	Predictors	DFS[a] (N = 110)			OS (N = 115)		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value
Dose held	Age group (≥ 55 y)				0.605	(0.279-1.312)	.203
	Dose held (Yes)[b]				1.452	(0.634-3.327)	.378
	Age < 55 y	0.626	(0.177-2.218)	.468			
	Age ≥ 55 y	4.185	(1.187-14.75)	.026			
	ER^+	0.725	(0.340-1.545)	.405	0.570	(0.257-1.263)	.166
	$HER2^-$	1.045	(0.413-2.646)	.925	1.595	(0.597-4.259)	.352
Dose reduced	Age group (≥ 55 y)	0.480	(0.220-1.047)	.065	0.604	(0.279-1.311)	.203
	Dose reduced (Yes)	1.065	(0.367-3.091)	.907	1.363	(0.514-3.616)	.534
	ER^+	0.723	(0.339-1.543)	.402	0.587	(0.266-1.299)	.189
	$HER2^-$	1.201	(0.480-3.000)	.696	1.553	(0.583-4.134)	.378
Early cessation	Age group (≥ 55 y)	0.507	(0.239-1.072)	.076	0.643	(0.305-1.359)	.248
	Early cessation (Yes)	1.377	(0.554-3.421)	.491	1.538	(0.647-3.655)	.329
	ER^+	0.666	(0.316-1.401)	.284	0.552	(0.252-1.209)	.552
	$HER2^-$	1.038	(0.439-2.457)	.932	1.285	(0.517-3.191)	.589

Abbreviations: CI = confidence interval; DFS = disease-free survival; ER = estrogen receptor status; HER2 = human epidermal growth factor receptor 2 status; HR = hazard ratio; OS = overall survival.
[a]Five subjects who progressed within 6 months after diagnosis were removed from the DFS cohort.
[b]Interaction between dose held and age group was statistically significant ($P = .038$).

Kaplan-Meier Survival Curves Analysis

Kaplan-Meier curves were generated. Log-rank tests revealed no significant differences in OS ($P = .32$) or DFS ($P = .098$) between women in the younger and older groups (Figure 1).

Cox Proportional Hazards Regression Model

There was no interaction between age group and treatment modifications for OS (Table 2). However, there was a significant interaction between age group and held dose for DFS ($P = .045$). Specifically, those diagnosed at 55 years of age and older, who had doses of chemotherapy held, experienced worse DFS compared with those who did not (hazard ratio [HR], 3.390; 95% confidence interval [CI], 1.013-11.34). In contrast, there was no difference in DFS between those who did and did not have doses held in patients diagnosed below 55 years of age (HR, 0.563; 95% CI, 0.159-1.986).

Discussion

Previous research has found higher rates of treatment modifications in older women with breast cancer. However, in our study, there were no differences in treatment modifications between the younger (< 55 years of age) and older (≥ 55 years of age) groups. This difference in findings may be owing to a variety of factors. For instance, this sample is comprised exclusively of Black women with breast cancer. It has been well established that Black women experience higher rates of chemotherapy modifications than their White counterparts.[2,3,8] It is possible that all Black women are at an increased risk for treatment modifications and that older age is not an increased risk factor for experiencing additional treatment modifications.

There is no consensus on the age cutoff to describe "younger" and "older" women with early-stage breast cancer. For this study, we divided the sample as < 55 years (these women are generally considered premenopausal and perimenopausal) and ≥ 55 years of age (these women would generally be considered postmenopausal).[19] Additionally, dividing the sample using these age ranges provided adequate and roughly equal group sizes for our analysis. However, other studies have used different age cutoffs such as 50,[10] 65,[4,5,7,10] and 70[6] years of age. Using a different age cut-point than previous studies may have impacted our findings.

Another important factor to consider is that we examined treatment modifications dichotomously (see limitations). In previous studies, some have calculated relative dose intensity (RDI). As a result, it is possible that the differences in DFS between younger and older women were owing to other group differences in RDI that were not examined in this study. For instance, the younger women may have experienced a similar rate of treatment modifications yet received actual higher RDI overall than the older women. This should be further explored in future studies.

It has been well-established that administering adjuvant chemotherapy improves OS and DFS.[20] However, relatively few studies have explored the relationship between modifications to adjuvant chemotherapy and its impact on clinical outcomes. The studies that have been conducted have been mixed: some have found poorer DFS and OS,[9-11] whereas others have found no difference.[12] In our study of Black women with early-stage breast cancer, age was a modifying factor in the relationship between adjuvant chemotherapy modifications and DFS, but not OS. These findings should be confirmed in future, larger studies. Future studies may explore additional modifying factors to better understand what patients are at greatest risk for poorer survival related to treatment modifications. Understanding of these factors may help to determine who is at greatest risk and target interventions to promote adherence to prescribed treatment to improve survival.

Strengths and Limitations

A strength of this study is a sample comprised exclusively of Black women with breast cancer, an underrepresented population. However, there were some limitations. This study includes a relatively small sample size; future studies should confirm findings in a larger sample. Also, this was a retrospective study that was limited by the information included in medical charts. Furthermore, partway through this study, there was a conversion from paper-based to electronic medical records. Thus, in this retrospective review several years later, we were unable to obtain full chemotherapy records for each patient containing exact dosages. This information would have allowed for more precise calculation of RDI. Prospective studies may be able to gather more detailed information about possible predictors that may further our understanding of the relationship between adjuvant chemotherapy treatment modifications and clinical outcomes.

Conclusion

In this study, Black women receiving adjuvant chemotherapy for treatment of early-stage breast cancer had roughly equal treatment modifications across the age groups. However, held doses of chemotherapy in older Black patients were associated with worse DFS. Further research is needed to elucidate the clinical implications of adjuvant chemotherapy treatment modifications, particularly in Black patients, and the subgroups of patients who are at greatest risk.

Clinical Practice Points

- Black women with breast cancer experience higher rates of adjuvant chemotherapy modifications than White women. However, the clinical implications of chemotherapy modifications were uncertain.
- Thus, we aimed to investigate whether there was an association between treatment modifications and survival (both DFS and OS) that was mediated by age. Our study revealed an association between held doses of chemotherapy and poorer DFS in women 55 years of age and older.
- Therefore, we believe that age may be an important factor in the relationship between adjuvant therapy modifications and survival, particularly in Black women.

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Disclosure

The authors have stated that they have no conflicts of interest.

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