Original Article

Impact of African ancestry on the relationship between body mass index and survival in an early-stage breast cancer trial (ECOG-ACRIN E5103)

Tarah J. Ballinger, MD [1]; Guanglong Jiang, MS[2]; Fei Shen, MD[1]; Kathy D. Miller, MD[1]; George W. Sledge, Jr, MD[3]; and Bryan P. Schneider, MD[1]

BACKGROUND: African ancestry (AA) and obesity are associated with worse survival in early-stage breast cancer. Obesity disproportionately affects women of AA; however, the intersection between ancestry and obesity on breast cancer outcomes remains unclear. **METHODS:** A total of 2854 patients in the adjuvant trial E5103 were analyzed. Genetic ancestry was determined using principal components from a genome-wide array. The impact of continuous or binary body mass index (BMI) on disease-free survival (DFS) and overall survival (OS) was evaluated by multivariable Cox proportional hazards models in AA patients and European ancestry (EA) patients. **RESULTS:** There were 2471 EA patients and 383 AA patients. Higher BMI was significantly associated with worse DFS and OS only in AA patients (DFS hazard ratio [HR], 1.25; 95% CI, 1.07-1.46; OS HR, 1.38; 95% CI, 1.10-1.73), not in EA patients (DFS HR, 0.97; 95% CI, 0.90-1.05; OS HR, 1.03; 95% CI, 0.93-1.14). Severe obesity (BMI ≥40) was significantly associated with worse survival in AA patients (DFS HR, 2.04; 95% CI, 1.21-3.43; OS HR, 2.21; 95% CI, 1.03-4.75) but had no impact on that of EA patients. In the estrogen receptor–positive (ER+) and triple-negative breast cancer subgroups, BMI was significantly associated with worse outcomes only in those AA patients with ER+ disease. Within the AA group, BMI remained associated with worse survival regardless of the AA proportion. **CONCLUSIONS:** Higher BMI was statistically significantly associated with worse breast cancer outcomes in AA but not EA patients. This association was most significant for severe obesity and those with ER+ disease. These observations help define optimal populations for weight change interventions designed to affect disparities and survival in early-stage breast cancer. ***Cancer* 2022;128:2174-2181**.

LAY SUMMARY:

- African ancestry and obesity are both risk factors for worse survival after early-stage breast cancer.
- Women of African descent are also disproportionately affected by obesity; however, it is unclear what impact body weight has on racial disparities in breast cancer.
- Data from a large phase 3 clinical trial in high-risk, early-stage breast cancer were used to determine how body weight affects survival outcomes in European versus African Americans.
- Study results demonstrate that a higher body mass index is associated with increased risk of breast cancer recurrence and worse survival in women of African ancestry but not in women of European ancestry.

KEYWORDS: African Americans, body weight, breast cancer.

INTRODUCTION

Despite improvements in breast cancer survival in recent decades, the racial gap has continued to widen. Black women with early-stage breast cancer have an approximately 40% increased risk of mortality, compared with White women.[1] The etiology for racial disparities in breast cancer is multifactorial, including socioeconomic inequities in access and care delivery, and differences in disease and host biology.[2]

Using genotyping to determine ancestry in the adjuvant chemotherapy trial E5103, we previously found a significantly inferior disease-free survival (DFS) in women of African ancestry (AA) compared with those of European ancestry (EA) (hazard ratio [HR], 1.4; $P = .013$).[3] Obesity disproportionately affects Black women, and in several large data sets, the proportion of AA is associated with a higher body mass index (BMI) and a higher risk of obesity.[4,5] Given obesity's association with worse outcomes in early-stage breast cancer, this may be important. Genetically determined AA contributes

Corresponding Author: Tarah J. Ballinger, MD, Division of Hematology and Oncology, Indiana University School of Medicine, 535 Barnhill Dr, Rt 473, Indianapolis, IN 46202-5116 (tarahb@iu.edu).

[1]Division of Hematology and Oncology, Indiana University School of Medicine, Indianapolis, Indiana; [2]School of Informatics and Computing, Indiana University Purdue University Indianapolis, Indianapolis, Indiana; [3]Stanford Cancer Institute, Palo Alto, Stanford, California

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to both worse outcomes in breast cancer and to increased obesity; however, the intersection between genetic ancestry and obesity on survival outcomes remains unclear.

Here, we investigate the impact of BMI on survival outcomes in patients of genetically defined AA or EA in the large, randomized, adjuvant chemotherapy trial E5103, which mirrors the modern approach to systemic therapy for early-stage breast cancer. Furthermore, we investigate how degree of AA relates to BMI, and whether this relationship modifies the effect of BMI on outcome in AA patients with early-stage breast cancer.

MATERIALS AND METHODS

Patient Population and Study Measures

E5103 was a phase 3 randomized controlled trial of adjuvant anthracycline and taxane- based chemotherapy, with or without bevacizumab, in 4994 patients with high-risk, early-stage breast cancer. Trial eligibility and schema have been previously published.[6] The study was open from November 2007 to February 2011. Participants eligible for this analysis included women with available baseline DNA for genotyping indicating AA or EA, available BMI, and survival outcome data. Weight and height were collected at baseline during screening evaluations by trained study personnel. BMI was calculated as the weight in kilograms divided by the squared height in meters and was analyzed as both a continuous variable in increments of 5 and as a categorical variable, in which patients were categorized as normal weight (18-24.9), overweight (25-29.9), obese class 1 (30-34.9), obese class 2 (35-39.9), and obese class 3 (≥40).

Genome-wide genotype data were available for genotyping in 3431 patients. Genotyping was performed using 2 distinct study subsets, as previously described.[7] Race assignment was performed using principal components (see the Supporting Methods and Supporting Fig. 1), and analyses were performed only in those genetically defined as AA or EA patients.

Statistical Analysis

Baseline patient characteristics and BMI were summarized using descriptive statistics. Comparisons between patient or tumor characteristics in ancestry groups were performed using t test for continuous variables and χ^2 test for categorical variables. Survival probability was estimated using Kaplan-Meier method. DFS was defined as the duration of time from randomization to a DFS event, which included local invasive disease, regional recurrence, distant disease recurrence, contralateral breast cancer or in situ disease, or death from any cause.[8] Overall survival (OS) was defined as the time from randomization to death from any cause. Univariate and multivariable Cox proportional hazards models were used to estimate HRs and 95% CIs. In multivariable analysis of the association between BMI and survival, covariates considered included age, estrogen receptor (ER) status, lymph node involvement (negative, 1-3 positive, or 4 or more positive), tumor size (<2, 2-5, >5 cm), histological tumor grade (1, 2, or 3), treatment arm (A, B, or C), and menopausal status. A bidirectional stepwise Cox regression procedure was used for covariate selection based on the Akaike information criterion statistic. A P value <.05 was used as the cutoff to retain a covariate in the final regression model. The multiplicative interactions between proportion of AA and BMI on both DFS and OS were evaluated using the Cox proportional hazards model, with the correction of the same covariates. A P value <.05 was considered significant in all analyses. The statistical analyses and data visualization were conducted in statistical environment R v3.6.0.

Admixture Estimation

Estimating admixture proportions was conducted with fastSTRUCTURE v1.0.[9] The genotype data for E5103 data sets were collected as described previously.[7] In brief, DNA samples for 3431 patients were genotyped using Illumina BeadChip array platforms Human Omni1-Quad (>1 million single-nucleotide polymorphisms [SNPs]) or Human OmniExpress (741,000 SNPs). The prior E5103 genotype data imputation was adopted for population structure analysis using reference populations from the Human Genome Diversity Project (HGDP).[10] The HGDP data set used genotype data from 1043 individuals to filter 646,466 SNPs from Illumina 650Y arrays by removing SNPs with missing rate >5%, minor allele frequency <1%, and Hardy-Weinberg equilibrium exact test $P > 10^{-4}$; this defined 486 unrelated individuals with European, East Asian, and sub-Saharan African ancestry. The genotype data sets after quality control from E5103 and HGDP were merged and kept SNPs genotyped in all 3 platforms, which resulted in 357,884 SNPs and 3607 individuals. The fastSTRUCTURE was run with default parameters and assuming 3 clusters, and the posterior mean of admixture proportions for AA patients was adopted for association analyses using the nonparametric Kendall rank correlation method in R v3.6.0.

RESULTS

Patient Demographics, Ancestry, and Disease Characteristics

We previously reported data from the parent trial, which showed no difference in the primary end point of invasive

DFS by study arm,[6] and exploratory analyses indicating women of AA had significantly higher incidence of paclitaxel-induced peripheral neuropathy and significantly inferior DFS.[3] Importantly, body weight did not entirely explain disparity in toxicity in this prior analysis. The final study set included 2854 patients with ancestry indicating EA or AA with BMI and survival outcome data (Fig. 1). Baseline characteristics of these participants are summarized in Table 1. A total of 383 participants (13.4%) were classified as AA patients, and 2471 (86.6%) as EA patients. Concordance was high between genetic ancestry and self-reported race; of those classified as AA patients, 349 self-identified as Black (91.1%), 31 as White (8.1%), 2 as Native American (0.5%), and 1 as Asian (0.3%). In those genetically classified as EA patients, 2465 identified as White (99.8%) and 3 as Black (0.1%). The mean BMI was higher in the AA population (32.3 vs 29.4 mg/m^2), and AA patients were more likely to have class 3 severe obesity (15.4% vs 8.5%).

Effect of Continuous BMI on Survival Outcomes by Ancestry

At a median of 47.8 months of follow-up, there were 427 DFS events and 216 deaths in the subset of 2854 patients with EA or AA genetic ancestry. In a univariate analysis to evaluate the impact of BMI as a continuous variable in increments of 5 on survival outcomes, BMI was not associated with DFS in the overall population (HR, 1.04; 95% CI, 0.97-1.11; P = .28), but significantly associated with OS (HR, 1.10; 95% CI, 1.005-1.20; P = .039). Multivariable analysis fully adjusted for statistically significant covariates included ER status, lymph node involvement, tumor size, and histological grade for EA patients, and ER status and lymph node involvement for AA patients. In this analysis, BMI was no longer statistically significantly associated with OS in the overall population (HR, 1.08; 95% CI, 0.99-1.19; P = .087). In the EA population, BMI was not associated with DFS or OS (DFS HR, 0.97; 95% CI, 0.90-1.05; P = .50; OS HR, 1.03; 95% CI, 0.93-1.14, P = .52). However, in the multivariable analysis, BMI was a statistically significant independent prognostic factor for worse DFS and OS in AA patients (DFS HR, 1.25; 95% CI, 1.07-1.46; P = .0042; OS HR, 1.38; 95% CI, 1.10-1.73, P = .0054) (Fig. 2). When this analysis was done using self-reported race in which n = 352 Black (349 AA and self-reported Black patients; 3 AA and self-reported White patients) and n = 2496 White (2465 EA and self-reported White patients; 31 EA and self- reported Black patients), the impact of BMI on survival was similar (self-reported White: DFS HR, 0.98; 95% CI, 0.91-1.06; P = .67; OS HR, 1.04; 95% CI, 0.94-1.15; P = .41; self-reported Black DFS HR, 1.23; 95% CI, 1.04-1.44; P = .014; OS HR, 1.36; 95% CI, 1.07-1.72; P = .012).

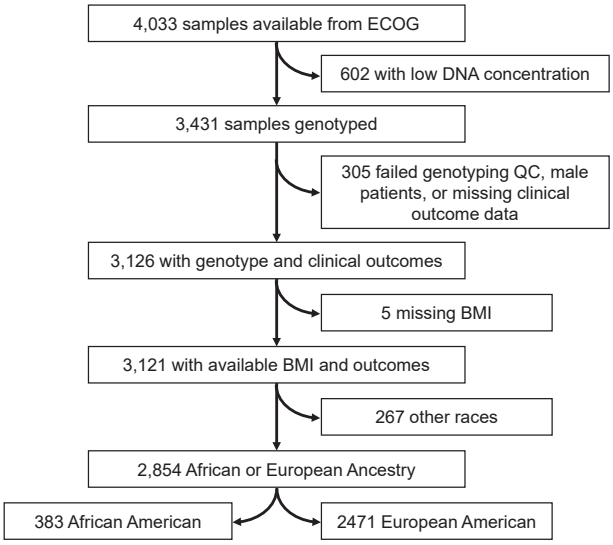

FIGURE 1. E5103 Consolidated Standards of Reporting Trials diagram. BMI indicates body mass index; ECOG, Eastern Cooperative Oncology Group; QC, quality control.

Subgroup Analysis by ER Status

Prior work has suggested the relationship between body weight and outcome is most substantial in those patients with ER+ tumors[11,12]; therefore, we also explored the relationship between continuous BMI and outcomes in subgroups of patients with ER+ or triple-negative disease. As shown in Table 1, AA patients were more likely to have triple-negative breast cancer (49.2% of AA patients vs 36.4% of EA patients). Despite this, as shown in Figure 3, the most statistically significant association of BMI with worse outcome was found in AA patients with ER+ disease.

Effect of Categorical BMI on Survival Outcomes by Ancestry

When looking at BMI categorically, obesity (BMI ≥30) was not statistically significantly associated with DFS or OS in either AA patients (DFS HR, 1.33; 95% CI, 0.83-2.13; P = .24; and OS HR, 1.78; 95% CI, 0.85-3.73; P = .13) or EA patients (DFS HR, 0.87; 95% CI, 0.70-1.08; P = .20; and OS HR, 1.07; 95% CI, 0.80-1.44; P = .64). However, World Health Organization class 3 obesity (BMI ≥40) compared with BMI <40 was significantly associated with worse DFS

and OS in the AA population (DFS HR, 2.04; 95% CI, 1.21-3.43; $P = .008$; and OS HR, 2.21; 95% CI, 1.03-4.75; $P = .043$); this was not seen in the EA population (DFS HR, 0.96; 95% CI, 0.65-1.40; $P = .82$; and OS HR, 1.30; 95% CI, 0.81-2.06, $P = .28$) (Fig. 4). In the multivariable analysis, the same finding of the effect of BMI ≥40 on survival outcomes was seen in EA patients and in DFS for AA patients, but OS in the AA population did not cross the level for statistical significance (AA patients: DFS HR, 1.98; 95% CI, 1.17-3.34; and OS HR, 2.07; 95% CI, 0.96-4.45; EA patients: DFS HR, 0.97; 95% CI, 0.66-1.42; and OS HR, 1.28; 95% CI, 0.80-2.04).

TABLE 1. Patient Baseline Characteristics by Genetic Ancestry Group

	EA Patients (n = 2471), No. (%)	AA Patients (n = 383), No. (%)
Age (continuous), mean ± SD, y	52.5 ± 9.9	49.7 ± 9.6
BMI (continuous), mean ± SD, kg/m^2	29.4 ± 6.9	32.3 ± 7.1
BMI (categories)		
<20	82 (3.3)	6 (1.6)
20-25	678 (27.4)	49 (12.8)
25-30	747 (30.2)	109 (28.5)
30-35	486 (19.7)	97 (25.3)
35-40	269 (10.9)	63 (16.4)
≥40	209 (8.5)	59 (15.4)
ER		
Positive	1574 (63.7)	194 (50.7)
Negative	897 (36.3)	189 (49.3)
Lymph node, no.		
Negative	666 (27.0)	112 (29.2)
1-3	1038 (42.0)	175 (45.7)
≥4	767 (31.0)	96 (25.1)
Tumor size, No. (%)		
<2 cm	858 (35.0)	130 (33.9)
2-5 cm	1301 (52.7)	211 (55.1)
>5 cm	310 (12.5)	42 (11.0)
Unknown	2 (0.1)	
Histological grade		
1	249 (10.3)	29 (7.7)
2	835 (34.6)	76 (20.3)
3	1329 (55.0)	270 (72.0)
Unknown	58 (2.3)	8 (2.1)

Abbreviations: AA, African ancestry; BMI, body mass index; EA, European ancestry; ER, estrogen receptor.

Proportion of AA, BMI, and Survival

In the 2854 patients included in this study, proportion of those with AA was associated with higher BMI ($P = 2.2 \times 10^{-7}$, Kendall $\tau = 0.071$), which is consistent with the higher BMI in AA patients compared with EA (Table 1). Additionally, we found a significant interaction between proportion of AA and continuous BMI on both DFS (coefficient = 0.25; 95% CI, 0.031-0.47; $P = .025$) and OS (coefficient = 0.35; 95% CI, 0.031-0.66; $P = .032$) with correction for statistically significant covariates. Within the 383 patients in the AA population, the mean proportion (SD) of AA patients was 0.78 ± 0.18. In these patients, proportion of AA was very weakly and nonsignificantly associated with BMI (Kendall $\tau = 0.040$, $P = .24$). Additionally, in the AA subgroup, there was no statistically significant interaction between proportion of AA and BMI on DFS (coefficient = –1.01; 95% CI, –2.09 to 0.057; $P = .064$) or OS (coefficient = –0.95; 95% CI, –2.53 to 0.63; $P = .24$) (additional data available in the Supporting files). In the multivariable Cox regression, BMI remained associated with DFS (HR, 2.78; 95% CI, 1.18-6.55; $P = .019$), suggesting that higher BMI is associated with worse DFS in this population, regardless of proportion of AA.

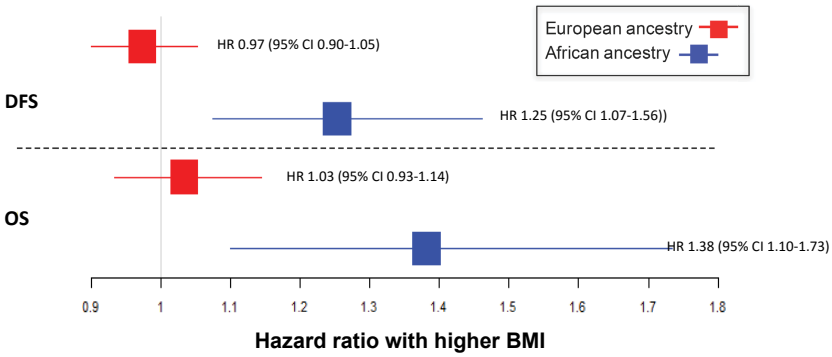

FIGURE 2. HRs (95% CIs) from multivariable analyses of DFS and OS with higher BMIs in women of European or African ancestry with high-risk, early-stage breast cancer. BMI indicates body mass index; DFS, disease-free survival; HR, hazard ratio; OS, overall survival

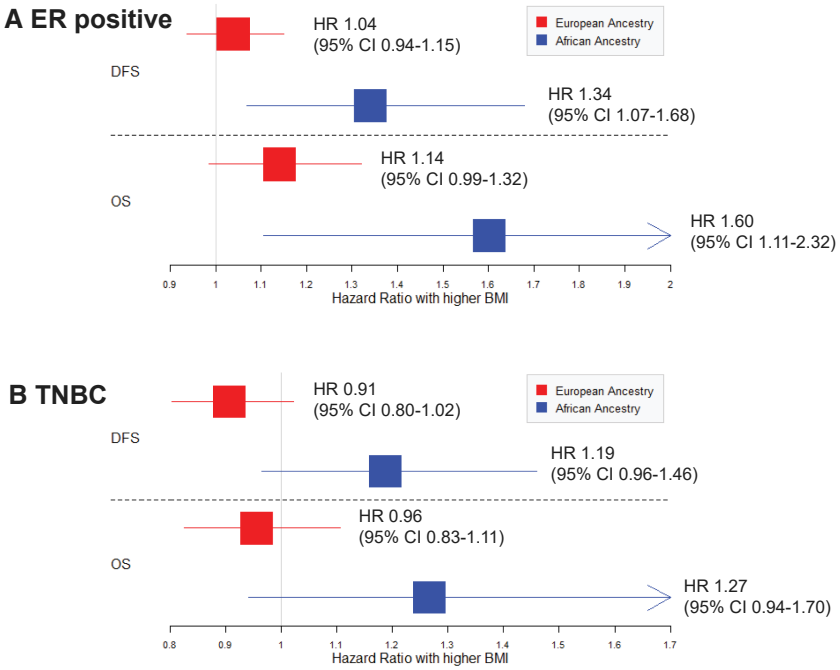

FIGURE 3. HRs (95% CIs) for DFS and OS with higher BMI in African or European ancestry patients with either (A) ER-positive breast cancer or (B) TNBC. BMI, body mass index; DFS, disease-free survival; ER, estrogen receptor; OS, overall survival; TNBC, triple-negative breast cancer.

DISCUSSION

This analysis of 2854 patients with comprehensive genetic ancestry data from the phase 3, randomized controlled trial E5103 demonstrated a significant association between higher BMI and worse outcomes for women of AA, but not for women of EA. Severe class 3 obesity was present twice as often in AA patients and was associated with significantly inferior survival; however, there was no impact even of severe obesity on survival in EAs. The degree of obesity and adiposity has variable influence on physiologic metabolic processes by race; for example, Black patients have a disproportionately higher burden of diabetes mellitus across all BMI categories compared with White patients.[13] Additionally, severe obesity is more likely to result in comorbidities and functional limitations regardless of ancestry; however, these complications are present in higher rates in AA patients and may ultimately explain the impact of severe obesity on breast cancer outcomes in this group.[13-15] Furthermore, differences in socioeconomic factors, including barriers to access to care, may contribute to both obesity and worse breast cancer outcomes in Black patients, who represent the vast majority of AA patients.

The association of higher BMI with worse DFS and OS only in patients of AA is discordant from prior analyses of BMI and self-reported race. A retrospective analysis of the Women's Contraceptive and Reproductive Experiences study data found that obesity, defined as BMI ≥30, 5 years before breast cancer diagnosis was associated with higher all-cause and breast cancer–specific mortality; however, this association was only seen in self-reported White women.[16] Analysis from another randomized adjuvant chemotherapy trial, E1199, examined potential confounders of worse survival seen in Black women with ER+ breast cancers.[11,17] In that analysis, self-reported Black race was associated with worse survival in nonobese patients, but not in obese patients. The authors hypothesized that race matters, but its contribution is diminished if patients are already at a higher risk for recurrence and mortality because of obesity. A major difference between E5103 and E1199 was in the use and schedule of taxane therapy. E1199 included either docetaxel or paclitaxel with variable schedules, whereas E5103 used weekly paclitaxel only. This difference may be important because weekly paclitaxel is associated with significantly higher rates of neuropathy and dose reductions in AA patients, which

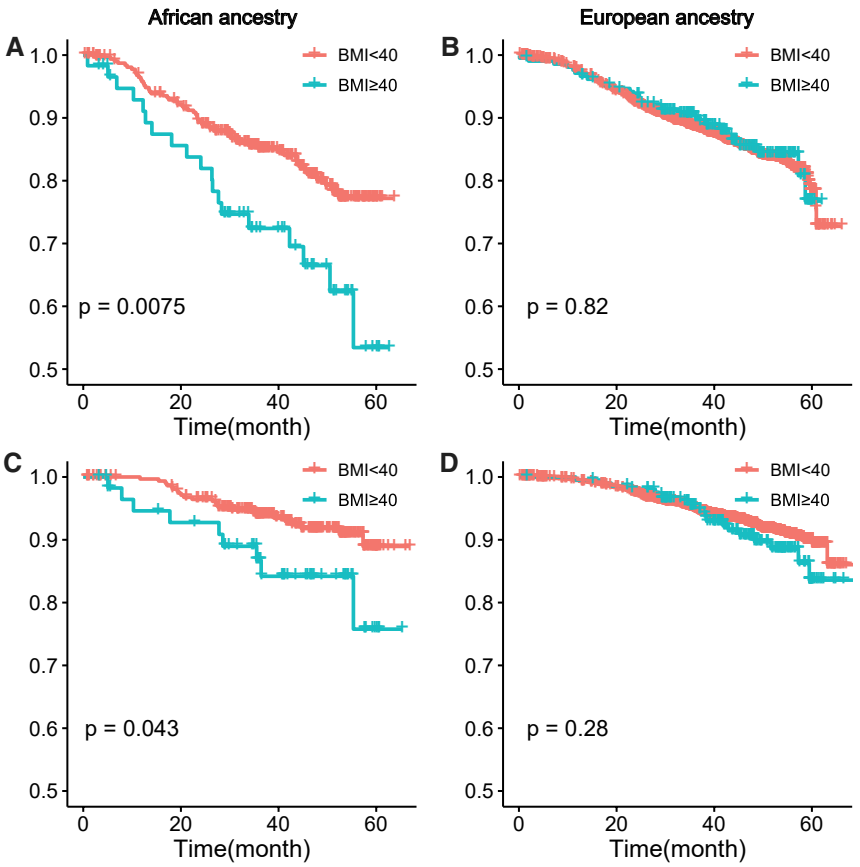

FIGURE 4. Kaplan-Meier plots of outcome probability according to the presence of severe class 3 obesity. (A) DFS in AA patients, (B) DFS in EA patients, (C) OS in AA patients, and (D) OS in EA patients. AA indicates African ancestry; BMI, body mass index; DFS, disease-free survival; EA, European ancestry; OS, overall survival.

ultimately was associated with inferior DFS.[3] Given that obesity is a predictor of both higher rates of neuropathy[18] and undertreatment in early-stage breast cancer,[19] it is possible that the differing taxane schedules and resulting toxicity in these trials may have modified the impact of BMI on outcome in AA patients.

Genetic ancestry is used to explain differences in genetic predisposition and disease or host biology. This differs from self-reported race, which is subject to documentation error in clinical research and does not always accurately reflect true ancestry.[20] In our study, 8.9% of participants who were genetically classified as of African descent did not identify as Black (or were not documented to have identified themselves as Black). Although this is an important finding and there are social and cultural implications for self-identified race, this difference is not likely to have altered the conclusions of this study. The purpose of this analysis was not to compare genetic and self-reported ancestry, but rather to investigate links specifically between AA, obesity, and breast cancer outcomes. Interestingly, the proportion of AA patients in our study population did not appear to positively modify the relationship between BMI and outcomes when analysis was confined to patients of African descent. Prior work in large data sets such as the Women's Health Initiative have found proportion of AA to be associated with BMI and risk of obesity; this association was more pronounced in US-born compared with non–US-born women.[5] It is possible that although genetics may predispose to obesity, lifestyle factors may be an important contributing variable in obesity's impact on breast cancer outcomes. The associations with proportional ancestry in this study are underpowered but suggest that, given no dose relationship of proportion of AA patients to worse outcomes in the African population, perhaps social factors play a greater role. This question is worthy of further exploration, and future, more comprehensive analyses are indicated.

Investigating the impact of weight on breast cancer outcomes across trials is complicated by inconsistent definitions and measures. Evaluations of the dichotomous

variable of obesity defined as BMI ≥30 have found the association of BMI and outcome to differ depending on the population studied.[1,12,21] Additionally, prior analyses of some adjuvant breast cancer trials find no impact of BMI on survival when using a cutoff of 30, but statistical difference in outcomes when considering cutoffs of 35 or 40.[14] Furthermore, BMI does not accurately reflect body composition, which varies substantially across racial groups.[22] Muscle mass and adipose mass are more clearly associated with survival outcomes in early-stage breast cancer than is BMI.[23] Thus, future analyses focused on unraveling the intersection of body composition (muscle mass and adiposity) and race on outcomes may provide more consistent and accurate results. In our study, use of severe obesity as the cutoff in our categorical assessment allowed for the comparison of an extreme phenotype that is less likely to be confounded by body composition.

This analysis found BMI to be most impactful on outcomes in AA patients with ER+ disease. Nonadherence or early discontinuation of endocrine therapy is associated with worse outcomes in early-stage, ER+ breast cancer.[24] Given that both obesity and Black race are associated with endocrine-related toxicities and Black race with higher rates of nonadherence,[25,26] this may contribute to disparities in ER+ disease. Information was not available on endocrine therapy adherence in E5103 and has been difficult to reliably collect in other early-stage breast cancer trials. More comprehensive future analyses that include detailed global health status, social determinants of health, treatment access, and adherence are certainly indicated to disentangle the social and biologic factors contributing to racial disparities in early-stage breast cancer.

This evaluation provides further insight into the complex relationship of both race and obesity with outcomes in early-stage breast cancer. It is likely that even greater survival disparities exist outside of a clinical trial, where patients are more likely to receive less than the standard of care because of comorbid conditions, lack of access, and provider bias. Implicit bias exists not just in the treatment of Black patients but also in those that are obese[27,28]; it is hypothesized that obese Black women may suffer additive bias and disparity in the delivery of care. Currently, the ECOG-ACRIN trial EAZ171 (NCT04001829) is enrolling Black women with early-stage breast cancer who are receiving neoadjuvant or adjuvant taxane-based chemotherapy with the primary objective of evaluating genotypic and phenotypic predictors of peripheral neuropathy in this population, including ancestry. This trial will provide a substantial amount of information specifically in this population, including BMI and functional status, to help define the relationship of factors contributing to ancestry and race disparities. Through this work and that of others, determining the optimal populations and interventions to personalize modification of host-related factors in the same way we are able to do for tumor-related factors will affect survival outcomes in early-stage breast cancer.

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CONFLICT OF INTEREST DISCLOSURES

Tarah J. Ballinger declares honoraria from Medscape and Novartis outside the scope of the current work. Bryan P. Schneider reports research support from Genentech, Foundation Medicine, Pfizer, and Epic Sciences and an honorarium from Eli Lilly outside the current work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Tarah J. Ballinger: Project conception, data analysis, and manuscript writing. **Guanglong Jiang:** Data analysis and manuscript writing. **Fei Shen:** Data analysis. **Kathy D. Miller:** Data collection in the original clinical trial. **George W. Sledge, Jr:** Data collection in the original clinical trial. **Bryan P. Schneider:** Data analysis and manuscript writing. All authors contributed edits to the final version of the manuscript.

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