Effect of Aromatase Inhibitor Therapy on the Cardiovascular Health of Black and White Breast Cancer Patients

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Abstract

A prospective cohort study was conducted to examine racial differences in the cardiovascular health effects of aromatase inhibitor (AI) treatment, analyzing data from 77 white and 35 black breast cancer patients initiating AI therapy and followed for 1 year. Results showed no large adverse cardiovascular health changes over the first year of AI therapy among black and white patients.

Background: The present study examined racial differences in the cardiovascular health effects of aromatase inhibitors. **Patients and Methods:** Data were analyzed from 77 white and 35 black patients with early-stage breast cancer initiating aromatase inhibitor therapy and subsequently followed for 1 year. At baseline and a 1-year follow-up clinic visit, a comprehensive cardiovascular health assessment was conducted, which included measurement of carotid intima-medial thickness and a blood draw to measure high-sensitivity C-reactive protein and cholesterol concentrations. A detailed questionnaire was also completed. The information collected was used to calculate each patient's 10-year risk of atherosclerotic cardiovascular disease events at both measurement points. Paired *t* tests were used to examine the changes in the continuous outcome variables within groups during the study period. Independent *t* tests were conducted to examine the changes over time between the 2 groups. **Results:** No statistically significant changes in carotid intima-medial thickness, atherosclerotic cardiovascular disease risk score, or the other cardiovascular-related outcomes (high-sensitivity C-reactive protein, cholesterol levels, blood pressure) during the first year of aromatase inhibitor therapy were observed among either the black or white breast cancer patients or between the 2 groups. Mean grip strength in the dominant hand decreased significantly and similarly during the 1-year period for the white and black breast cancer patients. **Conclusion:** The findings from the present study suggest no large adverse cardiovascular health effects from aromatase inhibitors during the first year of therapy among either black or white breast cancer patients. However, the results of the present study cannot rule out the potential for long-term adverse changes over the duration of aromatase inhibitor therapy or beyond.

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Introduction

Black women experience poorer survival after a breast cancer diagnosis compared with white women despite having a lower incidence rate.[1,2] Recent studies have shown that this difference in mortality persists after accounting for access to care, tumor characteristics at diagnosis, biologic markers, and treatment.[3] An unanswered question is whether the racial disparity in mortality after breast cancer results from other comorbid conditions that can be adversely affected by cancer treatment. Answering this question requires specific investigation into how comorbid conditions might be affected by breast cancer treatment.

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Effect of AI Therapy on Cardiovascular Health

Of particular concern among patients with breast cancer, especially among those who are of black race, is cardiovascular disease. The cardiotoxicity of radiation and chemotherapy agents such as doxorubicin and trastuzumab have been well documented.[4] However, researchers have also hypothesized that treatment with aromatase inhibitors (AIs), the adjuvant hormonal treatment of choice for postmenopausal patients with estrogen receptor-positive breast cancer, can be associated with adverse cardiovascular effects owing to the severe estrogen depletion resulting from AI use.[5] Numerous epidemiologic studies conducted of postmenopausal women in the general population have shown associations between low concentrations of estrogen and cardiovascular disease and its associated risk factors.[6-8] For example, data from the Estrogen in the Prevention of Atherosclerosis Trial have shown that in a sample of postmenopausal women, low estrone, total estradiol, and free estradiol concentrations were significantly associated with increased carotid intima-medial thickness (cIMT) after adjustment for age and body mass index (BMI).[6] In addition, findings from a number of randomized clinical trials, including the Women's Health Initiative, have indicated that, among women aged < 60 years old, taking estrogen-containing hormone therapy resulted in fewer coronary heart disease events compared with not receiving hormonal therapy.[9] The converse, a total estrogen blockade, might, therefore, increase the risk of cardiovascular disease among postmenopausal breast cancer patients taking AIs.

Despite the concern that low estrogen levels might increase the risk of cardiovascular disease among patients with breast cancer taking AIs, few prospective studies have focused specifically on the associations between these drugs and cardiovascular disease risk factors or events. Existing data have primarily been from randomized clinical trials comparing the effects of AIs versus tamoxifen or placebo on breast cancer recurrence.[10-14] In these trials, cardiovascular disease was not the primary outcome; therefore, detailed information on cardiovascular effects was not provided. Even less is known about the cardiovascular effects of AIs among black women, who have been underrepresented in clinical trials investigating the safety profiles of these drugs. Because black women in general have a higher number of existing cardiovascular disease risk factors compared with white women of the same age,[15] black patients with breast cancer might be particularly vulnerable to cardiovascular disease and death after AI treatment. Thus, the present study was conducted to examine the racial differences in the cardiovascular health effects of AIs and the effect of pre-existing cardiovascular disease risk factors on this relationship.

Materials and Methods

Study Sample and Procedures

A prospective cohort study was conducted from October 2011 to July 2015 of 146 early-stage black and white breast cancer patients (stage I-III) initiating AI treatment at Mercy Medical Center (Baltimore, MD). Details of recruitment and enrollment of participants into the study will be reported by Gallicchio et al.[16] Women who self-identified as being of black or white race, who had undergone surgery, and who had or had not undergone previous radiation or chemotherapy were eligible. The Institutional Review Board of Mercy Medical Center approved this study. All the participants included in the study provided informed consent.

Women who agreed to participate in the present study were asked to undergo a clinical evaluation before initiating AI therapy (baseline) and again at 3, 6, 9, and 12 months after the start of AI treatment. At the baseline and 1-year clinic visits, the participants underwent a comprehensive cardiovascular health assessment, including cIMT measurement, had their height, weight and blood pressure measured, donated a blood sample, and completed a questionnaire to collect data on the demographic characteristics, family history of cardiovascular disease, cardiovascular disease risk factors, and symptoms. At the interim follow-up points, a shorter visit was conducted that included questionnaire completion. Blood samples at baseline and 1 year were assayed for high-sensitivity C-reactive protein (hsCRP) and a cholesterol panel. These measurements and the information obtained from the medical record and questionnaire were used to calculate the participants' 10-year risk of atherosclerotic cardiovascular disease (ASCVD) events, which include nonfatal myocardial infarction, fatal coronary heart disease, and nonfatal and fatal stroke.[17] This risk calculator, based on the Pooled Cohort Equations,[18] is available at my.americanheart.org.

Of the 146 women who enrolled in the study and had baseline data available, 112 had 1-year follow-up data for either cIMT (n = 108) or ASCVD risk (n = 112), the main study outcomes, and were thus included in the analytic study sample. Of the 34 women enrolled in the study who were not included in the analytic study sample, 9 did not complete the study because they discontinued their AI treatment and 3 withdrew from the study before their 1-year follow-up visit despite still taking their AI. In addition, 22 women, most of whom were within the first 6 months of follow-up, did not have a 1-year follow-up visit because the study was terminated due to the lack of extended funding.

Cardiovascular Health Assessment

cIMT was measured using a carotid artery ultrasound scan performed by 1 of 2 registered vascular technologists following standardized procedures on a single machine with the Philips IU22 system (Philips Healthcare, Bothell, WA). All participants had scans performed bilaterally, and cIMT was obtained during end-diastole (between P and Q wave of the electrocardiographic trace) in the far wall of the bilateral distal common carotid arteries using a standardized protocol.[19] cIMT was then measured using Philips Q lab edge-detection software. The primary outcome was the average of the mean right and left cIMT.

Blood pressure was measured with the patient in a seated position using a mercury sphygmomanometer after a 5-minute rest period, in accordance with the current American Heart Association guidelines.[20] At baseline and the 1-year follow-up visit, 2 blood pressure measurements were taken, and the average was recorded. Patient height was measured at each visit using a standard stadiometer; the waist circumference was also measured at each visit at the bilateral upper iliac crests at the end of breath expiration. Grip strength was assessed using a Jamar hydraulic hand dynamometer. Each participant alternated squeezing with the dominant and nondominant hands until 3 trials were completed with each hand. The average (in pounds per square inch) of the 3 trials for each hand was recorded.

Questionnaire and Medical Record Review

Self-administered questionnaires were completed by the participants at baseline and at all follow-up points. Information was