Understanding drivers of the Black:White breast cancer mortality gap: A call for more robust definitions

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Black women, relative to all other women, suffer a 40% higher mortality rate from all types of breast cancer.[1] To elucidate drivers of this racial disparity, it is important to consider multiple potential drivers including but not limited to 1) social determinants of health (SDH), 2) lack of equitable access to care, and 3) the heterogeneity of the disease itself. Estrogen receptor–negative (ER–) breast cancer typically has a worse prognosis than ER+ breast cancer. A higher prevalence of the ER– subtype among Black women has been hypothesized to be a driver in mortality differences between White and Black women with breast cancer. However, ER+ breast cancer is more prevalent that ER– disease and makes up approximately 70% of all breast cancer cases; ER+ disease is responsible for more breast cancer deaths in both Black and White women.[2] Understanding disparities within ER+ breast cancer is of utmost importance to bridge the Black:White mortality gap.

Black:White breast cancer disparities are far greater for ER+ (vs ER–) breast cancer. The death rate from ER+ breast cancer in Black women is 4 to 5 times higher than for non-Hispanic White women.[3,4] As demonstrated by Gabram et al, in ER+ breast cancer, Black women are more likely to have a high-risk Oncotype score.[5] Unfortunately, Black women are also less likely to have an Oncotype score performed. The lack of Black women receiving standard of care illustrates the complexity of both social and biologic factors contributing to disparity in survival from ER+ breast cancer.

Numerous studies have illuminated the effect of disparate clinical care on racial differences in breast cancer mortality rates.[6-8] Although clinical trials provide standardization of care to all enrollees regardless of race, the lack of representation limits broad applicability of the observed findings. In clinical trials leading to US Food and Drug Administration drug approval, Black/African Americans made up only 3.1% of clinical trial participants, although they represent 13% of the general population.[9] Similarly, Hispanic American/Latino populations made up 6.1% of participants, although they make up 18.1% of the US population.[9] Increasing the racial/ethnic diversity of individuals enrolled in clinical trials has the potential to broaden applicability of the findings and decrease the mortality gap. In addition, combining the results from multiple trials in pooled analyses may provide a way to mitigate the lack of representation and provide further insights into drivers of disparities in the setting of standardized care.

In this issue of *Cancer*, Kim et al[10] harness the power of pooled national trial data to clearly define racial disparities in ER+ breast cancer outcomes. The primary end point of distant recurrence-free survival (DRFS) rates was examined in 8 National Surgical Adjuvant Breast and Bowel Project trials including 9702 women (1070 Black, 8632 White) with nonmetastatic breast cancer receiving neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (AC). Ethnicity was not considered in this analysis and Hispanic patients were encompassed in the Black and White categories. The authors took great care to eliminate confounders when possible, selecting specific trials because of their use of doxorubicin, cyclophosphamide, with or without a taxane, to control for type of chemotherapy administered, and even eliminating trials in which Black participation was low. DRFS was evaluated among the AC and NAC groups; the NAC groups were further stratified by pathologic response. Furthermore, this analysis was completed in ER+ and ER– groups separately to control for the effect of the more aggressive ER– subtype on mortality.

The authors found Black race was associated with worse DRFS overall as well as in the ER+ subgroup, but not in the ER– population. Furthermore, worse DRFS was seen in the ER+ patients who had less than complete pathologic response (pCR)

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after NAC, but no racial disparity was seen in any other NAC group, including those that attained pCR as well as the ER– patients without pCR. Kim et al also note that Black women had a higher pCR than White women in the analysis and attribute this to a possibly higher prevalence of basal-like or triple-negative subtypes. Compared with 30% to 40% in triple-negative and 60% to 70% in HER2 enriched phenotypes, the pCR rate in ER+ breast cancer is 10% to 13% in response to current chemotherapy.[11] However, Ma et al recently demonstrated in a National Cancer Database analysis that pCR rates were higher among Black women with ER+ breast cancer treated with NAC compared with White women.[12] These results are concordant with the observations noted by Kim et al and underscore the importance of elucidating differences in ER+ breast cancer biology across races.

ER+ breast cancers are extremely heterogeneous. Currently, defined by immunohistochemical expression of estrogen and progesterone receptors, as well as of ERBB2 and proliferation markers, ER+ breast cancer is further divided into luminal A and B subtypes.[13] Although luminal A cancers have higher ER/progesterone receptor expression, lower proliferation marker expression, and better overall survival than luminal B cancers,[14] the luminal B subtype is more commonly diagnosed in Black women.[15] The 8 National Surgical Adjuvant Breast and Bowel Project trials included were conducted between 1984 and 2010, before molecular subtyping was used to ascertain therapy benefit in trial design. It is likely that more extensive categorization of ER+ disease would affect observed DRFS in these trials. More recent clinical trials have taken this into consideration in their design; the novel I-SPY platform uses the 70-gene assay MammaPrint in the inclusion criteria to further define subtypes.[16] This will revolutionize our ability to unpack drivers of survival differences in ER+ breast cancer.

Now is the time to incorporate additional biology-based definitions of ER+ subtype into both clinical trials and management. Better biology-based classification of ER+ breast cancers is essential to understand the complex underpinnings of recurrence and treatment resistance. However, additional subtyping of ER+ breast cancer cannot be done in isolation: race/ethnicity, access, and ZIP code also affect outcomes.[17] As so eloquently stated by Borrell et al, race is a complex interplay of not just social and historical factors, but also ancestry.[18] Elucidating the role of ancestry is necessary to fully understand the drivers of aggressive ER+ breast cancer biology in Black women.[19] Kim et al rightly address the potential power of exploring the impact of ancestry and country of origin on outcomes and management. As demonstrated by Serrano-Gomez et al,[20] ancestry can impact variation of gene expression and outcomes in women with ER+ breast cancer. The authors, however, also note the limitation of noninclusion of SDH in many historical clinical trials. The fast pace at which novel trials promote precision medicine mandates more robust definitions of the people we treat. For example, the new addition of CDK 4/6 inhibitors to the treatment paradigm for ER+ breast cancer has affected DRFS, but a racial or even ancestral predilection has yet to be fully determined, and even less the impact of SDH on outcomes.

In summary, using pooled standardized national trial data, Kim et al clearly demonstrate worse survival among Black women with ER+ breast cancer, especially those treated with NAC without pCR. Their study serves as an important platform from which to dive deeper into the mechanisms driving this disparity. To do so, we must provide precise molecular definitions of ER+ disease as well as integrate the societal and biological factors that contribute to the all-encompassing term "race." Biology and treatment resistance likely play a role in outcomes, and further research is needed to explore these areas while incorporating better definitions of disease characteristics and the populations affected. Only then will we be able to move the needle in comprehensively understanding and addressing survival disparities in Black women with ER+ breast cancer.

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