Letter to the Editor

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Comment on Genetic Ancestry-Specific Molecular and Survival Differences in Admixed Breast Cancer Patients

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We read with interest the article by Telonis and colleagues (December 11, 2023).[1] The article explores the association between "genetic ancestry" and clinical and molecular characteristics of breast cancer with a focus on the continental ancestral categories of West African (WA) and European (EU). We agree that addressing the racial and ethnic inequities in breast cancer outcomes is a priority and that molecular pathways are important to elucidate.

However, we are concerned that the article's use of continental genetic ancestry groups retains flawed assumptions that genetic differences between "continental ancestral populations" are categorical and are main drivers of breast cancer inequities. We believe the article would be strengthened by discussing the limitations of genetic ancestry measures and explicitly stating that structural racism, socioeconomic status, and environmental exposures can alter gene expression and confound the relationship between marginalized populations and breast cancer outcomes.

Racial and ethnic categories have tremendous impacts on health due to structural racism, not because of any inherent categorical genetic differences between population.[2,3] Telonis and colleagues importantly note that race is a social construct; they also mention that researchers are increasingly using genetic ancestry to avoid some of the methodologic issues with race. However, the authors do not mention that the use of genetic ancestry in biomedical research does not resolve all these methodological problems. As a recent article explains, "the reality is that ancestry has many of the same issues as race and ethnicity, and is not useful as a marker of complex, non-Mendelian diseases."[4] Genetic ancestry groups are created based on a chosen dimension of genetic similarity; they are not clear natural categories. The groups cannot be assumed a priori to differ meaningfully and categorically along the axis of genetic determinants of breast cancer, in part due to the large amount of heterogeneity within each continental ancestry category, called subcontinental admixture.[5]

We cannot assume that some degree of genetic relatedness between people predicts the presence of different disease-causing alleles, or even different frequencies of disease-causing alleles.[4–6] A recent report by the National Academies of Sciences, Engineering, and Medicine recommends that "careful consideration should be given to whether descent-associated population descriptors are needed at all."[6] If the goal is to examine genetic associations, the focus should be on specific genes, not broad categories of similarity, which can also capture nongenetic effects.[4,6] Without acknowledging the systemic issues that underpin definitions of ancestry and the possibility of residual confounding, the authors could inadvertently perpetuate the harmful misconception that race is a genetically meaningful category.[4,6,7]

This is particularly important to consider in the context of breast cancer, as it is well documented that redlining and socioeconomic status are associated with higher rates of breast cancer in minoritized populations.[3,8,9] Due to the long history of racial essentialism in medicine, it is vital that biomedical researchers thoughtfully define race or ancestry, while centering the social determinants of health that inform these categories.

Another concern is that the described association between continental ancestry group designation and observed gene expression works in opposite directions in luminal and basal cancers.[1] In our view, the authors do not adequately explain this issue. If both continental ancestry groups can both increase and decrease expression of the same genes, it seems to imply that something else mediates the association between gene expression and breast cancer.

Beyond the study design, the authors occasionally conflate race with genetic ancestry in their discussion. The authors state, "relative to women with increasing European ancestry, women with increasing West African ancestry had shorter odds of survival, consistent with literature where Black patients consistently have a higher breast cancer mortality." This statement directly equates genetic ancestry with race and undermines the authors' stated goals of moving away from the binary racial categories.

Finally, the authors seem to claim causation when correlation more appropriately describes the observed association. For example, the authors conclude that these "novel genomic differences" are "driven by ancestral percentage."[1] The usual criteria for establishing causation in research include (1) temporal precedence, (2) covariance, and (3) disqualification of alternative explanations.[10] The present study design and the inability to adequately adjust for confounders as alternative explanations for breast cancer inequities and gene expression differences mean that the correlation between ancestral category group and gene expression cannot be assumed to be causal.

It is laudable to diversify research and explore the systemic forces that influence disparate health outcomes for diverse communities. However, we must avoid predicating studies of racialized populations on flawed assumptions of inherent categorical genetic differences. Without considering the systemic forces that underpin health inequity and drive health disparities, readers could misattribute the described associations to an essentialist view of continental ancestry groups. This article would be strengthened by a more careful consideration of the socioeconomic, environmental, and structural factors that influence health outcomes among Black women and those of West African ancestry.

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