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Impact of Genetic Ancestry on Outcomes in ECOG-ACRIN-E5103

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Abstract

Purpose—Racial disparity in breast cancer outcomes exists between African American and Caucasian women in the United States. We have evaluated the impact of genetically determined ancestry on disparity in efficacy and therapy-induced toxicity for breast cancer patients in the context of a randomized, phase III adjuvant trial.

Patients and Methods—This study compared outcomes between 386 patients of African ancestry (AA) and 2473 patients of European ancestry (EA) in a randomized, phase III breast cancer trial; ECOG-ACRIN-E5103. The primary efficacy endpoint, invasive disease free survival (DFS) and clinically significant toxicities were compared including: anthracycline-induced congestive heart failure (CHF), taxane-induced peripheral neuropathy (TIPN), and bevacizumab-induced hypertension.

Results—Overall, AAs had significantly inferior DFS (p=0.002; HR=1.5) compared with EAs. This was significant in the estrogen receptor-positive subgroup (p=0.03); with a similar, non-significant trend for those who had triple negative breast cancer (TNBC; p=0.12). AAs also had significantly more grade 3-4 TIPN (OR=2.9; $p=2.4 \times 10^{-11}$) and grade 3-4 bevacizumab-induced hypertension (OR=1.6; p=0.02), with a trend for more CHF (OR=1.8; p=0.08). AAs had significantly more dose reductions for paclitaxel ($p=6.6 \times 10^{-6}$). In AAs, dose reductions in paclitaxel had a significant negative impact on DFS (p=0.03); whereas in EAs, dose reductions did not impact outcome (p=0.35).

Conclusion—AAs had inferior DFS with more clinically important toxicities in ECOG-ACRIN-E5103. The altered risk to benefit ratio for adjuvant breast cancer chemotherapy should lead to additional research with the focus centered on the impact of genetic ancestry on both efficacy and toxicity. Strategies to minimize dose reductions for paclitaxel, especially due to TIPN, are warranted for this population.

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Keywords

disparity; race; genetic ancestry; breast cancer; DFS; toxicity

Introduction

African American breast cancer patients have inferior efficacy outcomes when compared to other races.[1,2] The reason for this imbalance is multifactorial and includes higher stage, higher grade, more triple negative breast cancer (TNBC), and poorer responsiveness to chemotherapy.[3,4] These clinical imbalances have previously been attributed to both socio-economic factors and a different underlying biology of the tumor.[2,5] AAs also experience more adverse drug reactions; including an increase in clinically important toxicities for chemotherapeutic agents. Although less well characterized, these toxicity disparities are also likely multifactorial and include inherited genetic variation and comorbidities, among other factors.[6-10]

Much of the prior work has been based on self-reported race. Race, when assessed in this fashion, is typically based on skin color and often neglects the genetic ancestry. [11] Recent studies suggest there is substantial admixture and misclassification of race in the United States when based on self-reported skin color.[12] Genetic ancestry can be accurately determined using well-characterized ancestry informative germline markers.[13]

This correlative work aims to determine genetic ancestry accurately and elucidate its impact on efficacy and toxicity in the context of a randomized, phase III adjuvant breast cancer trial; ECOG-ACRIN-E5103.[14]

Methods

ECOG-ACRIN-E5103 Overview

ECOG-ACRIN-E5103 was a phase III adjuvant breast cancer trial that randomized 4994 patients with node-positive or high risk node-negative breast cancer to intravenous doxorubicin and cyclophosphamide (AC) every 2 or 3 weeks (at discretion of treating physician) for four cycles followed by 12 weeks of weekly paclitaxel (80 mg/m^2) alone (arm A) or to the same chemotherapy with either concurrent bevacizumab (arm B) or concurrent plus sequential bevacizumab (arm C); Figure 1A. Patients were all human epidermal growth factor receptor 2 (HER2) negative. Those patients who had TNBC had a tumor ≥ 1cm or were lymph node (LN)-positive. Those patients with estrogen receptor positive (ER+) disease, had LN +, a tumor ≥ 5cm, or a tumor = 1-5cm with a recurrence score ≥ 11.

Genome-wide association study

Germline DNA from whole blood and companion clinical outcome data were available from 3126 patients. Genome-wide SNP arrays (either Illumina HumanOmni1-Quad or Human OmniExpress) were performed in two distinct study subsets as described previously.[15] A principal component analysis was performed using Eigenstrat and reference data from 11 HapMap phase III populations to identify clusters using the first two eigenvectors computed

using all SNPs.[16] Samples clustering with those of African Ancestry (AA) and those of European Ancestry (EA) were used in these analyses; Supplemental figure 1.

Efficacy Analyses

ECOG-ACRIN-E5103 involved a randomization to a control treatment arm and two experimental treatment arms. The primary objective of this phase III trial was to determine whether the addition of bevacizumab improves disease-free survival (DFS). A two-step hierarchical approach was used to assess this objective. In the first step, arm C was to be compared to arm A. If arm C significantly improved DFS relative to arm A, then in the second step, a comparison of Arm B to Arm A was to be performed.[14] In this correlative study, DFS and overall survival (OS) were evaluated using Kaplan-Meier methodology. The differences in outcomes between AAs and EAs were compared with the application of Cox proportional-hazards (PH) models using either univariate or multivariate analysis that were corrected with significant covariates. Multivariate Cox PH model was used to test associations between independent variables and DFS. To identify the best regression model, a forward and a backward step-wise selection procedure were carried out separately to evaluate variable associations, and Akaike Information Criterion (AIC) was adopted to determine the inclusion of potential confounders such as race, menopausal status, age, weight, height, side of cancer involvement, ER status, histological Grade, nuclear Grade, LN status, type of surgery, types of AC schedule, and dose reductions of AC or paclitaxel. Both procedures returned the same model with six predictors listed in Supplemental table 1.

DFS was the primary endpoint of the parent trial and defined as invasive disease-free survival (IDFS) and calculated from the date of randomization to the date of first treatment failure (invasive ipsilateral, local/regional invasive, or distant recurrence, invasive contralateral breast cancer, invasive non-breast second primary, or death from any cause, whichever occurs first). Cases with incomplete follow up, without documented IDFS event (including those who developed squamous or basal cell skin cancers or *in situ* carcinomas of any site as their only event) were censored at the date of last disease evaluation. OS, a secondary endpoint was calculated from the date of randomization to the date of death.

Toxicity Analyses

We analyzed the classic and most severe toxicities (common toxicity criteria adverse event version 3.0; CTCAE v. 3.0) associated with doxorubicin (congestive heart failure; CHF), paclitaxel (peripheral neuropathy; TIPN) and bevacizumab (hypertension); Supplemental table 2-3. We had previously published biomarker data on each of these toxicities[15,17,18] and set out to compare the frequency of all toxicities between AAs and EAs and to assess the impact of race on dose modifications with the current study. Statistical analysis was performed using R (v3.3.0) and the chi-square test. Odds ratio (OR) was used to evaluate the significance and magnitude of the differences in the toxicity frequency between AAs and EAs.

CHF cases for this study included individuals that had centrally reviewed, cardiologist-adjudicated CHF. To be selected for inclusion in ECOG-ACRIN-E5103, patients must have not had a history of clinically significant cardiovascular disease. Cardiovascular health was

monitored at the start and during the trial by MUGA or echocardiograms. Additionally, a cardiac symptoms assessment was performed two years post-registration. Cardiac events including: CHF, decrease in left ventricle ejection fraction, acute coronary syndrome, supraventricular tachycardia, and myocardial dysfunction diagnosed by a cardiologist.

TIPN cases for this study were defined as those experiencing either grade 2-4 or grade 3-4 TIPN as assessed by CTCAE v. 3.0. To serve as a TIPN case, the patient had to have received at least one dose of paclitaxel and the neuropathy event had to have occurred during treatment or within 3 months of the last dose of therapy.

Hypertension cases for this study were defined as those experiencing a systolic blood pressure (SBP) >160mmHg (moderate), SBP >180 mmHg (severe), or grade 3-5 hypertension as determined by CTCAE 3.0 in arm B or arm C. Of note, a baseline SBP>160 mmHg was an exclusion criterion for eligibility to enrollment in the parent trial. Blood pressure values were collected as part of standard clinical assessment prior to administration of therapy throughout the conduct of the trial.

Results

Genotyped group from ECOG-ACRIN-E5103 and genetic ancestry

3394 germline DNA samples from patients were collected as part of the planned correlative protocol within ECOG-ACRIN-E5103; Figure 1B. Genome-wide assessment was conducted and allowed for the determination of genetic ancestry on 3126 patients who had clinical outcome data. 386 patients (12.3%) were classified as AA and 2473 patients (79.1%) were classified EA. Among 386 patients of African ancestry, 352 (91.1%) were self-reported African American. In the 2473 patients of European ancestry, 2467 (99.8%) were self-reported Caucasian. The outcomes of the entire genotyped cohort (all ancestries combined) used in this correlative study were almost identical to the parent trial; [4] Supplemental figure 2 and Supplemental table 4-5.

Demographic and disease comparisons

Table 1 summarizes the important demographic comparisons between AAs and EAs. We assessed for the differences in the parent trial stratification factors as well as other known outcome predictors including: age, hormone receptor status (ER+ *vs.* TNBC), LN status, height, weight, type of surgery, and tumor grade. Compared with EAs, AAs had a higher proportion of TNBC, and higher nuclear and histologic grade. AAs were younger, heavier, and more likely to undergo lumpectomy compared with EAs. There were no significant differences overall in LN status.

Genetic ancestry as a predictor of efficacy in ECOG-ACRIN-E5103

DFS was the primary efficacy endpoint of the parent trial. When combining all Arms of the study and with a median follow-up of 47.5 months, AAs had an inferior DFS compared to EAs on univariate analysis; Hazard ratio (HR) =1.5 (p=0.002); Figure 2A.

The finding remained significant (p =0.013; HR=1.4) after correction of ER status, histology grade, LN status, type of surgery and dose modification of cyclophosphamide; covariates

which were significantly associated with DFS in multivariate analysis (Supplemental table 1). Both genetic ancestry (Figure 2A) and self-reported race (Figure 2B) demonstrated an inferior DFS for AAs compared with EAs; with very similar conclusions. The difference in DFS did not yet result in a significant difference in a secondary endpoint of OS (p=0.22); Supplemental figure 3. When further evaluating the impact of genetic ancestry based on tumor subtype, the ER+ subgroup demonstrated a significantly inferior DFS for AAs; HR=1.5 (p=0.027); Figure 2C and Table 1. The inferior DFS for AAs in the TNBC subgroup did not reach statistical significance but was in favor of better outcomes for EAs; HR=1.3 (p=0.12); Figure 2D. An imbalance in associated comorbidities or environmental factors cannot be excluded as a contributing cause and unfortunately those data were not collected with ECOG-ACRIN-E5103. Thus, we evaluated the hazard ratio across the principal components and found an increasing hazard towards African ancestry (HR =1.5, p=0.004).

Genetic ancestry as a predictor of toxicity and dose modifications in ECOG-ACRIN-E5103

We assessed for the impact of genetic ancestry on likelihood of TIPN and found that AAs had markedly higher rate of grade 2-4 and grade 3-4; OR=2.2 ($p=5.8\times10^{-12}$) and OR=2.9 ($p=2.4\times10^{-11}$); respectively, compared to EAs; Figure 3. Previously, we reported that compared to all other races, AAs had higher risk of experiencing grade 2-4 TIPN; HR=2.1 ($p=9.4\times10^{-15}$) and grade 3-4 TIPN; HR=2.7 ($p=7.4\times10^{-13}$), respectively.[17] When assessed for impact of genetic ancestry on the risk of various definitions of hypertension in the bevacizumab containing arms (arms B and C), African ancestry was associated with significantly more grade 3-4 hypertension (OR=1.6; p=0.02), a trend toward more patients with one SBP measurement >160 mmHg (OR=1.4; p=0.07) or one SBP measurement >180 mmHg (OR=2.1; p=0.03); Figure 3. Finally, there was a trend for more AA patients that had CHF (OR=1.8; p=0.08); Figure 3.

We also assessed whether increased toxicity impacted dose reductions, modifications, or premature stoppage of therapy. When comparing AAs vs. EAs, there was no significant difference in the proportion of patients requiring dose reductions for doxorubicin (p=0.25) or cyclophosphamide (p=0.44); however, there were substantially more dose reductions for paclitaxel in AAs compared to EAs ($p=6.6\times10^{-6}$); Table 2. When considering all genetic ancestries combined, dose reductions in doxorubicin and cyclophosphamide negatively impacted DFS ($p=4.9\times10^{-4}$ and $p=3.3\times10^{-5}$, respectively) for all patients. However, since there was no difference in the percentage of AA's experiencing dose reductions in the doxorubicin and cyclophosphamide portion, this did not account for the difference in DFS between ancestries; Supplemental table 6. Dose reductions for paclitaxel also negatively impacted DFS for all ancestries (p=0.02) (Supplemental table 6); however, having a dose modification in paclitaxel did not impact DFS for EAs, but did significantly cause an inferior DFS for AAs; Figure 4. The difference may have been explained by more severe dose reductions in AAs. When comparing the mean normalized cumulative dose exposure of paclitaxel for those who had dose modifications, AAs had a significantly lower cumulative dose (548 mg/m^2) than EAs (603 mg/m^2); p=0.03.

Discussion

This correlative study from ECOG-ACRIN-E5103 supports prior findings that AAs have inferior outcome when compared to EAs.[1,2] While there was a statistically significant decrease in DFS for AAs, this did not yet translate to a difference in OS. This is likely due to insufficient events, statistical power, and follow-up duration. The inferior DFS was apparent for both the ER+ and the TNBC subgroup; although the latter was not statistically significant. Recent data have also supported a potential preferentially worse outcome for the ER+ subgroup of patients in AAs.[19,20] These findings support a fundamental difference in the biology of the disease in AAs compared with EAs; not just an imbalance in percentage of the more aggressive TNBC subtype.[2,21]

This study evaluated a subgroup of patients who had their race defined through genetic ancestry determination rather than self-assignment. The 91% and 99.8% concordance between the genetic ancestry and the self-reported race for both AAs and EAs, respectively, were in the agreement with the 1000 genome project.[22] The biological differences in tumor and in drug-toxicities are likely a reflection of the underlying and nuanced genetic differences rather than differences in skin color.

Ancestry determined with specific genetic markers rather than self-reported race should be more helpful for elucidating biological differences. [23] This is particularly true in populations largely composed of patients from the United States where admixture is common.[22,24] Because genetic ancestry information was only available in a subgroup of the parent trial, sample bias was possible. The outcomes for the subgroup genotyped, however, fared similarly to the parent population; minimizing the concern for subgroup bias.

We also compared the results of the genetic ancestry with self-reported race, and there was no significant difference in conclusion. This would support that for this phenotype, prior conclusions from self-reported race are likely valid. Work in other disease phenotypes, however, has demonstrated that use of self-reported race as a surrogate for genetic ancestry was not perfect.[25-27] Prior work has demonstrated that over 9% of patients cannot supply or choose not to supply ancestry information.[28] Thus, the real impact of accurate self-reported race is likely larger than the 9% seen here due to misclassification alone. This suggests that for research questions that center on racial disparity, investigators should consider use of ancestry informative markers, [29] and self-reported race should only be used as a surrogate when genetic ancestry is unavailable. While genotype may provide more insight toward underlying biological diversity, self-reported race still likely represents a reasonable surrogate for genotypic variation in the routine clinical setting for consideration of metabolism and drug toxicity.

We had previously evaluated for genetic markers to predict some of the most clinically important toxicities in ECOG-ACRIN-E5103: bevacizumab-induced hypertension (using various definitions), TIPN, and cardiologist-adjudicated anthracycline-induced CHF.[15,17,18] In this study we have compared the likelihood of each of these clinically relevant toxicities between AAs and EAs. We report a numerically higher likelihood for each of these toxicities for AA's; with odds ratios ranging from 1.4-2.9. This supports a marked genetic difference

in therapeutic tolerability. These data support prior work from a single institution retrospective analysis as well as data from pediatric populations that revealed higher likelihood of anthracycline induced CHF in AAs. Similarly, a prior single-institution retrospective analysis demonstrated higher risk of TIPN for AAs.[8-10]

Since AAs experience greater toxicity, it is highly unlikely that the imbalance in efficacy is a result of exposure due to pharmacokinetic considerations; as the end organs are clearly being impacted. We further assessed whether the adverse impact on toxicity and resultant increase in dose reductions might have accounted for inferior outcomes. As expected, all ancestries that had dose reductions from the AC portion of the chemotherapy had inferior DFS; this difference, however was true for both EAs and AAs. The inferior difference (as defined by p-value) in DFS seen for those who had dose reductions from paclitaxel (p=0.02) was less significant for the whole population when compared to those who had dose reductions for doxorubicin ($p=4.9 \times 10^{-4}$), or cyclophosphamide ($p=3.3\times10^{-5}$). The inferior DFS, however, appeared to be uniformly driven by the AA subgroup, implying dose intensity of paclitaxel is more important to the AA population. The significant difference in DFS due to paclitaxel dose modifications for AAs may have been due to the markedly more severe dose reductions; evidenced by a lower mean normalized dose in those who had dose reductions (p=0.03); in large part due to TIPN. This study did not evaluate socio-economic factors, which are known to be an important variable in outcome.[5] However, in the context of a randomized phase III trial, many of these inequities are minimized.

Conclusion

The current study highlights the need to better understand the biological differences in normal breast biology, tumor biology, and the inherited genetic differences between AA and EA women. It also highlights the need to better personalize counseling when discussing the risk to benefit ratio for AAs where the disease specific outcomes are inferior and drug-specific toxicities are higher. These data would suggest that the lack of the full, intended doses of paclitaxel is at least one factor in inferior outcomes in ECOG-ACRIN-5103. Taxanes have been proven to be important in the curative setting for breast cancer and that point is further illustrated here. ECOG-1199 previously demonstrated that the every three-week dosing of docetaxel was as effective but had less dose reductions for AAs in a similar clinical setting.[20] Future trials should investigate whether another taxane, such as docetaxel, with less risk of TIPN might be more effective for AAs in the adjuvant breast cancer setting. These data also highlight the need to validate predictive biomarkers for toxicities specific to AAs. Most importantly, these findings underscore the need to include more AAs in clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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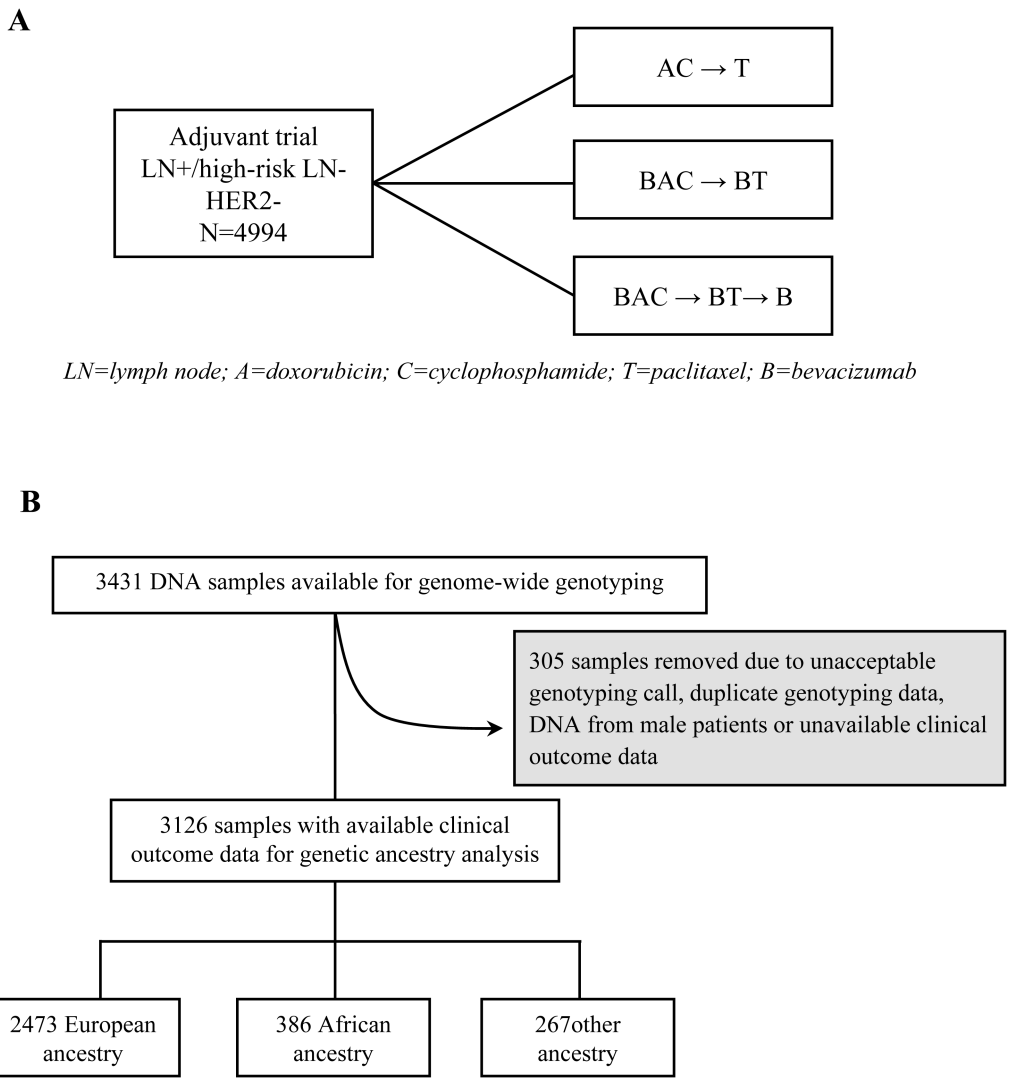
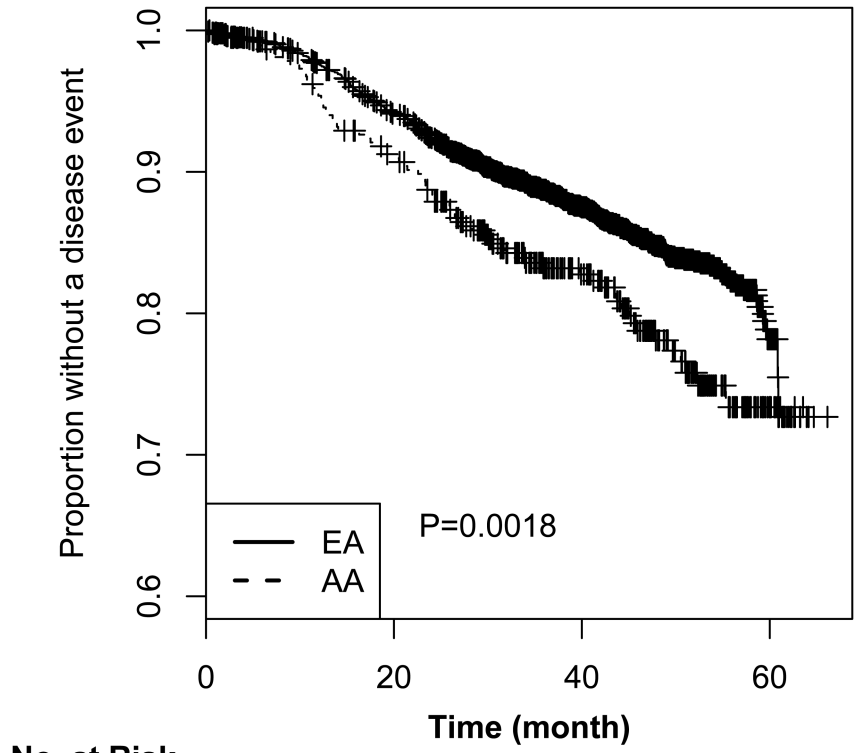
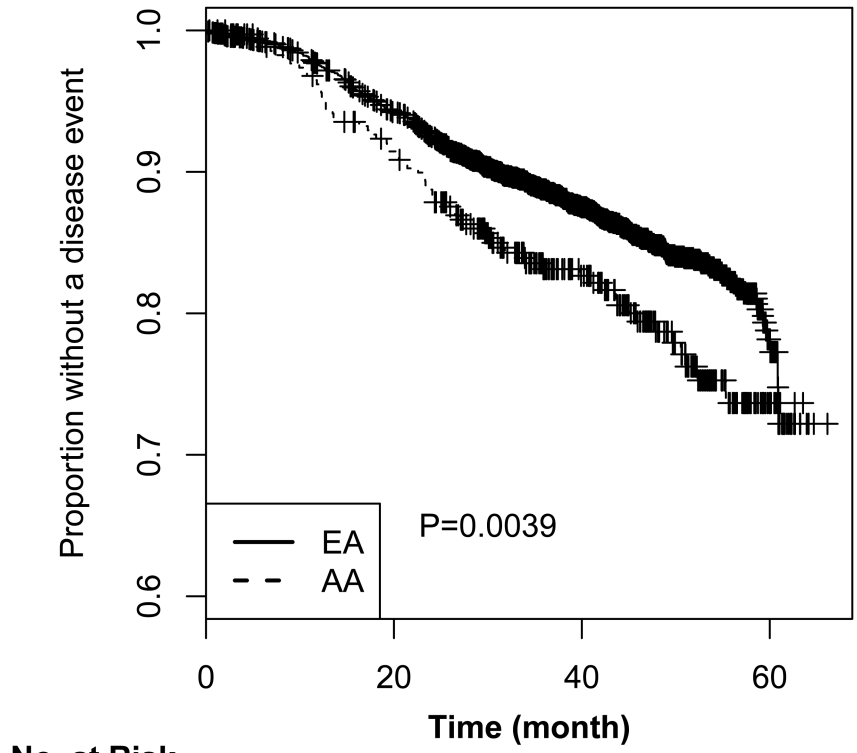


Figure 1.
Schema for ECOG-ACRIN-E5103 (A), and CONSORT for ECOG-ACRIN-E5103 (B).



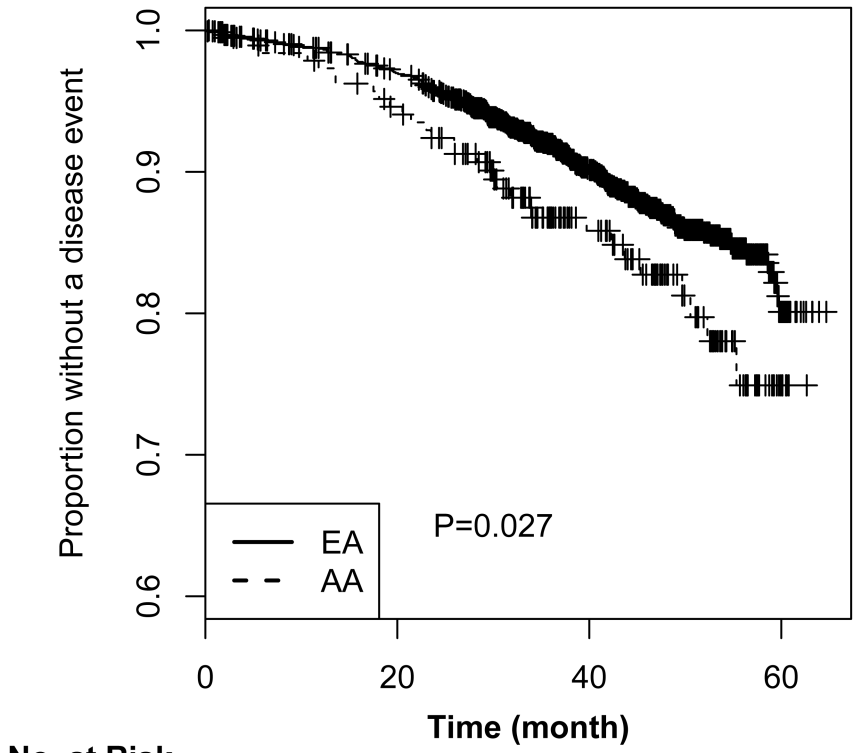
No. at Risk

EA	2473	2249	1476	86
AA	386	328	189	12



No. at Risk

EA	2667	2420	1586	95
AA	358	306	174	12



No. at Risk

EA	1561	1463	974	52
AA	191	172	92	5

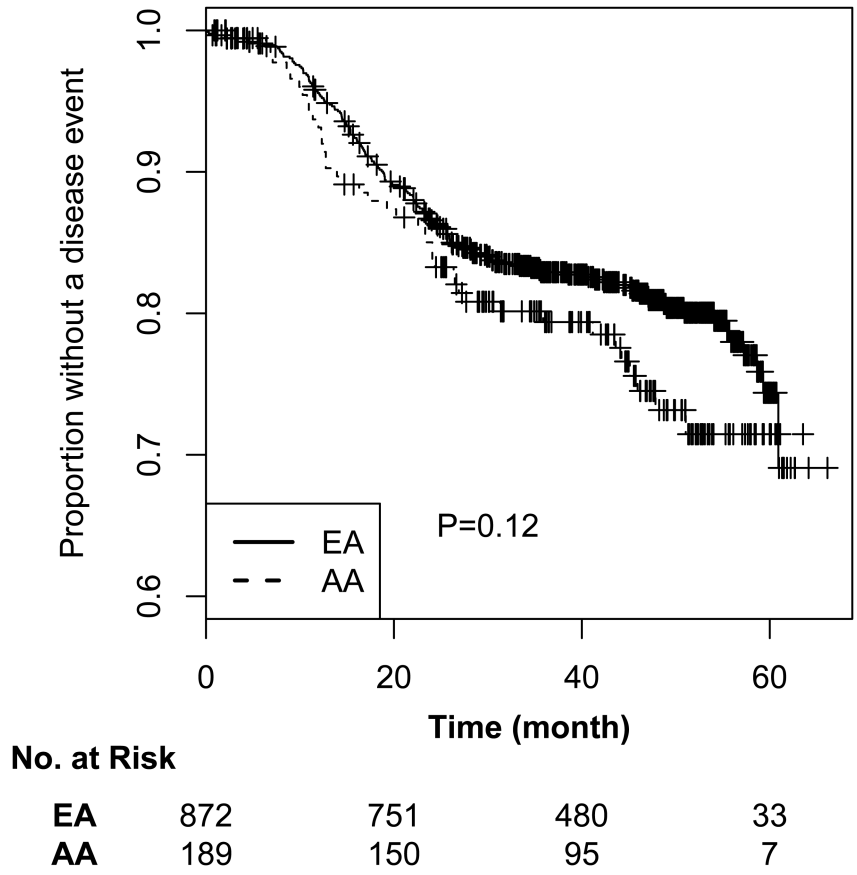
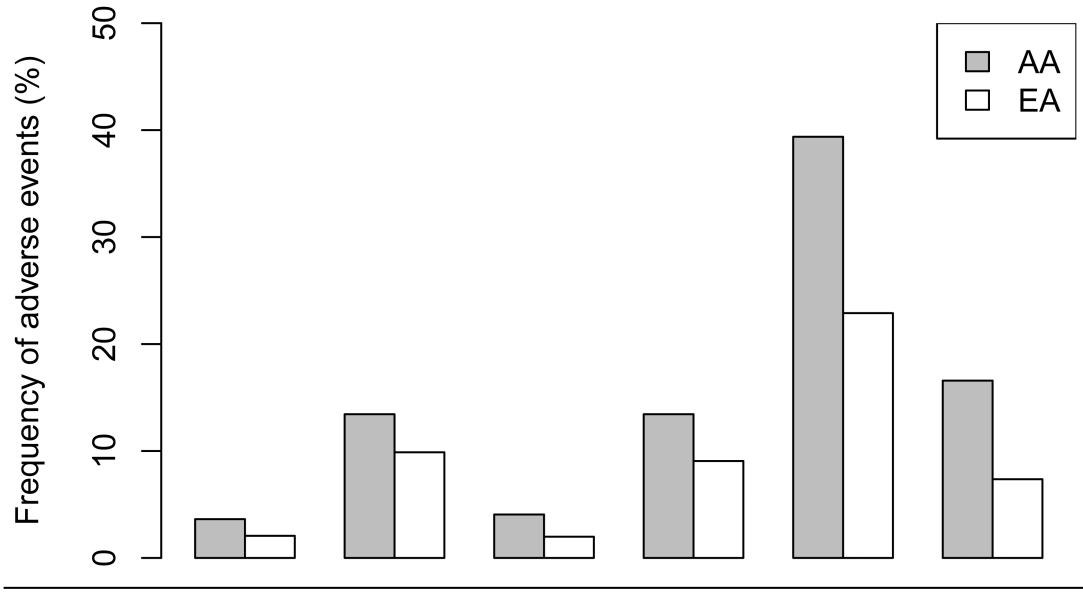


Figure 2.

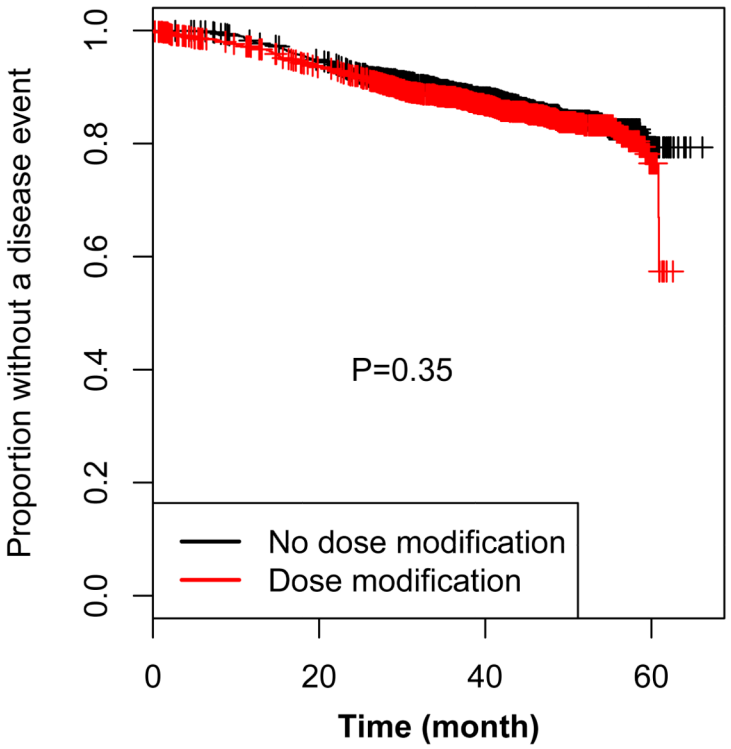
Disease Free Survival (DFS) for African ancestry (AA) compared with European ancestry (EA) for all patients (A), DFS for all self-reported patients (B), DFS for genetic ancestry with estrogen receptor or progesterone receptor positive disease (C), and for genetic ancestry with triple negative breast cancer (D).



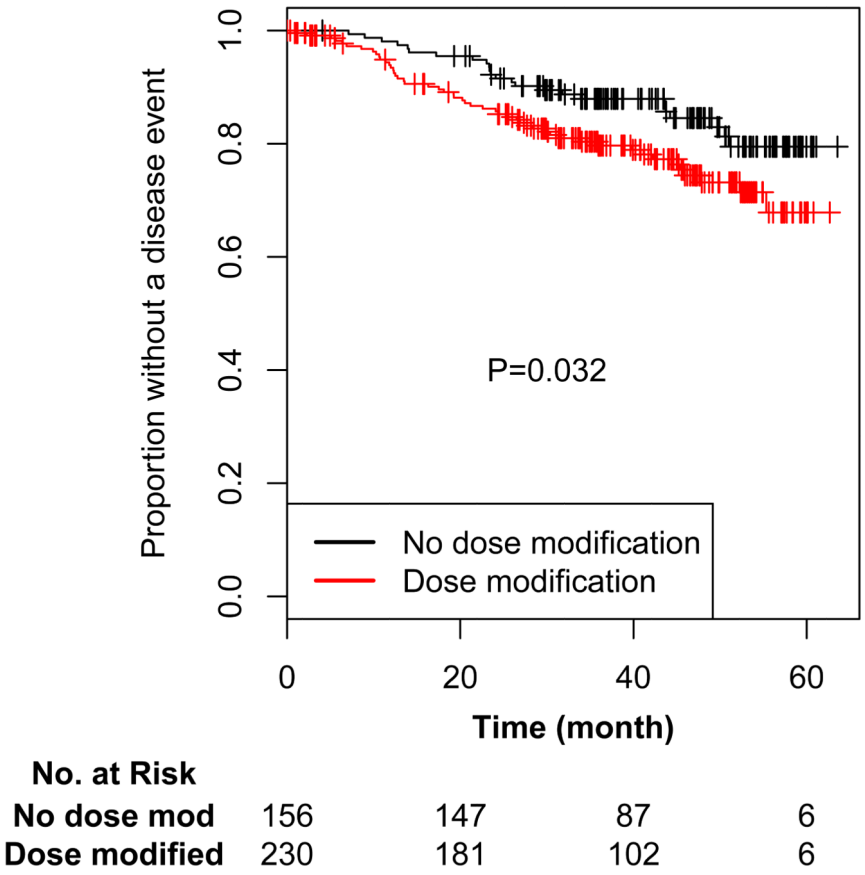
	CHF	SBP>160	SBP>180	HTN Grade 3−4	TIPN Grade 2−4	TIPN Grade 3−4
Odds Ratio	1.79	1.42	2.13	1.56	2.19	2.87
P value	0.083	0.066	0.031	0.019	5.8e−12	2.4e−11

Figure 3.

Frequency of anthracycline-induced congestive heart failure (CHF), systolic blood pressure greater than 160mmHg (SBP>160), systolic blood pressure greater than 180mmHg (SBP>180), hypertension (HTN) grade3-4, and paclitaxel-induced peripheral neuropathy (TIPN) in patients of African ancestry (dark bar) versus those of European ancestry (light bar) in genotyped patients.



No. at Risk				
No dose mod	1308	1221	820	54
Dose modified	1165	1028	656	32



No. at Risk				
No dose mod	156	147	87	6
Dose modified	230	181	102	6

Figure 4.

DFS for European ancestry (left) and African ancestry (right) patients who experienced any dose reduction or early cessation of paclitaxel compared with those who did not have a dose reduction or early cessation.

Table 1
Demographic comparison between genetic ancestries

Demographics	AA[1] (N=386)	EA[2] (N=2473)	P value	Type of test
Age (yr) (mean ± SD)	49.8 ± 9.6	52.5 ± 9.9	6.30×10^{-7}	T test
Height (cm) (mean ± SD)	163.6 ± 6.3	163.8 ± 6.9	0.48	T test
Weight (kg) (mean ± SD)	86.4 ± 19.5	78.8 ± 19.0	4.71×10^{-12}	T test
ER status (%)				
ER+/PR+[3]	50.3	64.2	2.73×10^{-7}	Chi-square
TNBC[4]	49.7	35.8		
Histology Grade (%)				
1	7.7	10.3		
2	20.3	34.6	3.75×10^{-9}	Chi-square
3	72.0	55.1		
Nuclear Grade (%)				
1	4.8	6.58		
2	23.6	37.2	1.55×10^{-6}	Chi-square
3	71.7	56.2		
Positive lymph node (%)				
0	29.0	27.0		
1-3	45.9	42.0	0.06	Chi-square
≥4	25.1	31.1		
Type of Surgery (%)				
Conserving	55.4	43.7	2.00×10^{-5}	Chi-square
Mastectomy	44.6	56.3		

[1] AA=African ancestry;

[2] EA=European ancestry;

[3] ER= estrogen receptor; PR=progesterone receptor;

[4] TNBC=triple negative breast cancer

Table 2

Comparison of dose reductions in ECOG-ACRIN-E5103 between ancestries

	Doxorubicin		Cyclophosphamide		Paclitaxel	
	EA[2]	AA[1]	EA[2]	AA[1]	EA[2]	AA[1]
No dose modification(%)	2211(89.4)	337(87.3)	2220(89.8)	341(88.3)	1308(52.9)	156(40.4)
Dose modification(%)	262 (10.6)	49(12.7)	253(10.2)	45(11.7)	1165(47.1)	230(59.6)
p-value	0.25		0.44		6.6×10^{-6}	

[1]AA=African ancestry;

[2]EA=European ancestry;