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ORIGINAL ARTICLE

Outcome of African-American compared to White-American patients with early-stage breast cancer, stratified by phenotype

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Abstract

Background: Breast cancer mortality rates are 39% higher in the African-American (AA) women compared to White-American (WA) women despite the advances in overall breast cancer screening and treatments. Several studies have undertaken to identify the factors leading to this disparity in United States with possible effects of lower socioeconomic status and underlying aggressive biology.

Methods: A retrospective analysis was done using a prospectively maintained database of a metropolitan health system. Patients were selected based on diagnosis of early-stage breast cancer between 10/1998 and 02/2017, and included women over age of 18 with clinically node-negative disease. Patients were then stratified by phenotype confirmed by pathology and patient-identified race.

Results: A total of 2,298 women were identified in the cohort with 39% AA and 61% WA women. The overall mean age at the time of diagnosis for AA women was slightly younger at 60 years compared to 62 years for WA women (p = 0.003). Follow-up time was longer for the WA women at 95 months vs. 86 months in AA women. The overall 5-year survival was analyzed for the entire cohort, with the lowest survival occurring in patients with triple-negative breast cancer (TNBC). Phenotype distribution revealed a higher incidence of TNBC in AA women compared to WA women (AA 16% vs. WA 10%; p < 0.0001). AA women also had higher incidence of HER2 positive cancers (AA 16.8% vs. WA 15.3%; p < 0.0001). WA women had a significantly higher distribution of Non-TNBC/HER2-negative phenotype (AA 55% vs. WA 65%; p < 0.0001). Furthermore, a subgroup analysis was done for a sentinel lymph node (SLN) negative cohort that showed higher rates of grade 3 tumors in AA (AA 35% vs. WA 23%; p < 0.0001); and higher rates of grade 1 and grade 2 tumors in WA (30% vs. 21% and 44% vs. 40%). Despite higher grade tumors in AA women, five-year overall survival outcomes in SLN-negative cohort did not differ between AA and WA women when stratifying based on tumor subtype.

Conclusion: Breast cancer survival disparities in AA and WA women with SLN-negative breast cancer are diminished when evaluated at early-stage cancers defined by SLN-negative tumors. Our evaluation suggests that when diagnosed early,

phenotype does not contribute to racial survival outcomes. The lower survival rate in AA women with breast cancer may be attributed to later stage biology between the two races, or underlying socioeconomic disparities.

KEYWORD
early-stage breast cancer

1 | INTRODUCTION

Despite a convergence of the population-based incidence rate of breast cancer between African-American (AA) and White-American (WA) women over the past decade, there has been a divergence in outcome disparities.[1,2] Indeed, the current 5-year relative survival rate for WA and AA women is 92% and 83%, respectively, with mortality rates 39% higher in AA women.[3] And, while the incidence of breast cancer for the total population have equalized over the past decade, young AA women (≤40-years) continue to have higher incidence rates compared to similarly aged WA women.[2]

The survival disparity observed between WA and AA has been attributed to numerous factors, including later stage of diagnosis; socioeconomic factors (eg, delivery of care disparities and/or access to adequate healthcare); variation in treatment response; and/or an increased predisposition to develop biologically aggressive cancer phenotypes.[2]

In addition to poorer survival outcomes, AA women have a two-fold higher population-based incidence of aggressive tumor subtypes, including tumors that are negative for (1) the estrogen receptor; (2) the progesterone receptor; and (3) that do not overexpress HER2/neu—otherwise known as triple-negative breast cancer (TNBC).[4] Moreover, TNBC (80% of which belong to the inherently aggressive basal intrinsic subtype) are associated with poorer prognoses due to limited systemic therapy options.[5]

While the difference in TNBC survival rates between AA women and WA women has been investigated, these studies have yielded unsatisfying results with regard to identifying the underlying cause of the disparity. A study evaluating the effect of race on treatment showed no differences in pathologic response and survival outcomes between AA and WA when patients received similar treatment and follow-up for locally advanced TNBC breast cancer.[6] Another study evaluating tumor biology of TNBC revealed no difference in treatment response or biological profile between AA and WA women, demonstrating that survival disparities could not be attributed to tumor biology.[7] Other studies have reported consistently lower breast cancer survival associated with AA women as an independent risk factor for survival compared to WA women after adjusting for tumor biology and treatment received.[8,9]

Because of the outcome disparities reported between AA and WA women, we sought to evaluate the survival rate and phenotype of patients with early-stage breast cancer with negative sentinel lymph node (SLN) biopsy—a stage where opportunities for a favorable outcome is optimized—in order to determine whether the outcome disparities are a function of inadequate access to care and/or underlying genetic predisposition.

2 | METHODS

A prospectively maintained, IRB-approved data base for patients with early-stage breast cancer with SLN biopsy was utilized for data collection. The data was collected from a hospital system, Henry Ford Health System, featuring a large employee-based health insurance plan and serving a diverse community of the Metropolitan-Detroit area in Michigan.

The data was collected for women over 18 years old and diagnosed between 10/1998 (ie, around the date Tamoxifen became standard care) to 02/2017 with clinically early stage, node-negative breast cancer. Race and ethnicity identification were self-reported and collected during the initial encounter.

Tumor phenotype of each breast cancer was evaluated for hormone receptors, estrogen and progesterone, and HER2 status. Hormone receptor evaluation was performed via immunohistochemistry for estrogen and progesterone receptors with invasive carcinoma positivity defined as any cell uptake >1%.[10] Additional fluorescence in situ hybridization (FISH) was done for HER2 immunostaining for equivocal immunohistochemistry. TNBC was defined as negative in the absence of expression of estrogen, progesterone and HER2 markers. Non-TNBC with HER2-positive pathology was defined as positive for estrogen and/or progesterone in the presence of a positive HER2 marker. Finally, Non-TNBC with HER2-negative was defined as the presence of positive estrogen and/or progesterone markers, while showing an absence of expression of a negative HER2 marker. Pathological evaluation was also performed on the sentinel lymph nodes for local invasion of breast cancer. The median follow-up time was 60 months.

To determine the significant differences in clinicopathological variables between race groups, we used chi-square tests for categorical variables (ie, Hormone Receptor (HR) status and survival outcomes) and two sample student's *t*-test for continuous variables (ie, age at diagnosis and survival times between race groups). The overall survival of all patients was censored at 5 year after diagnosis, and log-rank test was used to assess the difference in survival among groups. Kaplan-Meier plots were used for visualization. Additionally, a multivariate analysis was done to assess the variables risk jointly. Cox proportional Hazard models were deployed to assess the

association of survival with race, tumor subtypes, pathological grade and age at diagnosis jointly. All analyses were conducted using the R statistical programming version 3.6.1.

3 | RESULTS

A total of 2,298 women were identified in the cohort. The population breakdown consists of 39% of AA women (n = 907) and 61% WA women (n = 1,391). Both groups had a similar proportion of negative SLN biopsy (AA 46% vs. WA 52%; p = 0.509). The overall mean age at the time of diagnosis for AA women was 60 years old, and 62 years old for WA women (p = 0.003). Follow-up time in months was longer for the WA women at 95 months vs. 86 months in AA women. SLN biopsy results were evaluated for 58% of AA women, and 66% of WA women (SLN biopsy results were unavailable in the remaining unscored AA women and WA women). There was no significance demonstrated between SLN positive and negative cohorts between the two races (Table 1).

The overall 5-year survival was analyzed for the entire cohort, with the lowest survival occurring in patients with TNBC, followed by Non-TNBC/HER2-positive. The best survival outcomes were observed in patients with the Non-TNBC/HER2-negative phenotype (Figure 1). In the multivariable cox proportional hazard modeling where age at diagnosis, pathological T grade, and self-reported race were adjusted, TNBC remains at highest risk compared with Non-TNBC/HER2-positive and Non-TNBC/HER2-negative patients (Supplementary Table S1).

TABLE 1 Distribution of all variables in the entire cohort

Features	AA (n = 907)	WA (n = 1,391)	p-value
Sentinel lymph node biopsy status			
Negative	420 (46.3%)	727 (52.3%)	0.509
Positive	102 (11.2%)	195 (14.0%)	
Missing	385 (42.4%)	469 (33.7%)	
Subtype			
Non-TNBC (Her2-)	494 (54.5%)	905 (65.1%)	<0.0001
Non-TNBC (Her2+)	152 (16.8%)	213 (15.3%)	
TNBC	141 (15.5%)	145 (10.4%)	
Missing	120 (13.2%)	128 (9.2%)	
Tumor grade			
1	189 (20.8%)	370 (26.6%)	<0.0001
2	371 (40.9%)	639 (45.9%)	
3	304 (33.5%)	348 (25.0%)	
Missing	43 (4.8%)	34 (2.4%)	
Age, Years (mean, range)	60.1 (21,92)	61.6 (23,91)	0.003
Follow-up time, Months (mean, range)	85.8 (3,218)	95.3 (0,218)	0.0001

Phenotype distribution revealed a higher incidence of TNBC in AA women compared to WA women (AA 16% vs. WA 10%; p < 0.0001) (Table 1). AA women also had slightly higher incidence of Non-TNBC/HER2-positive phenotype (AA 16.8% vs. WA 15.3%; p < 0.0001). Furthermore, WA women had a significantly higher distribution of Non-TNBC/HER2-negative phenotype (AA 55% vs. WA 65%; p < 0.0001).

There were significant differences in the incidence of SLN-negative breast cancer when stratifying based on race and phenotype (Table 2). While AA had a lower incidence of the Non-TNBC/HER2-negative phenotype than WA women (AA 54% vs. WA 65%; p = 0.0002), there was a higher incidence in AA women for both the Non-TNBC/HER2-positive tumors (AA 14% vs. WA 13%; p = 0.0002) and TNBC phenotypes (AA 17% vs. WA10%; p < 0.0001) (Table 2). Finally, no differences were found when comparing age at diagnosis and follow-up times between the two races (Table 2).

The AA SLN-negative patients had a higher rate of tumor grade 3 at diagnosis (AA 35% vs. WA 23%; p < 0.0001) (Table 2). In contrast, WA SLN-negative women had higher rates of grade 1 and 2 tumors (30% vs. 21% and 44% vs. 40%) (Table 2). Surprisingly, there was no difference observed in the survival probability for early stage, SLN-negative patients when stratified based on tumor phenotype (Figure 2). The five-year overall survival outcome between AA and WA women with SLN-negative breast cancer, and when stratifying based on tumor subtype, showed no significant difference (Figures 3–5). Similarly, despite a lower five-year overall survival in AA women compared to WA women, this difference was not found to be significant in the SLN-negative patients (Figure 3). Furthermore, multivariable analysis adjusting for age at diagnosis and pathological T stage was completed to evaluate for possible effects of the race and phenotype subtypes (Supplementary Tables: S2–S5). No additional statistical significance was found in this analysis.

4 | CONCLUSION

AA women have been shown to have a significantly lower overall survival rate than WA women during all stages of breast cancer, especially when they have received a late-stage diagnosis.[2] And, despite numerous studies evaluating the underlying biological differences, socioeconomic factors (eg, access to care), and/or delay in diagnosis, the cause of the overall survival disparity remains unclear.

Regardless of race, both AA women and WA women with TNBC exhibit significantly lower survival rates compared to those with HER2-overexpressing and/or hormone receptor-positive disease.[11] TNBC is known to occur at a higher rate in AA women, specifically premenopausal AA women in population-based studies.[12-15] Accordingly, the higher incidence of TNBC in AA women has been evaluated as a contributing factor to lower survival in AA women. Furthermore, when evaluating racial disparities in cancer survival with controls for stage, socioeconomic variable, tumor biology and treatment patterns, AA women possess an overall lower survival for breast cancer in both endocrine-responsive and

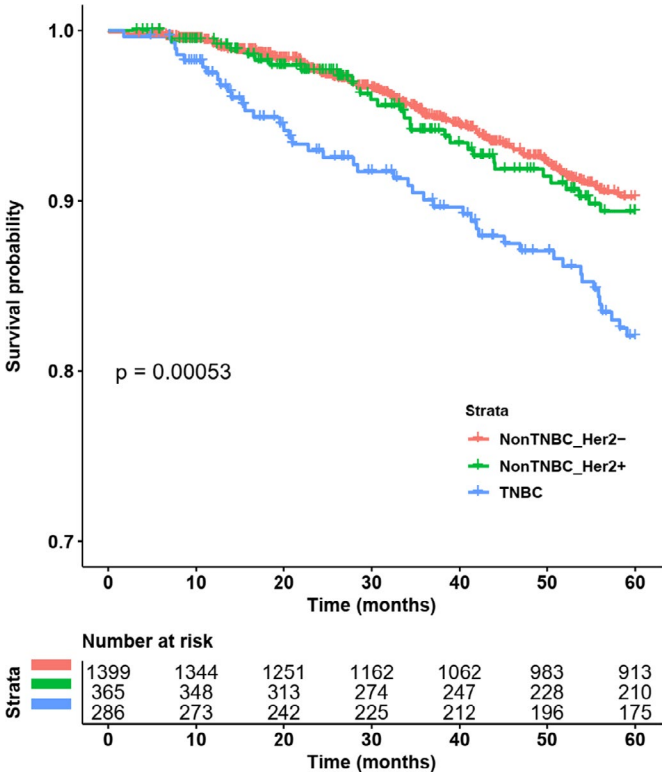

FIGURE 1 Five-year overall survival stratified by breast cancer subtypes in the entire cohort.

Tumor Subtype	5-year survival probability	95%CI
Non-TNBC(Her2-)	0.90	0.89-0.92
Non-TNBC (Her2+)	0.89	0.86-0.93
TNBC	0.82	0.77-0.87

TABLE 2 Distribution of variables in SLN-negative patients

Features	AA	WA	*p*-value
Tumor subtype			
Non-TNBC (Her2-)	224 (53.3%)	475 (65.3%)	0.0002
Non-TNBC (Her2+)	60 (14.3%)	95 (13.1%)	
TNBC	72 (17.1%)	73 (10.0%)	
Missing	64 (15.2%)	84 (11.6%)	
Grade			
1	89 (21.19%)	224 (30.81%)	<0.0001
2	170 (40.48%)	322 (44.29%)	
3	148 (35.24%)	170 (23.38%)	
Missing	13 (3.10%)	11 (1.51%)	
Age, Years (mean, range)	60.4 (27,92)	61.8 (31,91)	0.062
Follow-up time, Months (mean, range)	116 (3,218)	121 (1,214)	0.130

endocrine-unresponsive early-stage breast cancer.[9]Here, we identified possible pathologic trends in early-stage breast cancer that could account for the known disparities in survival between the AA and WA women with breast cancer.[1,2] Breast cancer survival disparities between AA and WA women with SLN-negative breast cancer are diminished when accounting for tumor phenotype (Figure 2). Moreover, the results presented here suggest that TNBC, when diagnosed early, does not result in a disparate survival outcome between AA and WA women (Figure 3). Accordingly, this study shows that the overall lower survival rate in AA women with TNBC may be

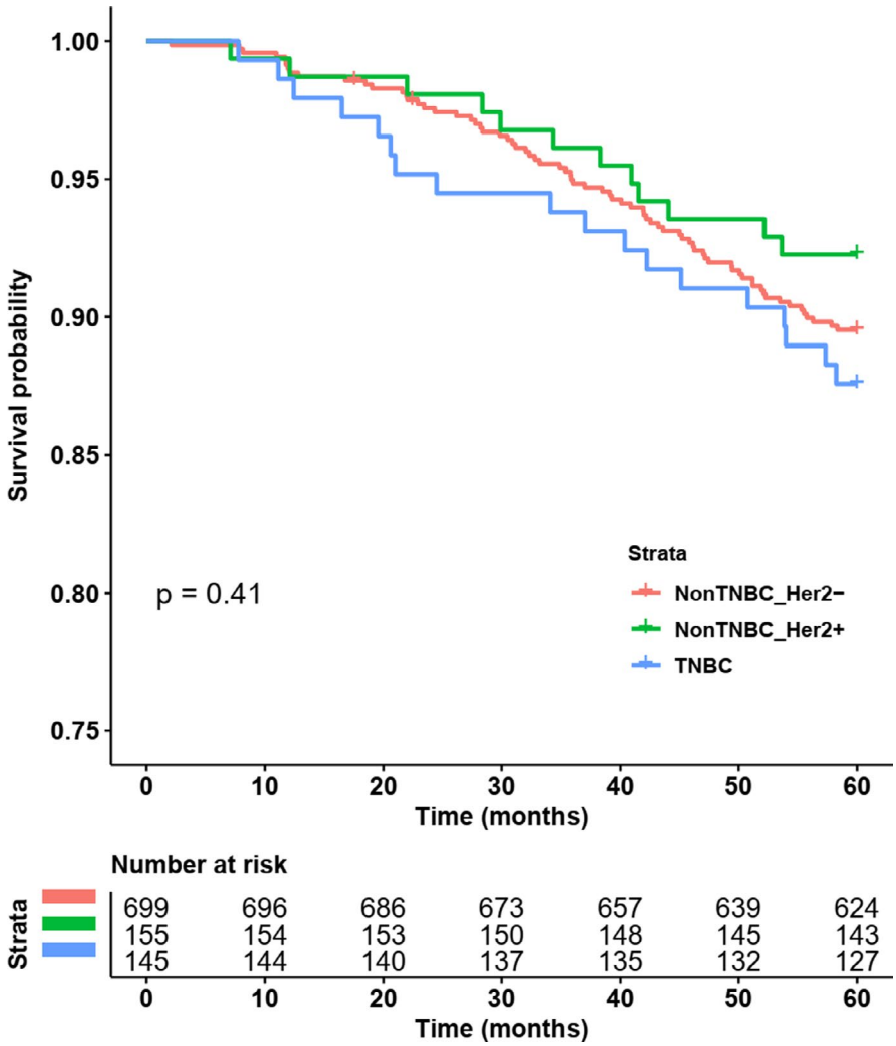

FIGURE 2 Five-year overall survival by phenotype in SLN-negative breast cancers

attributable to factors other than underlying genetic or biological factors, for example, later presentation for diagnosis and/or access to care.

Within the entire cohort, AA women had a higher incidence of TNBC compared to WA women; this difference became more pronounced when isolating for SLN-negative patients (ie, 17% in AA vs. 10% in WA; Table 2). These results would seem to suggest that AA women have a biological predisposition to the TNBC phenotype; thus, one would expect to find a lower survival rate for SLN-negative AA women with TNBC. However, when analyzing the overall survival outcome of AA and WA women, there was no significant difference between the two groups (Figure 3). Consequently, the lack of outcome disparity observed here between AA and WA women with SLN negative, TNBC could be attributable to some nonbiological factor such as socioeconomic disparities (eg, reduced access to care) and/or later presentation for diagnosis, incomplete therapy, or decreased access to follow-up.

Alternatively (and notwithstanding experimental design flaws, eg, sample size, etc.), the disparate survival outcome shown for the overall cohort, but absent when isolating based on SLN-negativity, could be attributable to biological differences observed at later stages between WA and AA patients. However, it is worth noting that the results of this study concur with similar studies evaluating the effect of race on TNBC. Alcantara et al. evaluated the incidence and prognosis of TNBC among Chinese, Malay, and Indian patients and found that race/ethnicity did not impact TNBC prognosis.[16] Likewise, recent studies have shown that the mutational landscape between AA women and WA women with TNBC is similar.[17]

Finally, the differences observed in median survival between AA and WA patients—within the strata of HER2-overexpressing and/or hormone receptor-positive disease—suggest the possible influence of compliance/access to targeted therapy and/or differences in response to targeted therapy. In other studies, evaluating treatment effects and outcomes between AA and WA have shown more pronounced disparities in overall and disease-free survival among estrogen-positive AA women.[18-20] However, in this retrospective study, a larger proportion of AA were included in the sample with a wider inclusion criteria (ie, not excluding patients based on comorbidities)—which is more reflective of the general AA population. However, in light of differences in our findings compared to other studies based on hormone positive outcomes, further prospective studies would be vital to determine underlying racial differences that could contribute/suggest to different biological response or perhaps decreased compliance.

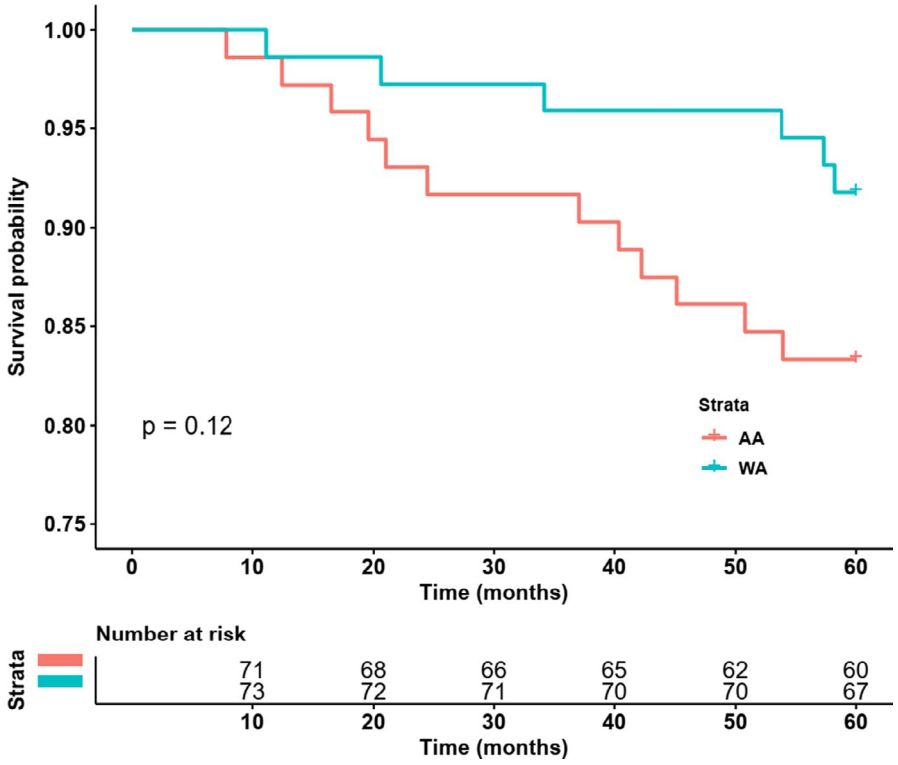

FIGURE 3 Five-year overall survival by race in TNBC SLN-negative patients

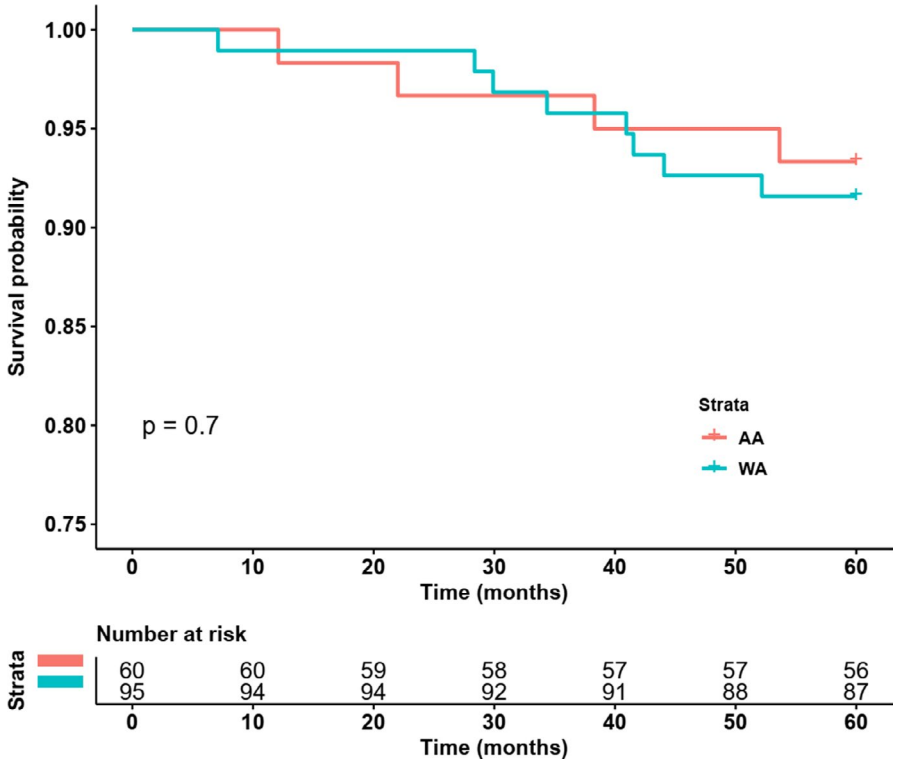

FIGURE 4 Five-year overall survival in Non-TNBC/Her2-positive SLN-negative patients

This study is limited by its retrospective and nonrandomized study design. As such, it is subject to misclassification and selection bias. Furthermore, our database has limited information on type of adjuvant chemotherapy which could contribute to cancer response based on race as well as agents used as suggested by other studies by Schneider, Sparano and Tichy.[18,19,21] Moreover, despite being a multi-center study in the state of Michigan, conclusions may not be directly generalizable to other institutions or geographical locations.

Finally, in conclusion, stratifying patients based on stage (ie, SLN-negative, or early breast cancer analysis) reveals no difference with regard to survival outcome between AA and WA women based on tumor phenotype. This significant finding suggests that either

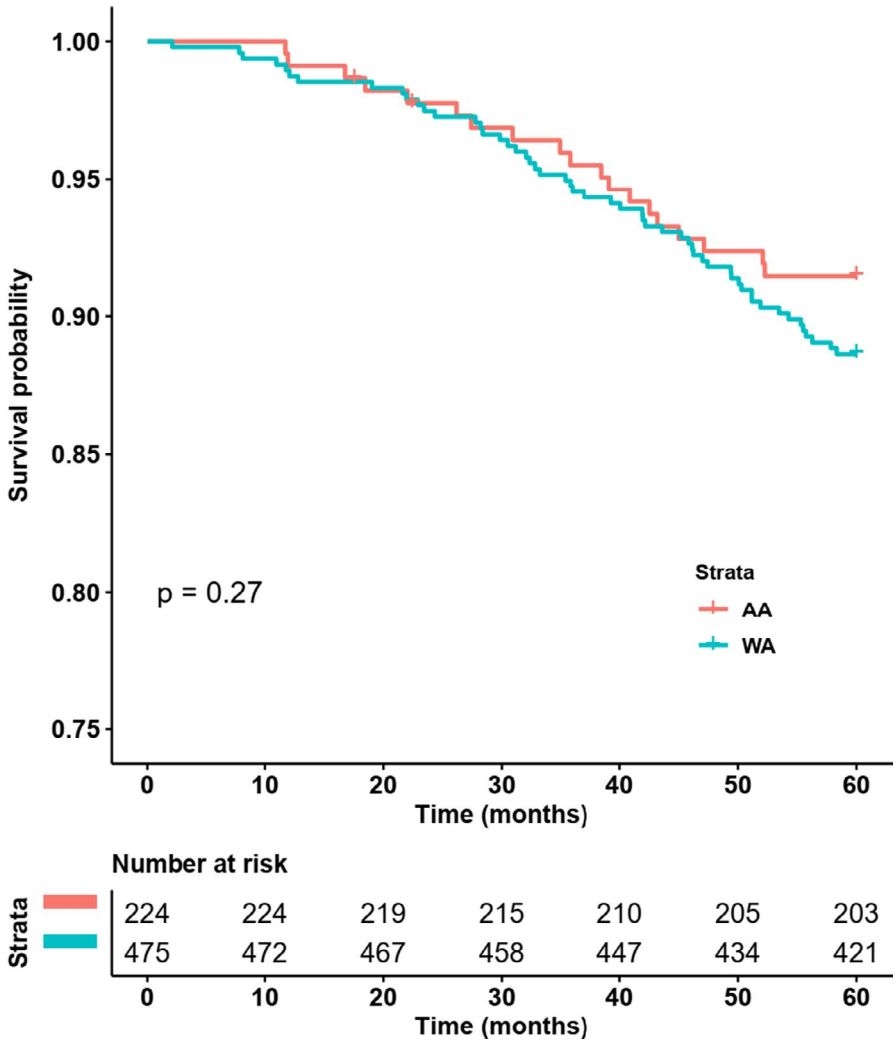

FIGURE 5 Five-year overall survival by race in Non-TNBC/Her2-negative SLN-negative patients

later stage biology differs between the two races, or the access and medical treatment diverges due to factors such as access to treatment; this finding is important because other studies have shown that TNBC and HER2+ cancer in AA women had worse survival compared to WA women. Accordingly, further inquiry is required to determine whether earlier or more rigorous screening and/or better follow-up procedures have an effect on outcome disparities between AA and WA women with breast cancer.

CONFLICT OF INTEREST

The authors have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Troester MA, Hoadley KA, Olopade OI, et al. Racial differences in PAM50 subtypes in the Carolina breast cancer study. *J Natl Cancer Inst*. 2018;110(2):176-182.
2. American Cancer Society, Breast Cancer 2017-2018: Facts and Figures at 10.
3. Sturtz LA, Melley J, Mamula K, Shriver CD, Ellsworth RE, et al. Outcome disparities in African American women with triple negative breast cancer: a comparison of epidemiological and molecular factors between African American and Caucasian women with triple negative breast cancer. *BMC Cancer*. 2014;14:62.
4. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975–2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *J Natl Cancer Inst*. 2015;107(6):djv048.
5. Jiagge E, Chitale D, Newman LA. Triple-negative breast cancer, stem cells, and African ancestry. *Am J Pathol*. 2018;188(2):271-279.
6. Dawwood S, Broglio K, Kau SW, et al. Triple receptor-negative breast cancer: the effect of race on response to primary systemic treatment and survival outcomes. *J Clin Oncol*. 2009;27(2):220-226.
7. Dean-Colomb W, Yan K, Liedtke C, et al. Transcriptional profiles of triple receptor-negative breast cancer: are Caucasian, Hispanic, and African-American women different? *J Clin Oncol*. 2008;26:S22014.
8. Lund MJ, Trivers KF, Porter PL, et al. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. *Breast Cancer Res Treat*. 2009;113:357-370.

9. Albain KS, Unger JM, Crowley JJ, Coltman CA Jr, Hershman DL. Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology Group. *J Natl Cancer Inst*. 2009;101:984-992.[PubMed: 19584328].
10. Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol*. 1999;17:1474-1481.
11. Newman LA. Breast cancer in African-American women. *Oncologist*. 2005;10(1):1-14.
12. Stark A, Kleer CG, Martin I, et al. African ancestry and higher prevalence of triple-negative breast cancer: findings from an international study. *Cancer*. 2010;116(21):4926-4932.
13. Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. *Cancer*. 2007;110:876-884.
14. Stead LA, Lash TL, Sobieraj JE, et al. Triple-negative breast cancers are increased in black women regardless of age or body mass index. *Breast Cancer Res*. 2009;11:R18.
15. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer registry. *Cancer*. 2007;109:1721-1728.
16. Alcantara VS, Lim GH, Lim SH, Sultana R, Lee JA Incidence and prognosis of non-metastatic triple negative breast cancer (TNBC) among different races in Southeast Asia. *J Surg Oncol*. 2017;115(5):523-537.
17. Ademuyiwa FO, Tao Y, Luo J, Weilbaecher K, Ma CX. Differences in the mutational landscape of triple-negative breast cancer in African Americans and Caucasians. *Breast Cancer Res Treat*. 2017;161(3):491-499.
18. Schneider B, Shen F, Jiang G, et al. Impact of genetic ancestry on outcomes in ECOG-ACRIN-5103. *JCO Precision Oncol*. 2017;1:1-9. PO.17.00059.
19. Sparano JA, Wang M, Zhao F, et al. Race and hormone receptor-positive breast cancer outcomes in a randomized chemotherapy trial. *J Natl Cancer Inst*. 2012;104(5):406-414. https://doi.org/10.1093/jnci/djr543.
20. Albain KS, Gray RJ, Makower DF, et al. "Race, ethnicity and clinical outcomes in hormone receptor-positive, HER2-negative, node-negative breast cancer in the randomized TAILORx trial". *J Natl Cancer Inst*. djaa148. 28 Sep. 2020, doi:10.1093/jnci/djaa148
21. Tichy JR, Deal AM, Anders CK, Reeder-Hayes K, Carey LA. Race, response to chemotherapy, and outcome within clinical breast cancer subtypes. *Breast Cancer Res Treat*. 2015;150(3):667-674. https://doi.org/10.1007/s10549-015-3350-2.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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