Editorial Commentary

Racial disparities in triple-negative breast cancer: insights from the E5103 trial and beyond

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Comment on: Leonard S, Jones AN, Newman L, *et al.* Racial disparities in outcomes of patients with stage I-III triple-negative breast cancer after adjuvant chemotherapy: a post-hoc analysis of the E5103 randomized trial. Breast Cancer Res Treat 2024;206:185-93.

Keywords: Triple-negative breast cancer (TNBC); racial disparities; structural racism

Submitted Oct 24, 2024. Accepted for publication Feb 03, 2025. Published online Feb 25, 2025.
doi: 10.21037/gs-24-460
View this article at: https://dx.doi.org/10.21037/gs-24-460

Introduction

Persistent racial disparities in breast cancer outcomes remain a significant concern in oncology, with Black women facing disproportionately higher mortality rates despite overall advances in care (1,2). A key factor contributing to this disparity is the higher prevalence of triple-negative breast cancer (TNBC) among Black women. TNBC, classified under the hormone receptor-negative (HR–)/human epidermal growth factor receptor 2-negative (HER2–) subtype, shows a markedly lower 5-year relative survival rate of 78.0% compared to other subtypes: 17.1 percentage points below HR+/HER2– (95.1%), 13.5 points lower than HR+/HER2+ (91.5%), and 7.7 points below HR–/HER2+ (85.7%) (3). This aggressive subtype is more common in Black women, accounting for 19% of their breast cancer diagnoses compared to only 9% in White women, thus significantly impacting the overall survival (OS) disparities observed between racial groups (2).

A key question is whether Black women with TNBC have worse prognosis compared to White women. While a U.S. study reported poorer survival for Black women with TNBC (4), the prevailing belief in the field is that racial disparities are more pronounced in other subtypes, largely due to inequities in access, adherence, and completion of effective targeted therapies (5). However, questions regarding the extent of racial disparities in TNBC outcomes between White and Black patients, and the specific factors contributing to these disparities, remain inadequately answered.

Key takeaways from the post-hoc analysis of the E5103 randomized clinical trial

The recent post-hoc analysis of the E5103 randomized clinical trial, published in *Breast Cancer Research and Treatment*, provides valuable insights into this complex issue. This study, led by Saskia Leonard and colleagues, examined racial differences in disease-related outcomes among TNBC patients treated with adjuvant chemotherapy (6). The original E5103 trial, published in the *Journal of Clinical Oncology* in 2018, demonstrated that incorporating bevacizumab into sequential anthracycline- and taxane-containing adjuvant therapy did not improve invasive disease-free survival (IDFS) or OS in patients with high-risk HER2– breast cancer (7).

This unplanned, secondary analysis of the E5103 clinical trial focused on 1,742 patients with TNBC and known self-reported race from the original cohort of 4,994 patients with stage I–III HER2– breast cancer. All patients received standardized adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) with or without bevacizumab. The study examined locoregional recurrence

(LRR), distant recurrence (DR), IDFS, and OS as primary endpoints. Researchers employed unadjusted Kaplan-Meier curves and adjusted Cox-proportional hazards models to analyze outcomes by race.

Of the 1,742 TNBC patients analyzed, 81.6% were White, 15.4% were Black, and 2.9% were Asian. White women were more likely to be node-negative compared to Black and Asian women, while other baseline characteristics were similar across racial groups. At a median follow-up of 46 months, there were no statistically significant differences in LRR, DR, IDFS, or OS by race in either unadjusted or adjusted analyses. Notably, in Cox-proportional hazards models adjusted for patient, treatment, and tumor factors, race was not associated with any disease event or survival outcome. Instead, increasing tumor size and nodal involvement were significantly associated with all disease events and survival outcomes across all racial groups.

Implications and broader context of the E5103 study

The study's findings suggest that when access to care and treatment is standardized, as in a clinical trial setting, racial disparities in TNBC outcomes between Black and White women may be minimized. A recent systematic review and meta-analysis examining racial differences in breast cancer survival by subtype between Black and White women in the United States provides valuable insights into this question (8). The study included 18 publications from 2000 to 2022, encompassing a total of 228,885 breast cancer patients (34,262 Black and 182,466 White). The results showed that Black women had worse survival outcomes compared to White women across all breast cancer subtypes examined. For breast cancer-specific survival, the disparity was greatest for HR+/HER2– tumors (50% higher risk of death for Black women), followed by HR+/HER2+ tumors (34% higher risk), HR–/HER2+ tumors (20% higher risk), and smallest for triple-negative tumors (17% higher risk).

This study's more favorable results for Black women with TNBC, compared to the systematic review, can likely be attributed to the fact that the systematic review included observational studies, which reflect real-world clinical practice data. In contrast, the findings of E5103 study were based on a clinical trial setting with more controlled conditions. This distinction highlights the crucial role of social determinants, including structural racism, in TNBC care for Black women. These findings suggest that addressing social determinants and structural barriers could eliminate racial differences in breast cancer treatment outcomes between White and Black patients.

In real-world clinical settings, it is well recognized that structural racism based on race exists in ways that cannot be fully captured or explained by apparent social determinants of health alone (9). This systemic form of discrimination operates on multiple levels and through complex mechanisms that often elude straightforward measurement or observation. Structural racism can significantly impact the outcomes of Black women with TNBC through multiple interconnected pathways. It contributes to widespread socioeconomic inequality, leading to lower individual- and area-level socioeconomic status among Black populations (10). This results in limited access to high-quality healthcare, including academic medical centers and breast specialty care (11,12). Racial residential segregation and higher rates of uninsurance or public insurance further exacerbate these disparities (8). Black patients are more likely to receive care in facilities with lower-quality ratings and limited resources (13,14). These factors can lead to delays in diagnosis (15) and suboptimal completion of adjuvant treatments, including delayed initiation and early discontinuation of chemotherapy and radiation therapy (16,17). Experiences of racism in healthcare settings can lead to lower trust, poor communication, and reduced adherence to medical recommendations (18). The cumulative effect of these structural barriers can result in more advanced disease at diagnosis, less optimal treatment, and ultimately poorer survival outcomes for Black women with TNBC.

To address structural racism affecting Black women with breast cancer, a comprehensive and multi-level approach is essential. In the United States, patient navigation has emerged as a promising intervention, showing significant improvements in access to cancer treatment through various support services, including transportation assistance, interpretation services, insurance navigation, appointment coordination, psychosocial support, and patient education (19). These benefits extend beyond the U.S., as similar navigation services in low- and middle-income countries have demonstrated positive effects on major health outcomes (20). Evidence suggests that patient navigation effectively addresses structural barriers and improves breast cancer outcomes for Black women by increasing screening participation, reducing delays in diagnosis and treatment, and enhancing quality of life throughout survivorship. While initial studies indicate cost-effectiveness, particularly in screening programs, additional research is needed to fully evaluate its impact across the

cancer care continuum and optimize implementation in diverse healthcare settings.

From a research perspective, there is a pressing need for more quantitative studies that examine the impact of racial disparities between White and Black individuals on prognosis across different breast cancer subtypes. In the recent study by Parab *et al.*, non-Hispanic Black and non-Hispanic American Indian and Alaska Native women were more likely to have breast tumors with high-risk recurrence scores compared to non-Hispanic White women, with area-level socioeconomic position, urban residence, and insurance status mediating 17% of the racial difference for non-Hispanic Black women, and racial differences in recurrence scores between non-Hispanic Black and White women observed only among urban residents (21). Such investigations are crucial as they can provide a more nuanced understanding of how race influences outcomes (21,22) and potentially enable more targeted interventions.

Yet, breast cancer disparities discussions often focus on U.S. racial differences, neglecting the global context. In 2020, over 2.3 million new cases and 685,000 deaths occurred worldwide, with breast cancer being the most diagnosed cancer among women in 157 of 185 countries and the leading cause of cancer death in 110 (23). Circumstances vary widely across countries and environments, even within racial groups, and racial diversity is too complex for simple classification. For example, in low- and middle-income countries, access to cancer treatment facilities and specialists is often limited (24). Within such resource-constrained settings, disparities are likely to be further exacerbated. In this sense, quantifying genetic ancestry from genomic data offers a more nuanced approach, as the distribution of breast cancer subtypes across ethnicities likely results from complex interactions between intrinsic and extrinsic factors (25). Large-scale collaborative studies using standardized methodologies are needed to examine the multiomics profile of breast cancer in diverse populations globally.

Conclusions

The post-hoc analysis of the E5103 trial offers important insights into racial disparities in TNBC outcomes. The results indicate that when treatment protocols and access to care are uniform, as in a clinical trial setting, the differences in outcomes between Black and White women with TNBC may be significantly reduced or eliminated. However, this finding contrasts with real-world data, highlighting the significant impact of structural racism on TNBC care for Black women outside clinical trial settings.

To address these disparities, a comprehensive approach is needed, including patient navigation programs, improved access to high-quality care, and efforts to combat systemic discrimination in healthcare. Furthermore, there is a pressing need for more research examining racial disparities across different breast cancer subtypes, as well as studies that consider the global context of breast cancer.

Ultimately, addressing racial disparities in TNBC and breast cancer more broadly requires a multifaceted approach that combines standardized care protocols, targeted interventions to overcome structural barriers, and a deeper understanding of the complex interplay between genetic, environmental, and social factors that contribute to breast cancer outcomes across diverse populations worldwide.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gland Surgery*. The article has undergone external peer review.

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-460/prf

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-460/coif). A.O. receives consulting fees from MNES Inc. and Becton, Dickinson and Company, unrelated to the submitted work. In addition, he receives honoraria from Kyowa Kirin Inc., Daiichi Sankyo, and Taiho Pharmaceutical Co., Ltd., also unrelated to the submitted work. He has been granted funds for his research on financial relationships between the healthcare industry and healthcare professionals by the Daiwa Japan Anglo-Japan Foundation. Furthermore, he serves as a committee member for the Japan Society for Medical Education, focusing on professionalism as a physician. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Nashimoto M, Ozaki A. Racial disparities in triple-negative breast cancer: insights from the E5103 trial and beyond. Gland Surg 2025;14(2):252-256. doi: 10.21037/gs-24-460