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Race and Ancestry in Immune Response to Breast Cancer

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Summary:

Martini and colleagues performed genetic ancestry estimation on a unique, international triple-negative breast cancer (TNBC) study enriched for participants with African ancestry. They identified gene signatures indicative of ancestry in race-associated TNBC and found ancestry-associated immunological differences that may contribute to racial disparities in breast cancer.

Black women and women with African Ancestry have higher frequency of aggressive breast cancer subtypes, namely triple-negative breast cancer (TNBC) or basal-like breast cancer. This has been shown in several United States consortia[1, 2] and in studies in Africa[3]. Evidence that race associations persist across social and cultural contexts suggests that genetic ancestry may play a role in subtype frequency disparities. These questions are of increasing urgency almost two decades after health disparities in the prevalence of TNBC were first recognized[4] because recognition of TNBC's immunogenic properties have led to the promise of applying immune-targeted therapies (pembrolizumab). However, it remains unclear whether immune differences are driven by race or ancestry or occur secondary to tumor subtype. In either case, race- and ancestry-associated immunologic differences among TNBC are an important consideration for the efficacy of immune-targeted therapy. In aforementioned investigations of tumor biology disparities, most studies have emphasized self-reported race, making it difficult to interpret results with respect to ancestral lineage. However, a new study has highlighted heterogeneity between and among African populations and suggests novel approaches for addressing admixed African ancestry in tumor genetics.

In the current issue of Cancer Discovery, Martini and colleagues leveraged collaborations with International Center for the Study of Breast Cancer Subtypes (ICSBCS), an international consortium committed to breast cancer in diverse populations, to collect genetic samples from European Americans, West African/Ghanaians, East African/

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Ethiopians, and admixed African Americans[5]. Using this large study resource, they applied RNA sequencing (RNA-seq) to a specific subgroup composed of TNBC specimens (n = 45). Gene expression analysis and ancestry quantification were performed for five superpopulations (African, American, East Asian, European, South Asian) and 23 African subpopulations [Yoruba in Ibadan, Nigeria (YRI), Esan in Nigeria (ESN), Gambian in Western divisions in the Gambia (GWD), Mende in Sierre Leone (MSL), and Luhya in Webuye, Kenya (LWK), among others]. Findings were validated in two independent cohorts using additional RNA-seq data, but also with classic IHC approaches and protein-based digital spatial profiling using the GeoMx platform. The authors identified 2,567 genes associated with five African populations, and subpopulation specific associations were identified for YRI, ESN, GWD, MSL and LWK. Their work highlights a significant diversity of African admixture among African Americans (ranging from 0% to 90%). The heterogeneity and diversity of African ancestry were more extensive among African Americans than among Ghanaians or Ethiopians, with African Americans in this study having high proportions of ESN ancestry. The largest overlaps in gene expression existed between countries that were geographically proximal; however, the two closest West African groups, YRI and ESN of Nigeria, shared no associated genes. Overall, these findings highlight the importance of selecting relevant reference genomes in GWAS risk allele studies.

Given the importance of immune response in TNBC and previous work identifying higher immune infiltrates in tumors from African American breast cancer patients[6,7], Melissa Davis's lab has done the important work of placing these findings in context of African ancestry. Martini and colleagues found the highest expression of immune-checkpoint markers, specifically PD-1, among tumors from patients with West African ancestry, and in particular, among those with MSL subgroup ancestry. Such findings may be of clinical importance as PD-1 inhibitors become more widely used for the treatment of TNBC. In this relatively small cohort, the authors also observed that tumor subtypes from the Vanderbilt TNBC subtyping tool[8] seemed to vary in prevalence by ancestry, with immunomodulatory subtypes being most common in tumors from Ghanaians with high AFR ancestry and African American individuals.

Collectively, the combined associations between African subpopulations, TNBC subtype and immune microenvironments point toward an ancestral influence on TNBC biology and immunological responses that could be leveraged therapeutically.

The associations between ancestry and tumor immunologic differences shown in this study underscore the need for larger studies with diverse genetic lineage. Previous work has also shown that associations between germline variation and transcription vary by race[9], highlighting that ancestry is likely part of a multilevel constellation of factors that influence tumor expression. However, breast cancer disparities remain complex because ancestry and race also coincide with other social and environmental conditions that have potential to influence tumor biology and expression. Martini and coauthors have addressed this conceptual challenge by identifying 751 genes associated with self- reported race that were not associated with ancestry. Using hierarchical clustering, these genes separated African American patients from native African patients and had biological functions

implicated in comorbidities common in the United States (e.g., cardiac disease, obesity, diabetes, and insulin signaling) and that may reflect distinct environmental and structural influences. These findings emphasize that breast cancer in the United States occurs as part of a syndemic of overlapping conditions that are a consequence of structural racism and racialized social determinants of health[10]. The long term success of precision prevention will depend on adequate consideration of both genetic and environmental variables, ancestry and self-reported race, and ultimately will require multilevel interventions to address disparities within a conceptual framework that includes tumor biology, individual risk and behavioral factors, and community-level and structural factors, extending from cells to society[11].

In summary, Martini and colleagues have contributed a thorough RNA-seq investigation of samples representing a portion of the African diaspora, thereby identifying how ancestry and environmental influences work together in TNBC. As articulated by the authors, beyond characterizing causal factors influencing disparities, “finding novel biological traits presents an opportunity for therapeutic targets or interventions that incorporate these signatures in clinical treatment decision-making to improve outcomes.” Given the diversity of biology uncovered in this investigation, research with larger African American and admixed African study populations, together with immunologic profiles of tumors and individual and community level exposure data, has important implications for increasing health equity.

References

1. Allott EH, Cohen SM, Geradts J, Sun X, Khoury T, Bshara W, et al. , Performance of Three-Biomarker Immunohistochemistry for Intrinsic Breast Cancer Subtyping in the AMBER Consortium. Cancer Epidemiol Biomarkers Prev, 2016. 25(3): p. 470–8. [PubMed: 26711328]
2. Huo D, Hu H, Rhie SK, Gamazon ER, Cherniack AD, Liu J, et al. , Comparison of Breast Cancer Molecular Features and Survival by African and European Ancestry in The Cancer Genome Atlas. JAMA Oncol, 2017. 3(12): p. 1654–1662. [PubMed: 28472234]
3. Huo D, Ikpatt F, Khramtsov A, Dangou JM, Nanda R, Dignam J, et al. , Population differences in breast cancer: survey in indigenous African women reveals over- representation of triple-negative breast cancer. J Clin Oncol, 2009. 27(27): p. 4515–21. [PubMed: 19704069]
4. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. , Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA, 2006. 295(21): p. 2492–502. [PubMed: 16757721]
5. Martini R, Delpe P, Chu TR, Arora K, Lord B, Verma A, et al. , African Ancestry Associated Gene Expression Profiles in Triple Negative Breast Cancer Underly Altered Tumor Biology Pathways and Outcomes in Women of African Descent. Cancer Discovery 2022.
6. Yao S, Cheng TD, Elkhanany A, Yan L, Omilian A, Abrams SI, et al. , Breast Tumor Microenvironment in Black Women: A Distinct Signature of CD8+ T Cell Exhaustion. J Natl Cancer Inst, 2021. 113(8): p. 1036–1043. [PubMed: 33395700]
7. Hamilton AM, Hurson AN, Olsson LT, Walens A, Nsonwu-Farley J, Kirk EL, et al. , The landscape of immune microenvironments in racially-diverse breast cancer patients. Cancer Epidemiol Biomarkers Prev. 2022 Jul 1;31(7):1341–1350. doi: 10.1158/1055-9965.EPI-21-1312. [PubMed: 35437570]
8. Chen X, Li J, Gray WH, Lehmann BD, Bauer JA, Shyr Y, et al. , TNBCtype: A Subtyping Tool for Triple-Negative Breast Cancer. Cancer Inform, 2012. 11: p. 147–56. [PubMed: 22872785]
9. Bhattacharya A, Garcia-Closas M, Olshan AF, Perou CM, Troester MA, and Love MI, A framework for transcriptome-wide association studies in breast cancer in diverse study populations. Genome Biol, 2020. 21(1): p. 42. [PubMed: 32079541]

10. Carlos RC, Obeng-Gyasi S, Cole SW, Zebrack BJ, Pisano ED, Troester MA, et al. , Linking Structural Racism and Discrimination and Breast Cancer Outcomes: A Social Genomics Approach. J Clin Oncol, 2022. 40(13): p. 1407–1413. [PubMed: 35108027]

11. Warnecke RB, Oh A, Breen N, Gehlert S, Paskett E, Tucker KL, et al. , Approaching health disparities from a population perspective: the National Institutes of Health Centers for Population Health and Health Disparities. Am J Public Health, 2008. 98(9): p. 1608–15. [PubMed: 18633099]